14

Indirectly transmitted microparasites

Many important microparasitic infections of humans are indirectly transmitted from person to person by biting arthropods such as mosquitoes. A list of the major infections is presented in Table 14.1. An idea of their global significance is provided by the observation that the protozoan malarial infections on the continent of Africa alone are estimated to cause in excess of one million child deaths annually (Walsh and Warren 1979). The term 'vector transmitted' is often used to describe these infections but it should be noted that the vector is invariably a true intermediate host, in the sense that the parasite undergoes a phase of obligatory development (and often reproduction) within the arthropod.

In this chapter we consider the complications that the involvement of a second species of host introduces in the study of transmission, control, and the interpretation of observed epidemiological patterns. By way of illustration we concentrate on one particular infection, namely malaria. This is because of the disease's global significance as a cause of human mortality, its role in the early beginnings of epidemic and endemic theory, and the relative wealth of empirical information available on the biology and epidemiology of this disease. The investigation of the transmission dynamics of malaria, however, illustrates a much broader class of problems that are relevant to the study of a wide range of infections transmitted by vectors. We attempt to emphasize this point at appropriate stages in the chapter by reference to other viral and protozoan infections.

14.1 Biology and life cycle

Malaria in humans is due to infection by one of four protozoan species belonging to the genus *Plasmodium*, namely *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. In some areas of the world, more than one species may be endemic in the same geographical locality, so that individuals may harbour concurrent infections of two or more species. The most pathogenic species is *P. falciparum* (falciparum malaria) which is a major cause of child mortality in many areas of the developing world. The different species have similar life histories but there are quite a number of differences in biological detail.

The infection in humans begins when sporozoites (infective stages) are injected into the blood by a female mosquito of the genus *Anopheles*; the females need blood-meals to produce their eggs. The sporozoites migrate to the liver where they enter liver cells (hepatocytes) and develop into schizonts which give rise, via asexual reproduction, to the form which invades the blood cells, the merozoites. These enter red blood cells and become first trophozoites and then

Table 14.1 Major indirectly transmitted microparasitic infections

Group	Disease	Infectious agent	Location	Intermediate host
Viruses	Yellow fever	Yellow fever virus	Africa, Central, and South America	*Aedes* spp. and *Haemagogus* spp.
	Dengue fever	Dengue fever virus	S.E. Asia, India, Pakistan, Africa, Caribbean, Pacific Islands	*Aedes* spp.
Rickettsiae	Q fever	*Coxiella burnetti*	World-wide	*Amblyomma* spp. and *Dermacentor* spp.
Protozoa	Malaria	*Plasmodium vivax*	World-wide; tropical, sub-tropical, warmer temperate	*Anopheles* spp.
	Malaria	*Plasmodium malariae*	World-wide; tropical, sub-tropical	*Anopheles* spp.
	Malaria	*Plasmodium falciparum*	World-wide; tropical, sub-tropical, warmer temperate	*Anopheles* spp.
	Trypanosomiasis	*Trypanosoma brucei*	West, East, Central Southern Africa	*Glossina* spp.
	Trypanosomiasis	*Trypanosoma congolense*	West, East, Central Africa	*Glossina* spp.
	Leishmaniasis	*Leishmania donovani*		
		L. d. donovani	Asia (including China, USSR, India), Africa	*Phlebotomus* spp.
		L. d. chagasi	Mexico, Central and South America	*Lutzomyia* spp.
	Leishmaniasis	*Leishmania mexicana*	Mexico, Central and South America, USA (Texas)	*Lutzomyia* spp.
	Leishmaniasis	*Leishmania braziliensis*	Central and South America	*Lutzomyia* spp.
	Leishmaniasis	*Leishmania tropica* and *Leishmania major*	Asia (including USSR, India), Africa, and Southern Europe	*Phlebotomus* spp.
	Leishmaniasis	*Leishmania peruviana*	Peru	*Lutzomyia* spp.
	Leishmaniasis	*Leishmania aethiopica*	East and N.E. Africa	*Phlebotomus* spp.

erythrocytic schizonts (by a phase of asexual reproduction). For each schizont, 12–24 merozoites are released to invade further blood cells. Some sporozoites may remain dormant in the liver as hypnozoites. They may later, after an interval of several months, develop into schizonts and then merozoites which enter the blood. Some merozoites develop into gametocytes and are ingested by a mosquito when it ingests human blood. Within the mosquito they develop into microgametes and macrogametes (the male and female gametes) that fuse to form a zygote (the sexual phase). This becomes a motile ookinete form which bores through the gut wall of the vector and forms an oocyst from which large numbers of sporozoites are released. These invade the salivary glands of the mosquito from which they are injected into the human host when the vector feeds (see Garnham (1966) for further details).

Bouts of fever are associated with the rupture of the schizonts, which event occurs approximately every 48 hours with *P. falciparum*, *P. vivax*, and *P. ovale* and every 72 hours with *P. malariae*. The liver and spleen are grossly enlarged in infected individuals and haemolytic anaemia may be severe.

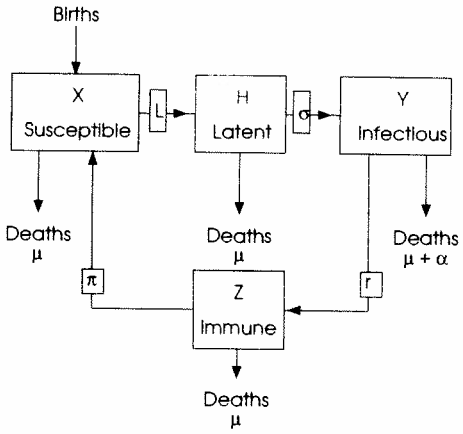


Fig. 14.1. Diagrammatic flow chart illustrating transitions between classes of the human population. The human population is divided into susceptibles (X), latent individuals (H), infectious individuals (Y) and immune individuals (Z). Rate parameters determine the flow of individuals between these classes: the per capita transmission rate L, the natural death rate μ, the disease-induced death rate α, the recovery rate γ, the rate at which individuals become infectious σ, and the rate of loss of immunity π.

The foregoing description is in broad qualitative terms and quantitative details vary from one species of the parasite to another and between different people and different species of vector. Mathematical studies of malaria transmission are conventionally based on the employment of the classical microparasite compartmental models (the prevalence framework) discussed in earlier chapters. A diagrammatic flow-chart of the principal population compartments based on such a framework is illustrated in Fig. 14.1. The basic malaria model described in a later section is based on this simple, idealized structure.

However, it should be noted that for protozoan parasites in particular, this framework ignores two important complications; these complications are less relevant for vector-transmitted viruses (the arboviruses). The first concerns the course of infection within an individual patient. In the case of malaria, for example, it is possible to obtain quantitative measures not just of prevalence (presence or absence of infection) but also of the intensity of infection (based, for example, on the proportion or number of infected red blood cells per sample). Furthermore, infection does not necessarily imply infectiousness since a patient may harbour many liver and blood cell stages of the parasites but no gametocytes (the stage infective to the vector). In other words, a more relevant quantitative measure of infectiousness is provided by counts of gametocytes per unit blood sample. In the epidemiological literature concerned with malaria, the proportion of the population with detectable levels of gametocytes in their blood stream is often defined as the 'gametocyte rate' of the population (Macdonald 1957). This is a misuse of the term 'rate' since prevalence is a

'standing crop' measure and not a rate. Similar criticisms apply to the use of the term 'trophozoite rate' (proportion of the population with infected red blood cells), and the overall 'parasite rate' (the proportion of the population with any evidence of infection).

The second problem concerns the nature of acquired immunity to malarial infection. Immunity appears to depend on both the duration and the intensity of past exposure to infection. Unlike many vector-transmitted viral infections (e.g. yellow fever virus), recovery from a primary infection with malaria does not imply fully protective immunity against reinfection. Parasite population growth may be slower, and the clearance of parasites from the blood more rapid, in second or subsequent infections but individuals may still be infectious to mosquitoes (i.e. gametocytes are often produced in second or subsequent infections). The mechanisms of immunity to malaria are not fully understood at present. Antibody and cell-mediated responses are important in limiting parasite population growth within individuals, but evidence of repeated infections in the same individuals in endemic areas argues that such mechanisms may only provide partial protection against parasite invasion (Molineaux and Gramiccia 1980). However, it is becoming increasingly apparent that genetic heterogeneity in parasite populations, both within an individual (antigenic variation within a clone) and within the community as a whole (parasite strain variation), may be an important determinant of the apparent absence of fully protective immunity following recovery from a primary infection (Forsyth *et al.* 1988). In short, the preceding discussion implies that the framework portrayed in Fig. 14.1, which embodies a class of 'immune' individuals, is an oversimplification of the true complexities of acquired immunity to certain vector-transmitted infections such as malaria. In later sections, however, this simple framework provides a useful point of departure for the development of more complex models.

14.2 Epidemiological patterns

Before turning to the development of a simple model to describe the basic features of malarial transmission, in this section we summarize the type of information available for estimating parameters and for testing the predictions of models.

14.2.1 *Infection in humans*

We consider empirical information on infection within the human host under four general headings. This is followed by parallel considerations of such factors for the intermediate hosts.

14.2.1.1 *Latent and infectious periods* The latent period for malaria is defined as the time from initial infection to the appearance of gametocytes in the blood. This period may depend on the duration of past exposure to infection (as a

Table 14.2 Latent periods of infectiousness for vector-transmitted protozoan and viral infections

Infectious agent	Latent period (days)	Duration of infectiousness	Reference
Plasmodium ovale	10–14	~2 months	Molineaux and Gramiccia (1980)
Plasmodium malariae	15–16	~4 months	Molineaux and Gramiccia (1980)
Plasmodium falciparum	9–10	~9.5 months	Molineaux and Gramiccia (1980)
Yellow fever virus	6	Short (4 days)	Anderson (1981*a*)
Trypanosoma brucei	10–14	Long (years?)	Anderson (1981*a*)

consequence of the build-up of acquired immunity). Average values for three species of human malaria are listed in Table 14.2. For comparison, the latent periods for other vector-transmitted viral and protozoan infections are also presented in this table. Note that the latent periods for malaria are relatively long in comparison with the viral infections such as yellow fever.

Periods of infectiousness are more difficult to determine (Table 14.2). In the case of malaria, infectiousness is defined as the presence of gametocytes in the blood. Their abundance (the degree of infectiousness, see Table 14.2) and the duration of their presence (the infectious period) depend both on the age of a given infection within an individual (the production of gametocytes varies during the course of a single infection) and the individual's past experience of malaria. For example, rates of recovery from infection with *P. ovale*, *P. malariae*, and *P. falciparum* appear to increase with age in endemic areas (Fig. 14.2) (Molineaux and Gramiccia 1980). Recovery is usually defined as the clearance of the parasite from the blood of a patient and it is not necessarily synonymous with the rate of clearance of gametocytes. However, the two are positively associated, with the latter being slightly more rapid than the former (Macdonald 1950).

In gaining an understanding of the duration of infectiousness, the most easily obtained information is that concerning the rate of clearance of parasites from the blood following a single response. The best series of observations on this subject is that collected by Earle *et al.* (1939) who studied a group of Puerto Ricans infected with *P. falciparum* who remained untreated over a period of 60 weeks. The data are presented in Fig. 14.3 and an analysis gives an expected duration of infection of roughly 200–300 days. A collection of estimates of infectious periods, some based on recovery rates, are presented in Table 14.2. Again note that the periods are much longer for protozoan infections than for vector-transmitted viruses.

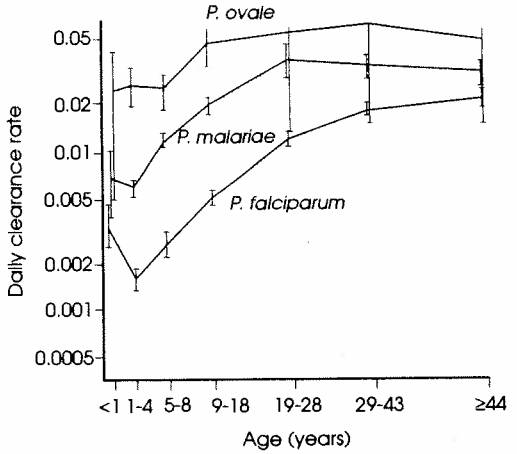


Fig. 14.2. Daily recovery rate from patent parasitaemia (clearance rate) for three species of *Plasmodium*, by age of the human host (from Molineaux and Gramiccia 1980).

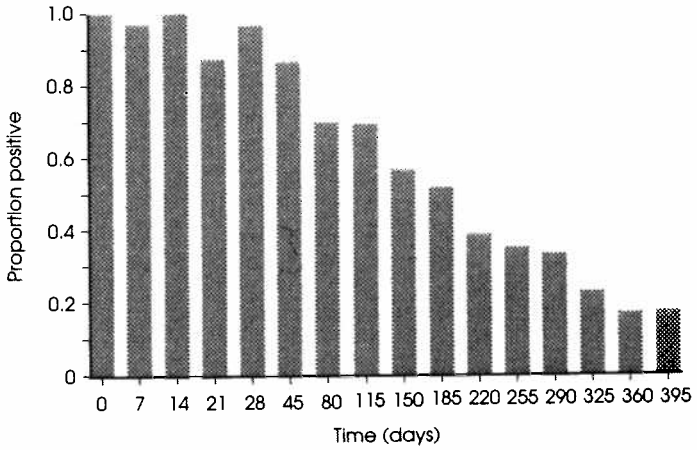


Fig. 14.3. The proportion of subjects remaining positive at succeeding intervals of time after a single infection with *P. falciparum* (Earle *et al.* 1939).

14.2.1.2 *Changes in prevalence and intensity with age* Observed patterns of change with age in the prevalence and average intensity (defined as some measure of the degree of red blood cell invasion) of malarial infection aredisplayed in Fig. 14.4. In areas of endemic *P. falciparum* infection, they characteristically rise steeply in early childhood to attain some maximum value (depending on the intensity of transmission, but often approaching 100 per cent prevalence) in the 5–10-year-olds and then decline steadily with increasing age. The rate of increase in early childhood, the maximum prevalence attained, and the rate of

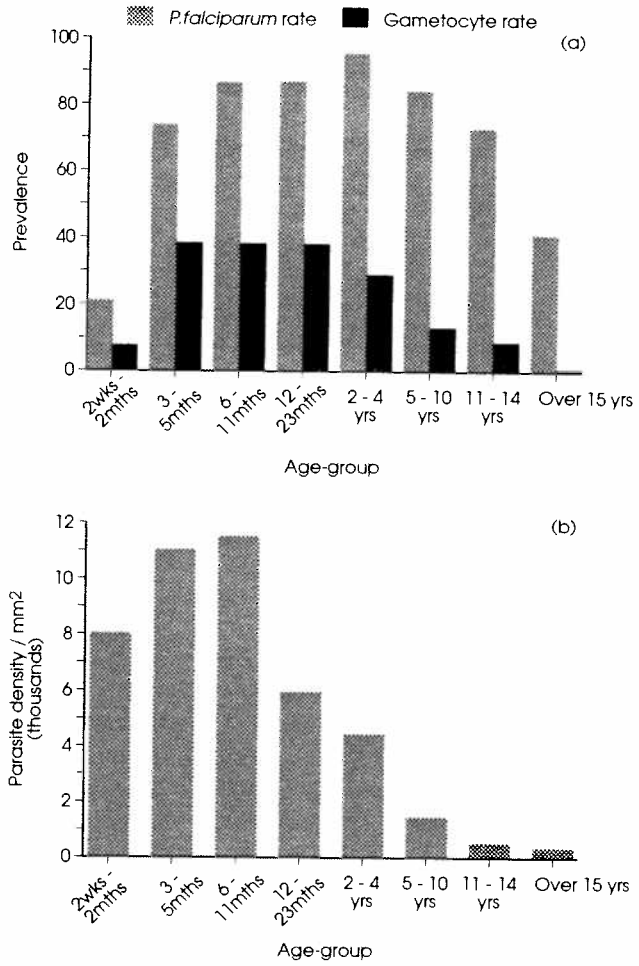


Fig. 14.4. (a) Age–prevalence profile for *P. falciparum*, showing total prevalence (sexual and asexual stages) and prevalence of people with gametocytes. (b) Age-intensity of infection pattern, as mean (arithmetic) positive *P. falciparum* density (Davidson and Draper 1953).

decline in the adult age groups from the maximum value are all positively associated with the intensity of transmission (Fig. 14.5). This association, with respect to the rate of decline in the teenage and adult age classes, is presumably a consequence of the dependence of the degree of acquired immunity on the duration and intensity of past exposure. In areas of high transmission where intensive studies have taken place, the decline in prevalence in older age classes is directly attributable to acquired immunity, because exposure to anophelene bites does not decrease with age (Carnevale *et al.* 1978) and mortality directly due to malaria is limited to the very young (Molineaux and Gramiccia 1980).

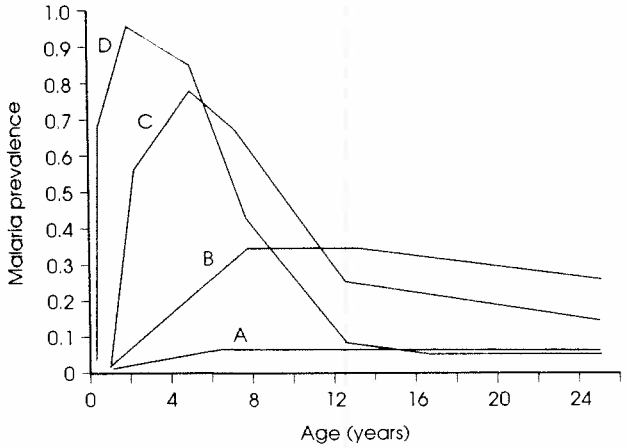


Fig. 14.5. Prevalence of acute malaria infection versus age in years, in stable indigenous populations, for differing levels of endemicity: A, low endemicity; B, moderate endemicity; C, high endemicity; D, hyperendemicity (from Boyd 1949*a*).

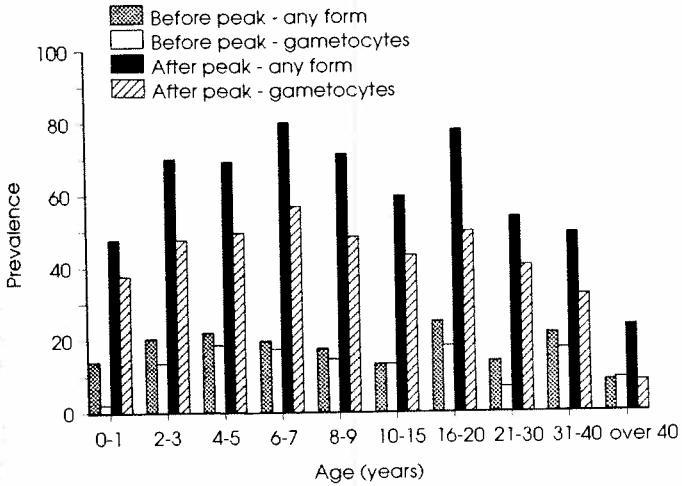


Fig. 14.6. Prevalence of gametocytes (*P. falciparum*) before and after the peak of malaria in Sundatar, Indonesia, according to age group (from Schuffner 1938).

Changes in the prevalence of people with gametocytes (infectious individuals) with respect to age (horizontal surveys) broadly reflect the patterns observed for the prevalence of infections, except that the proportions positive tend to be much lower (often by a factor 0.5 or less; see Earle (1939), Macdonald (1951)) (Fig. 14.6). Gametocytes appear an appreciable time after the first development of parasitaemia in non-immune subjects (James *et al.* 1932) and are subsequently

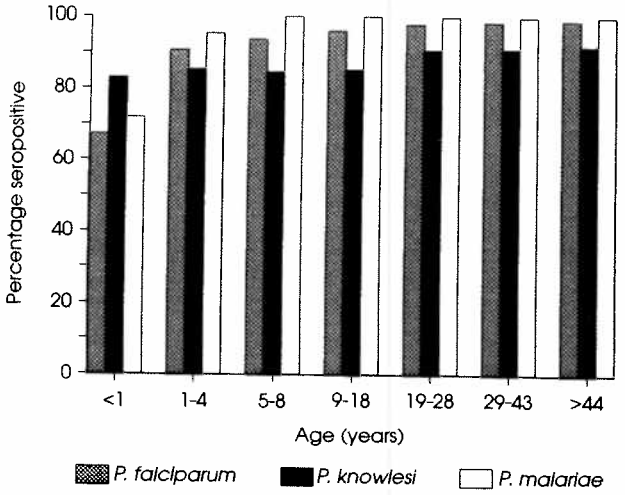


Fig. 14.7. Prevalence of antibodies to *P. falciparum*, *P. knowlesi*, and *P. malariae* according to age, determined by indirect haemagglutination antibody test (Molineaux and Gramiccia 1980).

present in the blood for a shorter time (perhaps 40 per cent of the total) than are asexual parasites.

Serological tests are available to detect the presence of antibodies specific to malarial antigens. These provide further tools for assessing the intensity of transmission within a given locality. Maternally derived antibodies are detectable in young infants; their prevalence decays rapidly with a half-life of between 3–6 months (similar to many viral infections) (Molineaux and Gramiccia 1980). Some examples of horizontal profiles of the proportion of individuals serologically positive in different age classes are recorded in Fig. 14.7. Note that the patterns of change are markedly different from those recorded for age-related changes in the prevalence of infection (compare Figs. 14.5 and 14.7). The relationship between seropositivity (with respect to particular antibodies) and mean antibody titres with past and current experience of infection is not understood at present. In general, the overall proportion seropositive within a community is positively associated with the intensity of transmission. Short-term reductions in the level of transmission (a few years) have little impact on the proportion seropositive in different age classes (Molineaux and Gramiccia 1980). However, long periods of no exposure to infection tend to result in lowered antibody titres within individuals and a reduction in the proportion seropositive within groups of people. This observation supports the notion that repeated exposure to infection is necessary to maintain a degree of acquired immunity. Longitudinal serological studies of infants in areas of endemic malaria reveal that maternally derived antibodies appear to provide little

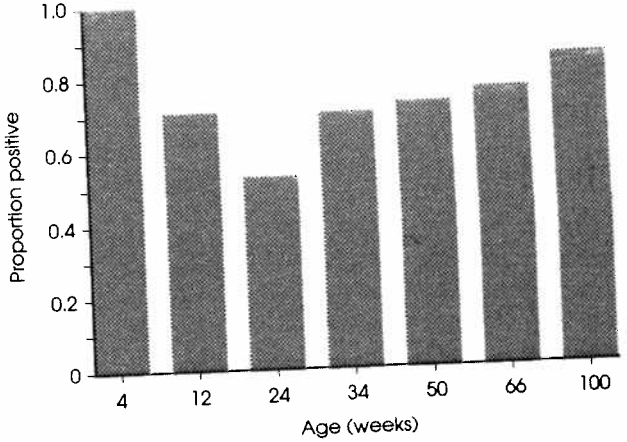


Fig. 14.8. Proportion of infants positive for malaria antibodies, by age, determined by a precipitin test (Molineaux and Gramiccia 1980).

protection against rapid infection in infancy (Fig. 14.8). Studies of the relationship between antibody titres and the prevalence of infection in different age classes have produced consistent patterns for a variety of different malarial species. In general, within areas of moderate to high transmission, the association is positive in young children and then becomes negative in older children and adults. The changeover point is often around 5 years of age. This pattern is further evidence of the significance of acquired immunity in reducing prevalence in the older age groups.

14.2.1.3 *Rates of infection and reinfection* The calculation of rates (or forces) of infection is made complicated in the case of malaria by the uncertain relationship between serology and past-plus-current experience of infection, and the build-up of acquired immunity within an exposed community. With respect to the prevalence of infection, the rate of increase over the first few years of a child's life (before immunity restricts parasite establishment) provides good data on the 'pristine' force of infection (the λ of microparasite models). Some examples of the estimation of the rate of infection in children with various species of *Plasmodium* are presented in Fig. 14.9. The data employed in these studies were collected by horizontal studies. Longitudinal observations on cohorts of children provide similar information. Provided the infection is endemic and stable within a community, estimates of the rate of infection (rate of increase in prevalence with age or time) provide a means of estimating the basic reproductive rate of the parasite. This aspect will be discussed in more detail in the section dealing with models. Horizontal or longitudinal serological surveys in young infants and children similarly provide information on the rate or force of infection. This interpretation, however, needs care due to the

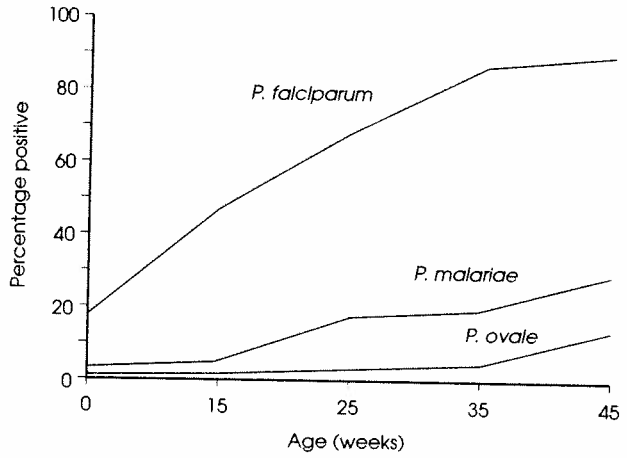


Fig. 14.9. Observed cumulative prevalence of *P. falciparum*, *P. malariae*, and *P. ovale*, by age of infants followed after birth at 10-weekly intervals (Molineaux and Gramiccia 1980).

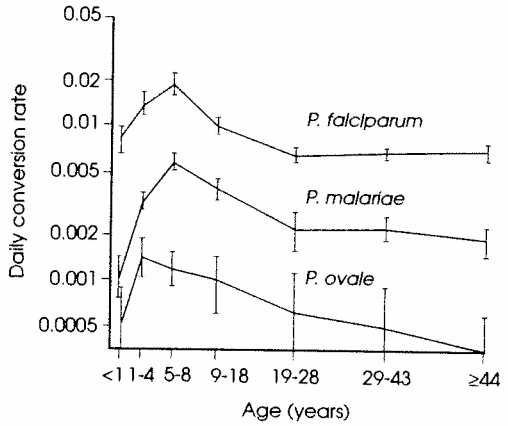


Fig. 14.10. Daily incidence rate of patent parasitaemia (i.e. conversion rate) for three species of parasite, by age (Molineaux and Gramiccia 1980).

complications introduced by maternally derived antibodies (particularly in areas of intense transmission where the percentage seropositive rises rapidly with age) (Fig. 14.8).

Longitudinal studies over a broad range of age classes enable us to assess the dependence of infection on host age. The so-called 'conversion rates' (the rate at which individuals change from parasite negative to parasite positive; see Bekessy *et al.* 1976) appear to alter with age (Fig. 14.10), although the factors involved are not clearly understood. They probably include age-related changes

in exposure to mosquito bites (although this factor is not thought to be the most important) and a relative change in the proportion of 'conversions' that are new infections versus relapses of old infections. It is thought that the rate of relapses decreases with age as acquired immunity builds up beyond the ages of 5–10 years (Molineaux and Gramiccia 1980).

Studies of rates of conversion in individual patients also help us gain an understanding of within-age-class heterogeneity in exposure or susceptibility to infection. Most interestingly, the best study of this problem—which was concerned with the transmission of *P. falciparum*, *P. malariae*, and *P. ovale* in northern Nigeria (the Garki district)—showed that within any given age class there is for any particular parasite an excess (over that predicted on the basis of random exposure to infection) of persons persistently positive and of persons persistently negative (Molineaux and Gramiccia 1980). Furthermore, an analysis of the frequency of mixed-species infections revealed an excess of multiple infections over that predicted on the basis of chance alone. In short, both observations suggest a degree of predisposition to single and mixed malarial infections in individual patients. The reasons for this are not understood at present, but they could involve explanations based on human behaviour relative to mosquito biting habits, spatial factors (e.g. where an individual's house is relative to mosquito breeding or resting sites), or immunocompetence (perhaps genetically based).

14.2.1.4 *Morbidity and mortality* Malaria, particularly falciparum malaria, is a major cause of morbidity and mortality throughout many regions of the world. Mortality is invariably greatest in young infants and children and declines dramatically amongst those who survive beyond the age of 4–5 years in areas of endemic infection (Fig. 14.11). Morbidity is normally estimated by reference to spleen measurements (Christophers 1924; Macdonald 1926). In endemic areas there is a clear association between the degree of spleen enlargement and both the presence or absence of infection and the intensity of infection (Fig. 14.12). At present insufficient data are available for case complication rates (morbidity and mortality) per case of infection in a naive person (no prior experience of infection) stratified by age across child and adult age-classes.

14.2.2 *Vector biology and malarial infection*

Over the past 50 years much research effort has been devoted to the study of the ecology and population dynamics of the *Anopheles* vectors of human malaria (see Garrett-Jones 1964; Gillies and Wilkes 1965). The quantitative character of much of this work is in part a consequence of the emphasis placed by Macdonald (1957), in his simple models of the dynamics of malaria, on the detailed entomological factors involved in transmission. Further impetus was provided by the necessity to monitor the impact of control programmes based on the widespread use of insecticides (DDT in the early days of control).

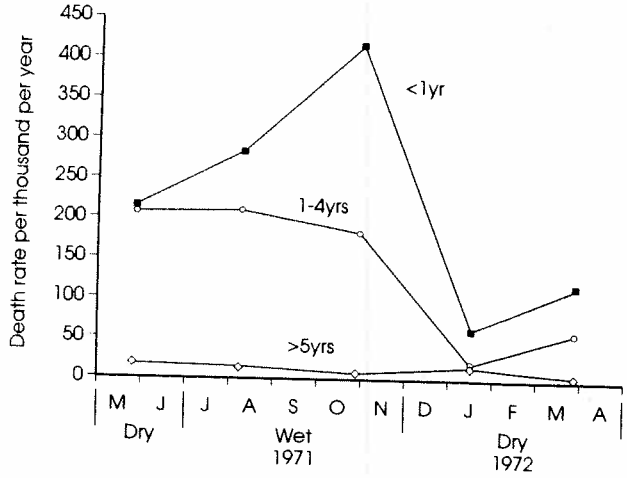


Fig. 14.11. Seasonal variation in the mortality rate, of the human host, by age (Molineaux and Gramiccia 1980).

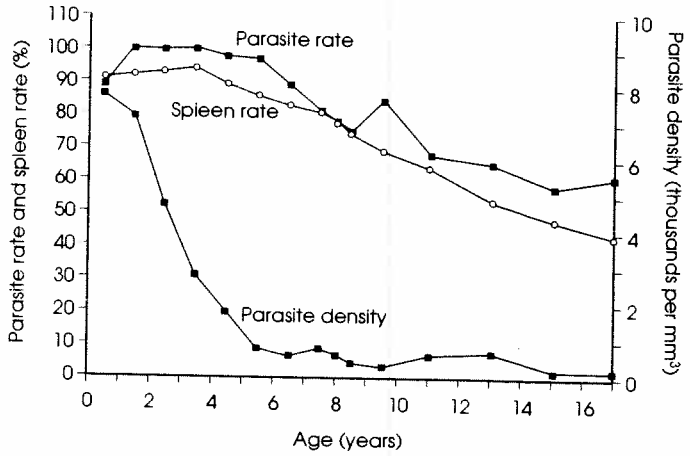


Fig. 14.12. Malaria survey in hyperendemic area of Tanzania. The parasite rate is the percentage of an age group with blood samples positive for malaria. The spleen rate is the percentage of an age group with enlarged spleens. The parasite density is the number of parasites per cubic millimetre (in thousands) in those blood samples which were positive for parasites (Christophers 1949).

Today, with the intense interest in the development of vaccines and the application of new molecular and biochemical techniques to the study of acquired immunity in humans, the research emphasis has changed from entomology to infections in humans. For completeness, however, we present in this section a brief review of the entomological data that are pertinent to an understanding of transmission. We consider this empirical information under a series of headings.

14.2.2.1 *Latent periods* The time period between infection and the beginning of infectiousness (sporozoites appearing in the salivary glands of the mosquito) varies greatly depending on extrinsic (e.g. temperature) and intrinsic (e.g. the species of mosquito) factors. A summary of the average latent periods for a range of vector transmitted infections is given in Table 14.3. In the case of *P. vivax* and *P. falciparum*, for example, the latent period depends critically on the prevailing temperature (Fig. 14.13) (Wenyon 1921; Jancso 1921; King 1929; Kligler and Mer 1937; Stratman-Thomas 1940; Knowles and Basu 1943; Siddons 1944; Boyd 1949*a*, *b*). However, over a very large range of the equatorial region of Africa temperatures show no great diurnal or seasonal fluctuations. With temperatures in the range of 25–27 °C, the latent periods for *P. falciparum* and *P. vivax* are approximately 12 days and 9 days respectively.

14.2.2.2 *Vector mortality* Arthropod vectors of microparasites have, in general, short life expectancies relative to the human host. As illustrated in Table 14.4, they range from a few days to a few months. Many factors influence survival including climatic, density-dependent, and age-related processes. For the anophelene vectors of malaria, a large number of studies have focused on the estimation

Table 14.3 Latent periods in which the vector is infected but not infectious

Parasite	Vector	Temp. (°C)	Incubation period (days)	Reference
Plasmodium falciparum	*Anopheles gambiae*	24	11	Baker (1966)
Schistosoma mansoni	*Biomphalaria glabrata*	24	35	Stirewalt (1954)
Onchocerca volvulus	*Simulium damnosum*	20	14	Blacklock (1929)
Dirofilaria immitis	*Aedes trivittatus*	22.5	16	Christensen and Hollander (1978)
Trypanosoma brucei	*Glossina morsitans*		15–35	Schmidt and Roberts (1977)
Wuchereria bancrofti	*Anopheles funestus*	20	13–15	Krafsur and Garrett-Jones (1977)
Yellow fever virus	*Aedes aegypti*		10–12	Burnet and White (1972)
SLE virus	*Culex p. pipiens*		7–19	Chamberlain *et al.* (1959)
Dengue virus	*Aedes aegypti*		7–10	Smith (1976)
Loa loa	*Chrysops dimidiatus*		10–12	Muller (1975)

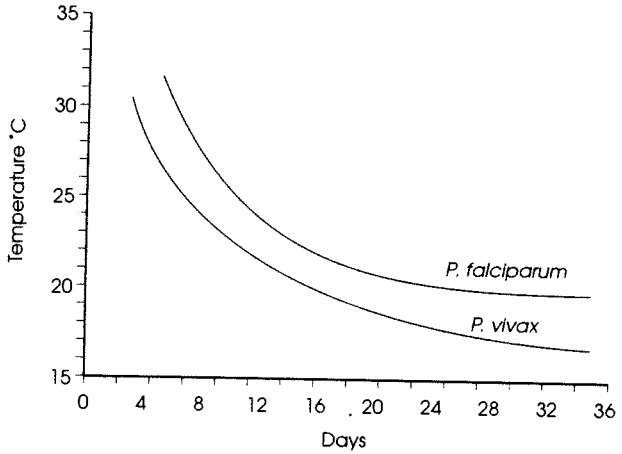


Fig. 14.13. The duration of sporogenic development (latent period) of malaria parasites in the mosquito host (*Anopheles* spp.) in relation to environmental temperature (°C) (Macdonald 1957).

Table 14.4 Expected life spans of arthropod vectors in natural environments and the laboratory

Vector	Expected life span (days)	Reference
Anopheles funestus	5.6 (field)	Krafsur and Garrett-Jones (1977)
Anopheles funestus	5.89 (field)	Gillies and Wilkes (1963)
Anopheles funestus	10.2 (field)	Garrett-Jones and Grab (1964)
Anopheles gambiae	11.26 (field)	Gillies and Wilkes (1965)
Anopheles gambiae	15.4 (field)	Garrett-Jones and Shidrawi (1969)
Anopheles gambiae	8.0 (field)	Garrett-Jones and Grab (1964)
Anopheles nili	5.8 (field)	Garrett-Jones and Grab (1964)
Anopheles coustani	8.5 (field)	Garrett-Jones and Grab (1964)
Aedes trivittatus	25 (lab.)	Christensen (1978)
Ornithonyssus bacoti	28 (lab.)	Williams and Kershaw (1961)
Glossina p. palpalis	127 (lab.)	Mulligan (1970)
Glossina morsitans	72 (lab.)	Buxton (1955)
Glossina morsitans	28–32 (field)	Jackson (1948)

of mortality rates under field and experimental conditions (for reviews see Boyd (1949*a*), Macdonald (1952), Brun (1973), and Garrett-Jones and Shidrawi (1969)). This body of data reveals that the life expectancy of mosquitoes under field conditions is often very short (a few days to a few weeks) and of not dissimilar magnitude to the latent period of infection. We might therefore expect the proportion of infectious mosquitoes to be low in natural populations. Infection, in most cases, is thought not to reduce life expectancy significantly below that of uninfected hosts.

14.2.2.3 *The prevalence and intensity of vector infection* In the context of malaria the prevalence of infection is conventionally referred to as the 'sporozoite rate' (defined as the proportion of the mosquito population with sporozoites in their salivary glands). Virtually without exception the prevalence of infection within vector populations is very low, irrespective of the type of disease agent or species of vector (Table 14.5). In general this is a direct consequence of the short life expectancies of vector species relative to the duration of infection in the human host and the latent period of infection in the vector. This point is well illustrated by a simple example. Suppose the mosquito population is of constant density with a stable age distribution and life expectancy of $1/\mu$ (where μ is the constant age-independent death rate). If the population is exposed to a constant rate of infection, λ, (independent of mosquito age) and the parasite has a latent period of τ time units, then the proportion of infectious vectors in the total population, p, is simply

$$p = \left(\frac{\lambda}{\lambda + \mu}\right) \exp(-\mu\tau). \qquad (14.1a)$$

For high infection rates, $\lambda \gg \mu$, eqn (14.1) reduces to

$$p \simeq \exp(-\mu\tau). \qquad (14.1b)$$

Table 14.5 Prevalence of infection in vector (intermediate host) populations

Vector	Parasite	Study area	Prevalence (per cent)	Reference
Anopheles gambiae	*Plasmodium falciparum*	Ethiopia	1.87	Krafsur and Garrett-Jones (1977)
Anopheles funestus	*Plasmodium falciparum*	Ethiopia	1.23	Krafsur and Garrett-Jones (1977)
Simulium damnosum	*Onchocerca volvulus*	West Africa	2.8	Holstein (1953)
Simulium damnosum	*Onchocerca volvulus*	Guatemala	5.0	Strong (1937)
Aedes trivittatus	*Dirofilaria immitis*	North America	1.0	Christensen (1978)
Biomphalaria glabrata	*Schistosoma mansoni*	St Lucia	1.3	Jordan (1977)
Bulinus nasutus productus	*Schistosoma haematobium*	Tanzania	3.1	Webbe (1962)
Oncomelania quadrasi	*Schistosoma japonicum*	Philippines	4.7	Pesigan *et al.* (1958)
Anopheles funestus	*Wuchereria bancrofti*	Tanzania	7.6	Krafsur and Garrett-Jones (1977)
Culex piplens fatigans	*Wuchereria bancrofti*	Sri Lanka	6.9	Samarawickrema and Laurence (1978)
Glossina swynnertoni	*Trypanosoma brucei*	Tanzania	0.24	Duke (1923)
Glossina pallidipes	*Trypanosoma brucei*	Uganda	0.09	Molvo *et al.* (1971)
Glossina swynnertoni	*Trypanosoma congolense* and *Trypanosoma vivax*	Tanzania	15.5	Molvo *et al.* (1971)
Glossina swynnertoni	*Trypanosoma vivax*	Tanzania	25.9	Rogers and Boreham (1973)
Glossina morsitans	*Trypanosoma vivax*	Nigeria	61.8	Riordan (1977)
Rhodnius pictipes	*Trypanosoma cruzi*	Brazil	30.0	Lainson *et al.* (1979)

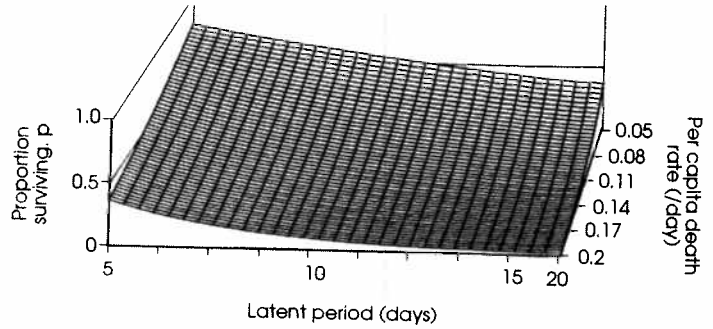


Fig. 14.14. The relationship between the proportion of infectious vectors in the total population as a function of the per capita death rate of the vector, μ, and the latent period of the parasite, τ (see eqn (14.1)).

Alternatively, eqn (14.1*b*) can be expressed as $p = q^{\tau}$ where q represents the probability of surviving one unit of time (see Macdonald 1957). If vector life expectancy, $1/\mu$, is of the same order or less than the latent period, τ, then the value of p is small (Fig. 14.14). For many vector-transmitted infections $1/\mu$ and τ are of similar magnitudes and hence we may expect the prevalence of infectious vectors to be low.

More generally, vector densities are rarely constant in size (they often exhibit marked seasonal changes in abundance) and the prevalence of infection is often related to human density, to the anthropophilic index (the proportion of blood meals taken from humans), and to the prevalence of infection in the human community. For malaria, there appears to be a positive association between the proportion of mosquitoes positive for sporozoites and the proportion of people positive for gametocytes (Fig. 14.15) (Macdonald 1952).

For protozoan parasites it is sometimes possible to score the intensity of infection and its distribution within the vector population. An example is presented in Fig. 14.16, which shows the frequency distribution of malarial oocysts in a sample of mosquitoes. This distribution is highly aggregated in form and the negative binomial probability model provides a good empirical description. The reasons for such observed heterogeneity are not fully understood at present, although genetic susceptibility to infection is undoubtedly of importance. For example, Ward (1963) in a series of laboratory selection experiments showed that the frequency distribution of oocysts of *P. gallinaceum* in anophelenes could be changed from an aggregated pattern to a random-underdispersed pattern by progressively selecting from resistant strains of the vector over many generations of laboratory inbreeding (Fig. 14.17).

14.2.2.4 *Human-biting rates* The rate at which vectors feed on humans per unit of time is of obvious importance to the transmission of vector-borne

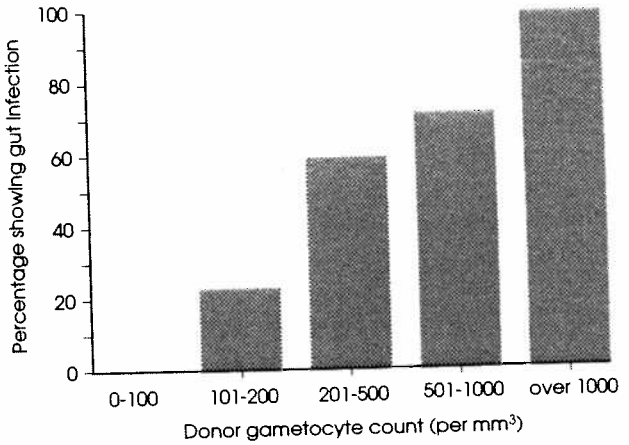


Fig. 14.15. Proportion of *Anopheles stephensi* acquiring infection, as a function of the gametocyte count of subjects infected with *P. falciparum* on which the insect hosts were fed (Knowles and Basu 1943).

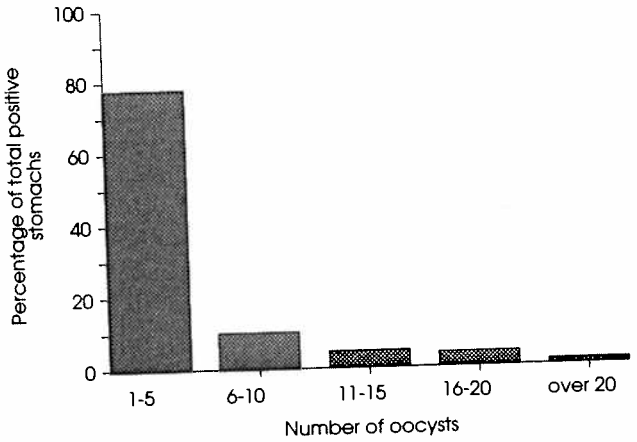


Fig. 14.16. Frequency distribution of oocysts in positive stomachs of wild-caught *Anopheles gambiae* and *Anopheles funestus* (from Muirhead-Thomson 1954).

infections. With respect to malaria this epidemiological parameter is termed the human-biting rate. Methods of data collection include the use of human volunteers to act as baits for defined units of time (the number of bites and the biting mosquitoes are recorded and collected over this interval (see WHO 1975; Molineaux and Gramiccia 1980), and the identification of blood meals (i.e. whether the meal is from humans or other mammalian species) by immunological tests (to calculate the anthropophilic rate). For the malarial vectors,

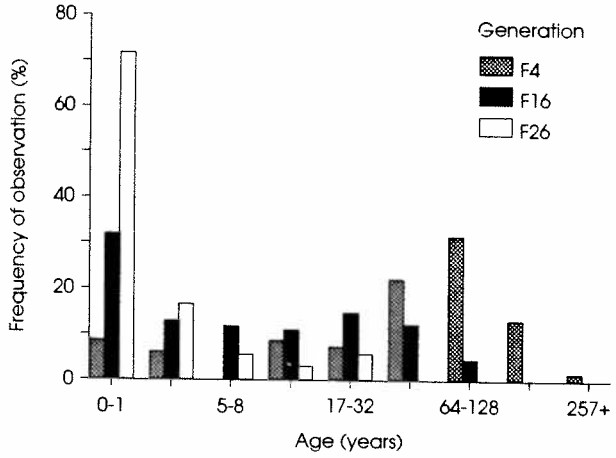


Fig. 14.17. Selection of a strain of *Aedes aegypti* resistent to infection by *Plasmodium gallinaceum*. The figure shows frequency distributions of malarial oocysts in hosts infected after varying intervals of selection. As the duration of selection progressed from generation 4 (F4) to generation 26 (F26) the distribution changed from an essentially unimodal form with a high mean oocyst count to a bimodal distribution with a low mean oocyst count (Ward 1963).

biting habits at night are usually of greatest importance in disease transmission and human-biting rates are often based on night-time sampling schedules (Molineaux and Gramiccia 1980) (Fig. 14.18). Biting habits, however, often vary on a regular diurnal and seasonal basis.

14.2.2.5 *Vector density* Standardized sampling schemes can be employed to record estimates of vector density, independent of records of human-biting activity. These may include the use of traps, visual searches of insect resting sites, or sampling for aquatic larval stages of, for example, mosquitoes. As might be expected for animal species with high intrinsic growth rates (true for the vast majority of microparasite vectors), population abundances tend to fluctuate over many orders of magnitude and are often strongly influenced by climatic factors (Fig. 14.19).

14.3 Basic model for malaria

The earliest attempt to provide a quantitative understanding of the dynamics of malaria transmission was that of Ross (1911, 1915, 1916, 1917). The focus of his original work was malaria, but he extended this to develop a rather general theory of disease transmission which he termed '*a priori* pathometry'. Essentially, the models consisted of a few differential equations to describe changes in the densities of susceptible and infected people, and—in the case of

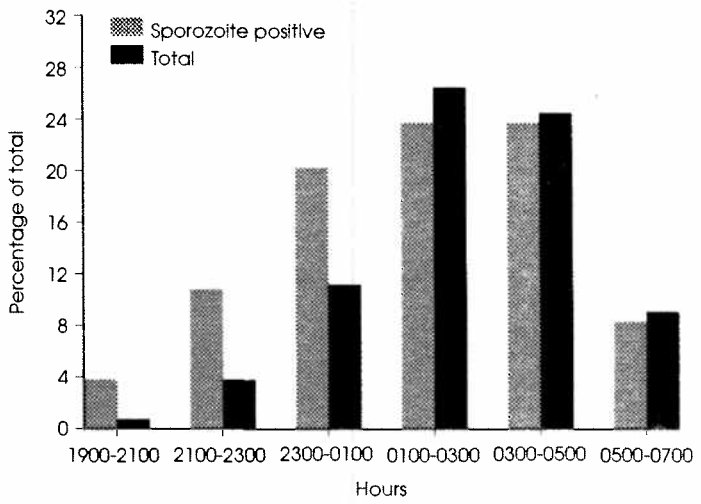


Fig. 14.18. Distribution by hour of the night of the sporozoite-positive bites, as a percentage of the total bites by *Anopheles gambiae* (from Molineaux and Gramiccia 1980).

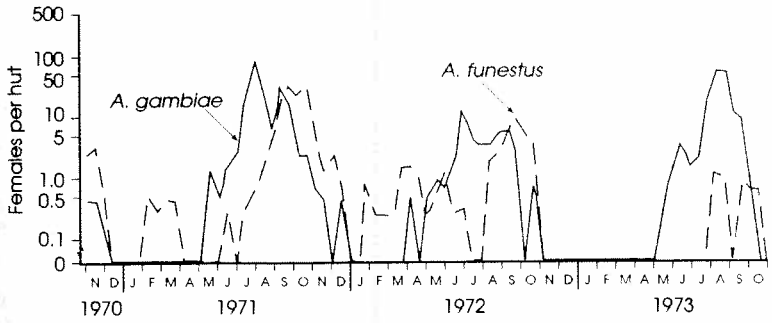


Fig. 14.19. Indoor resting densities of *Anopheles gambiae* and *Anopheles funestus*, estimated from pyrethrum spray collections in Kwaru, Northern Nigeria (Molineaux and Gramiccia 1980).

malaria—susceptible and infected mosquitoes. The analyses in Ross (1911) were extended by Lotka (1923). Then, in the early 1950s, an epidemiologist, George Macdonald, added a layer of biological realism to these early models by his careful attention to interpretation and estimation of parameters (Macdonald 1957). The value of mathematical studies to the design of malarial control programmes and the interpretation of observed epidemiological trends has been a topic of considerable controversy (Martini 1921; Moshkovskii 1950; Macdonald 1957; Bruce-Chwatt and Glanville 1973). Today, however, there is no doubt that the work of Macdonald in particular (based on Ross' early models) has

had a very beneficial impact on the collection, analysis, and interpretation of epidemiological data on malarial infection (Molineaux and Gramiccia 1980).

We start with the simplest of models (based on the work of Ross (1911) and Macdonald (1957)) incorporating the major features of transmission. We then progressively introduce additional factors and complications to facilitate the interpretation of observed trends (see Aron and May 1982).

The basic model, which captures the essentials of vector transmission, consists of two equations describing changes in the proportion of infected (=infectious) humans, y, and the proportion of infected (=infectious) mosquitoes, $\hat{y}$.

$$dy/dt = (ab\hat{N}/N)\hat{y}(1 - y) - \gamma y, \tag{14.2}$$

$$d\hat{y}/dt = acy(1 - \hat{y}) - \mu\hat{y}. \tag{14.3}$$

Here N is the size of the human population, $\hat{N}$ is the size of the female mosquito population (the ratio $m = \hat{N}/N$ defines the number of female mosquitoes per human host), a is the rate of biting on humans by a single mosquito ('the human-biting rate' defined as the number of bites per unit of time), b is the proportion of infectious bites on humans that produces a patent infection, γ is the per capita rate of human recovery from infection ($1/\gamma$ is the average duration of infection) c is the proportion of bites by susceptible mosquitoes on infected people that produce a patent infection, and μ is the per capita rate of mosquito mortality ($1/\mu$ is mosquito life expectancy).

In this simple model, the total population of both humans and mosquitoes is assumed to be constant, so that the dynamical variables are the proportion infected in each population (y and $\hat{y}$). The first equation (14.2) describes changes in the proportion of infected humans. New infections are acquired at a rate that depends on the number of mosquito bites per person per unit time, $a\hat{N}/N$, on the probabilities that the biting mosquito is infected, $\hat{y}$, and that a bitten human is uninfected, $1 - y$, and on the chance that an uninfected person thus bitten will actually develop a patent infection. The ratio $\hat{N}/N$ arises as a direct consequence of the fact that female mosquitoes only take a fixed number of blood meals per unit of time. Thus the net rate of transmission is held to an upper limit, irrespective of the absolute densities of mosquitoes and people, by the biting rate times the number of female mosquitoes per person. This term embodies the actual difference between vector and direct transmission (see Anderson and May 1979*b*; Anderson 1981*a*). Infections are lost by infected people returning to the uninfected class at a net recovery rate γy. In this simple model it is assumed that recovered individuals have no immunity to reinfection (this assumption will be altered in a later section). Human recovery is assumed to occur at a much faster rate than human mortality (see Table 14.2) such that the rate of mortality is of negligible importance in the loss of infected people (here again this assumption is relaxed at a later stage).

The second equation, eqn (14.3), describes changes in the proportion of mosquitoes infected. The gain term depends on the number of bites per mosquito per unit of time a, on the probabilities that the biting mosquito is uninfected, $1 - \hat{y}$, and that the bitten human is infected, y, and on the chance that an uninfected mosquito acquires infection from biting an infectious person, c. The loss term arises from the death of infected mosquitoes, $\mu\hat{y}$ (mosquitoes do not appear to recover from malarial infection).

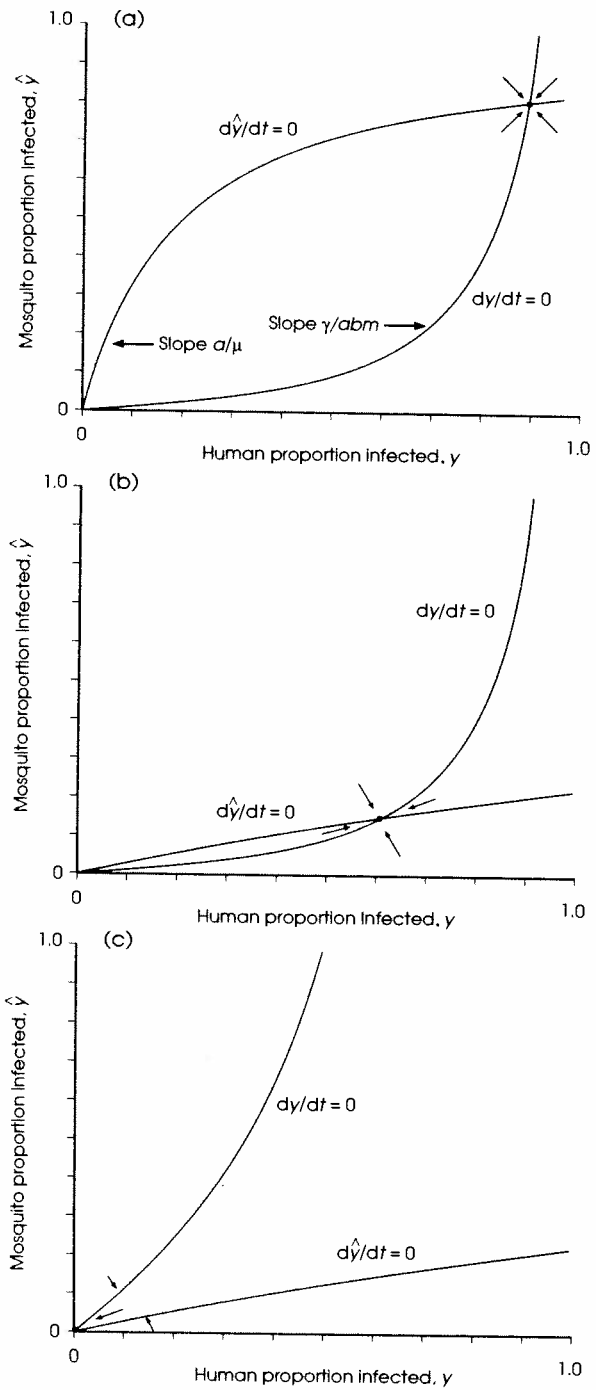
This model is, of course, highly simplified and its presentation is solely to illustrate the properties arising from vector transmissions. The major omissions, which are discussed in later sections, include the tendency of people to acquire immunity, the absence of parasite-induced mortality in humans and mosquitoes, and the absence of a class of infected but not yet infectious hosts in both the human and mosquito population (i.e. the inclusion of a latent period).

The basic reproductive rate in this simple vector transmission model is defined as follows

$$R_0 = ma^2bc/\mu\gamma. \tag{14.4}$$

(Note that in the literature on malaria R_0 is conventionally called z_0). An heuristic derivation is as follows. Take a single primary case with a recovery rate of γ; the average time spent in an infectious state is $1/\gamma$. During this time, the average number of mosquito bites received from m susceptible mosquitoes each with a biting rate a is am/γ; of these bites a proportion c are actually infectious, which gives a total of amc/γ mosquitoes infected by the primary human case. Each of these mosquitoes survives for an average time $1/\mu$ and makes a total of ab/μ infectious bites. The total number of secondary cases is thus $(ab/\mu)(amc/\gamma)$. Note that a enters twice in the numerator of eqn (14.4) since the mosquito biting rate controls transmission from humans to mosquitoes *and* mosquitoes to humans.

Equation (14.4) is usually derived algebraically by analysis of the stability properties of the differential equations (14.2) and (14.3) (Lotka 1923; Macdonald 1957; Dietz 1975; Anderson and May 1979*b*). A more transparent and more generalizable derivation can, however, be obtained by a geometrical 'phase-plane' analysis of the dynamical behaviour of the model (Aron and May 1982). Here, as illustrated in Fig. 14.20, the horizontal axis corresponds to the dynamical variable y, the proportion of people infected, and the vertical axis to the dynamical variable $\hat{y}$, the proportion of infected mosquitoes. In this figure, the variable $\hat{y}$ is unchanging along the isocline labelled by $d\hat{y}/dt = 0$; for a given value of y, $\hat{y}$ is increasing below this isocline and decreasing above it. Similarly, the variable y is unchanging along the isocline labelled $dy/dt = 0$; for given $\hat{y}$, y increases to the left of the isocline and decreases to the right of it. In the four domains of the y–$\hat{y}$ plane thus defined by the isoclines in Fig. 14.20(a), the dynamical trajectories of this system will move in the general direction indicated by the arrows. The intersection of the two isoclines represents the equilibrium state, to which all trajectories will tend in Fig. 14.20(a). The basic topological requirement for the two isoclines to intersect at positive values of y and $\hat{y}$ is that the initial slope of the $\hat{y}$ isocline (namely, ac/μ) exceed that of the y isocline



(namely, γ/abm). This gives eqn (14.4). Explicitly, the equilibrium proportion of infected humans (the prevalence of infection) is

$$y^* = (R_0 - 1)/[R_0 + (ac/\mu)]. \tag{14.5}$$

The corresponding equilibrium prevalence for mosquitoes is

$$\hat{y}^* = \left(\frac{R_0 - 1}{R_0}\right)\left(\frac{ac/\mu}{1 + ac/\mu}\right). \tag{14.6}$$

The initial slope of the $\hat{y}$ isocline, ac/μ, represents the average number of bites on human hosts made by a mosquito in its lifetime, that lead to mosquito infection. If this number is relatively large, the $\hat{y}$ isocline will rise steeply and the equilibrium point is likely to lie toward the top right-hand corner of the y–$\hat{y}$ plane in a relatively 'deep valley' in this dynamical landscape (Fig. 14.20(a)). In these circumstances small changes in mosquito density, m, or the biting rate, a, will have little effect on the equilibrium prevalence of infection in humans. This corresponds to what is called 'stable endemic malaria'. However, if ac/μ is relatively small, the $\hat{y}$ isocline will have the shallow form depicted in Fig. 14.20(b), and the equilibrium point is likely to lie in a 'shallow elongated canyon' (Aron and May 1982). In this case, small changes in mosquito density or the biting rate are more likely to result in substantial changes in the proportion of humans infected. This is the essence of Macdonald's (1957) conclusion that ac/μ is an index of stability; in areas where mosquito vectors bite humans relatively often and have relatively long life spans, this index is high and malaria tends to be endemic (Macdonald's 'stable malaria'); conversely, where mosquitoes bite on humans less often and have shorter life spans, the index is low and malaria tends to be subject to epidemic outbreaks (Macdonald's 'unstable malaria').

If the initial slope of the $\hat{y}$ isocline is less than that of the y isocline, we necessarily have $R_0 < 1$ and the infection cannot persist, being below the transmission threshold $R_0 = 1$ (Fig. 14.20(c)).

Fig. 14.20. The 'phase-plane' of the dynamical variables, y (proportion of humans infected), and $\hat{y}$ (proportion of mosquitoes infected); each point in the plane corresponds to a particular pair of values $y, \hat{y}$. The variable $\hat{y}$ is unchanging along the isocline $d\hat{y}/dt = 0$. The intersection of the two isoclines, if it exists, represents the equilibrium point of the system, and elsewhere trajectories move in the directions indicated by the arrows. In (a) the initial slope a/μ of the $\hat{y}$ isocline significantly exceeds the initial slope γ/abm of the y isocline, and the equilibrium point rests in a relatively deep valley, corresponding to Macdonald's 'stable' malaria. In (b), the initial slope a/μ is relatively small, but still exceeds γ/abm, and the equilibrium point exists, but now in a relatively shallow canyon, corresponding to Macdonald's 'unstable' malaria. In (c), the initial slope a/μ is less than γ/abm, so that the isoclines do not cross; all trajectories are directed towards the origin and the disease cannot maintain itself. (The figure follows Macdonald in putting $c = 1$.)

Table 14.6 Macdonald's stability index (ac/μ) for several regions where malaria is indigenous

Anopheles spp.	Location/time period	Stability index	Reference
A. punctulatus	Maprik, New Guinea (1957–8)	2.9	Peters and Standfast (1960)
A. balabacensis	Khmer (1960)	4.9	Slooff and Verdrager (1972)
A. minimus	Bangladesh (1966–7)	4.4	Khan and Talibi (1972)
A. gambiae	Kankiya, Nigeria (1967)	3.4	Garrett-Jones and Shidrawi (1969)
A. gambiae	Garki, Nigeria (1972)	3.9	Molineaux *et al.* (1979)
A. gambiae	Khashm, El Girba, Sudan (1967)	0.47	Zahar (1974)

Table 14.6 summarizes information about Macdonald's 'stability index', ac/μ, for several regions in which malaria is indigenous. The available data are rarely precise enough to permit a good estimate of both μ and a, so that the values of a/μ presented in Table 14.6 are very rough approximations (see Aron and May 1982). Often μ is inferred from age-structured data, which is permissible only if dealing with a vector population with a stable age distribution. In general, Aron and May (1982) found that sufficient information for even a rough estimate of ac/μ was available only for regions where malaria was, in Macdonald's classification, 'stable'. It is therefore not surprising that all ac/μ values in Table 14.6 are relatively large, corresponding to 'stable malaria'.

The table specifically excludes data from regions where intervention with insecticides (DDT) has occurred, because there are now additional complications in the interpretation of mosquito life-history parameters. One such complication arises from inhomogeneities in the effects of insecticides, which are usually applied to the interior surfaces of houses and are more effective against mosquitoes that rest indoors after taking a blood meal. If insecticides do not affect all mosquitoes equally, measurements of the biting rate and longevity may be severely distorted (Molineaux *et al.* 1979). For example, suppose after spraying there are two mosquito populations of roughly equal size: those that rest outdoors and are consequently unaffected by the spraying and those that rest indoors and suffer high mortality. For illustration $a_1 = 0.25$ bites per day and $\mu_1 = 0.05$ per day for the exophilic mosquitoes, and $a_2 = 0.5$ and $\mu_2 = 0.5$ for the endophilic ones. The correct way to calculate the index, a/μ, is to take the appropriate arithmetical average of the separate indices: $\frac{1}{2}(a_1/\mu_1 + a_2/\mu_2) = 3.0$. But if the endophilic and exophilic categories are not properly distinguished, then a/μ is likely to be estimated using average values of a and μ: $[\frac{1}{2}(a_1 + a_2)]/[\frac{1}{2}(\mu_1 + \mu_2)] = 1.4$. Molineaux *et al.* (1979) have analysed the consequences of this aggregation phenomenon in considerable detail. They emphasize that aggregating the groups will always underestimate the vectorial capacity of the mosquito population and hence the basic reproductive rate R_0. An excellent review of the methodology involved in the interpretation of epidemiologically relevant aspects of mosquito vector populations is by Garrett-Jones and Shidrawi (1969).

Although the basic model gives a good overview of the dynamics of malarial infection, particularly the basic factors that underlie 'stable' and 'unstable' malaria, many of its predictions are strikingly different from reality. In particular, it is clear from Fig. 14.20 that highly endemic areas ($y \to 1.0$, ac/μ relatively large) will show a high proportion of mosquitoes infected. It follows from eqn (14.6) that $\hat{y} \simeq 1$ when R_0 and ac/μ are significantly greater than zero. However, as shown in Table 14.5, the sporozoite rate in mosquitoes (the prevalence of sporozoite infection) is typically a few per cent even in areas of high prevalence within the human community.

14.4 Beyond the basic model for malaria

14.4.1 *Latent periods*

An obvious modification to the basic model is the incorporation of latent periods during which infected hosts are infected but not yet infectious (see Tables 14.2 and 14.3). We denote these periods as τ_1 and τ_2 in the human and mosquito hosts respectively. Further, we represent mortality in the human population as occurring at a rate μ_1, and that in the mosquito population as occurring at a rate μ_2 (i.e. the μ in eqns (14.3)–(14.6) is replaced by μ_2). The proportion of infected but not yet infectious hosts are defined as $h(t)$ and $\hat{h}(t)$ for man and mosquitoes respectively. The variables $y(t)$ and $\hat{y}(t)$ now denote infectious hosts. The model is of the form

$$dh(t)/dt = abm\hat{y}(t)(1 - y(t)) - \mu_1 h(t) - abm\hat{y}(t - \tau_1)(1 - y(t - \tau_1)), \quad (14.7)$$

$$dy(t)/dt = abm\hat{y}(t - \tau_1)(1 - y(1 - \tau_1)) - \mu_1 y(t) - \gamma y(t), \quad (14.8)$$

$$d\hat{h}(t)/dt = acy(t)(1 - \hat{y}(t)) - \mu_2 \hat{h}(t) - acy(t - \tau_2)(1 - \hat{y}(t - \tau_2)), \quad (14.9)$$

$$d\hat{y}(t)/dt = acy(t - \tau_2)(1 - \hat{y}(t - \tau_2)) - \mu_2 \hat{y}(t). \quad (14.10)$$

It is here assumed that latent and infectious hosts have identical mortality rates.

The equilibrium solution is found by putting $dy/dt = d\hat{y}/dt = dh/dt = d\hat{h}/dt = 0$, and solving the ensuing set of algebraic equations. The basic reproductive rate of malarial infection is now

$$R_0 = \left(\frac{ma^2cb}{\gamma\mu_2}\right)\exp(-\mu_1\tau_1 - \mu_2\tau_2). \quad (14.11)$$

Here b is now the proportion of bites by sporozoite-bearing mosquitoes that result in infection and c is the proportion of bites by susceptible mosquitoes on gametocyte-bearing people that result in mosquito infection. The introduction

of latent periods diminishes the value of R_0 compared with that derived from the basic model (eqn (14.4)) by a factor $\exp[-(\mu_1\tau_1 + \mu_2\tau_2)]$. The importance is therefore very much dependent on the magnitudes of the death rates μ_1 and μ_2 and the latent periods τ_1 and τ_2. In humans the death rate is normally very small on a scale relevant to the latent periods (i.e. $1/\mu_1 \simeq 40$–50 years, $\tau_1 \simeq 0.5$–1 year) such that the term $\exp(-\mu_1\tau_1)$ is essentially unity. This is not the case, however, for the mosquito population. Vector life expectancy ($1/\mu_2$) is often shorter than the latent period (τ_2) such that the factor $\exp(-\mu_2\tau_2)$ is significantly less than unity in value (see Table 14.3). Under the assumption that $\mu_1 \to 0$, the equilibrium prevalence of sporozoite-infected mosquitoes becomes

$$\hat{y}^* = \left(\frac{R_0 - 1}{R_0}\right)\left(\frac{ac/\mu_2}{1 + ac/\mu_2}\right)\exp(-\mu_2\tau_2) \qquad (14.12)$$

where R_0 is as defined in eqn (14.11) with $\mu_1 = 0$. In other words the prevalence of infection in humans, y^*, can approach unity but the prevalence of sporozoite-infected mosquitoes, $\hat{y}^*$, cannot exceed $\exp(-\mu_2\tau_2)$. Mosquito prevalence can be a few per cent even when R_0 and ac/μ_2 are significantly greater than unity.

This relatively simple refinement, which goes a long way to making the model more realistic, has been discussed by Macdonald (1957). Macdonald drew from eqn (14.11) the important qualitative conclusion that killing adult mosquitoes is more effective than killing larvae. The larval survivorship enters into R_0 (eqn (14.11)) linearly, via the absolute mosquito density $\hat{N}/N$. In contrast, the adult mosquito survivorship enters in a highly non-linear way via the factor $\exp(-\mu_2\tau_2)/\mu_2^2$ (allowing for the latent period and effects on absolute density) (Aron and May 1982). Reduction of larval recruitment by a factor of two would only halve the basic reproductive rate R_0, but a doubling of the adult mortality rate (doubling μ_2) would produce an exponentially severe decrease in R_0. The change in emphasis in control measures directed against the mosquito vectors of malaria, largely as a consequence of Macdonald's insights, is described by Harrison (1978).

14.4.2 *Variable mosquito density*

Macdonald (1957) used the simple model to make broad geographical comparisons between the 'stable' malaria of Africa and the unstable malaria of parts of India. On a smaller scale, the basic model suggests that areas of high transmission will be less sensitive to fluctuation in mosquito population density than areas of low transmission, with respect to observed changes in prevalence within human communities. In Sri Lanka, before control by DDT, there was considerable local variation in the endemicity of malaria. Figures 14.21(a) and 14.21(b) are hospital records of monthly malaria cases, over several years, from two different localities. Although Fig. 14.21(a), for the region of greater transmission, shows variability and marked decline following control measures

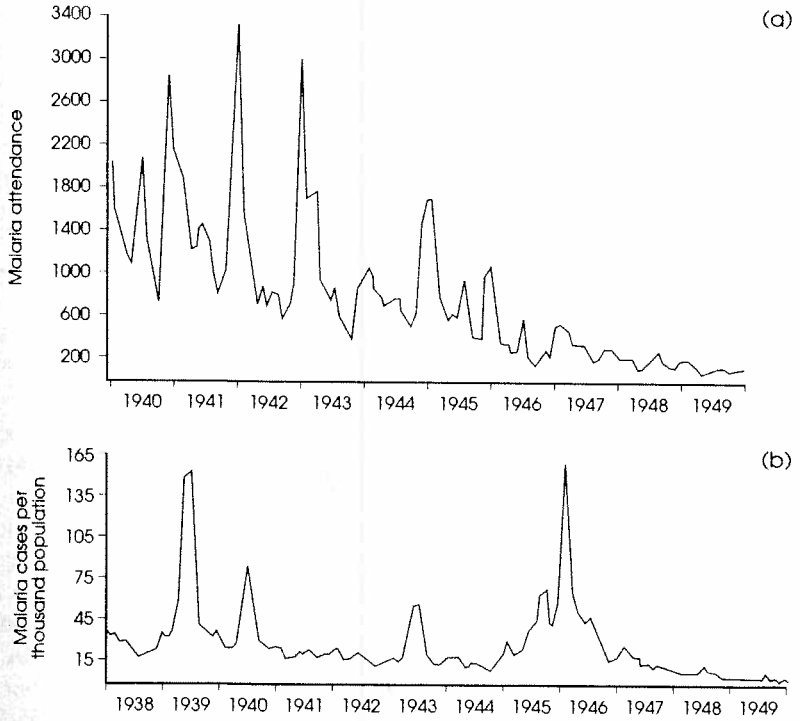


Fig. 14.21. (a) Monthly malaria attendance at the civil hospital in Anurodhapura in the endemic zone of Sri Lanka (Rayendran and Jayewickreme 1951*b*). (b) Monthly malaria attendance per 1000 population in the upper catchments of the Deduru Oya and Matia Oya basins in the epidemic zone of Sri Lanka (Rayendran and Jayewickreme 1951*a*).

after World War II, it nevertheless has a steady seasonal pattern from year to year. The region of lesser transmission, illustrated in Fig. 14.21(b), is prone to severe outbreaks which subside (Rayendran and Jayewickreme 1951*a*, *b*).

The basic model of eqns (14.2) and (14.3) demonstrates this pattern nicely if the total mosquito population, $\hat{N}$, varies seasonally with an amplitude that fluctuates randomly from year to year (Aron and May 1982). Figure 14.22 shows the dynamical behaviour of such a system when the transmission rate is very high (average value of $R_0 \gg 1$) and when the transmission rate is just above the threshold (R_0 slightly above unity in value). In both cases, the systems are subject to the same kind of (multiplicatively random) fluctuations, but the latter is much more affected than the former. Areas of low transmission are also more sensitive to sudden non-seasonal drops in the mosquito density, as happened when the plain of Philippi in Macedonia had a big drop in malaria following a dry year, while the neighbouring plain of Chrysopulis (where malaria transmission was more endemic) was scarcely affected (Boyd 1949*b*).

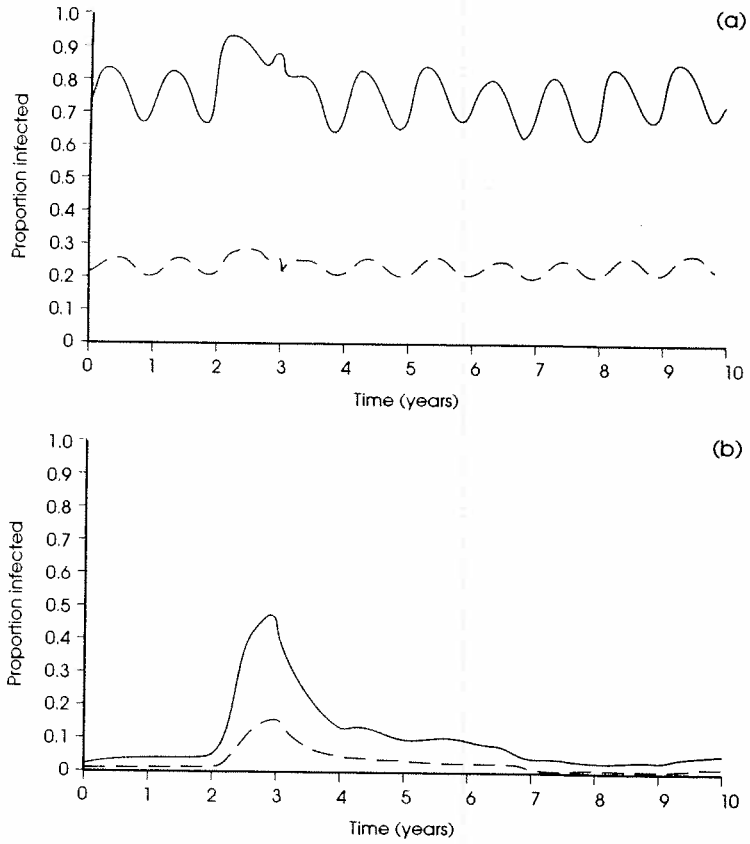


Fig. 14.22. (a) Proportion of infected humans (full curve) and mosquitoes (broken curve) versus time from simulation of basic model with a large reproductive rate R_0 and variable mosquito density $M(t)$. Explicitly, $M(t) = A[B + \varepsilon \sin(2\pi t)]$ where t is measured in years. Here, $B = 50$, $\varepsilon = 20$, and A is a random sequence which fluctuates around unity during the first half of the year (upper half of sine wave), but is otherwise equal to unity. The parameters used in the simulation are $a = 20\ \text{yr}^{-1}$, $\mu = 50\ \text{yr}^{-1}$, $\gamma = 4\ \text{yr}^{-1}$, $N = 20$, $b = 1$. When $M = B$, $R_0 = 5$. (b) Same as for (a) but with small reproductive rate R_0. Here, $B = 10.5$ and $\varepsilon = 1$, and A, a, μ, γ, N, and b are the same as for (a). When $M = B$, $R_0 = 1.05$. (From Aron and May 1982.).

Regular changes in mosquito population abundance caused by seasonality also helps explain other patterns in the overall dynamics of malaria. It is obvious that a rise in the mosquito population can lead to a malaria epidemic among the human population, but less obvious when the maximum prevalence in mosquitoes should occur relative to that in humans. Peters and Standfast (1960) note an inverse relationship, over the year, between mosquito abundance and the sporozoite rate (prevalence in mosquitoes). More detailed studies show that the peak of mosquito density occurs either before (Boyd 1949*b*) or during (Christophers 1949) the peak of human malaria cases, but that the maximum prevalence among mosquitoes follows both the peak in prevalence within humans and the peak of mosquito abundance.

There has been some confusion in the epidemiological literature concerning the mechanisms that underly these observations (see Boyd 1949*b*; Peters and Standfast 1960). Our view of the sequences of events is that, at first, mosquito density rises due to the seasonal increase in the number of emerging adults. As the total density rises, the density of infected mosquitoes also rises, followed by a peak in human cases. The rise in prevalence among mosquitoes occurs after the peak in human cases, not just from latent period delays, but because by then fewer mosquitoes are emerging into the population to swell the ranks of the uninfected vectors, thus causing the proportion infected to increase.

Exactly these patterns can be produced by the basic model of eqns (14.2) and (14.3). For the dynamics of the mosquito population, $\hat{N}$, we write

$$d\hat{N}/dt = E(t) - \mu_2 \hat{N}. \tag{14.13}$$

Here μ_2 is as defined earlier, and $E(t)$ is the rate of emergence. We take $E(t)$ to vary sinusoidally over the year; the mosquito density will then also be sinusoidal, with a lag of about the mean lifetime of a mosquito (Aron and May 1982). Note that it is assumed that the variation in mosquito density arises from the periodicity in the rate of adult emergence; the mortality rate may also vary but we believe seasonality in emergence is of greater importance. Equation (14.2) for the proportion of humans infected is as before. Equation (14.3), for the proportion of mosquitoes infected, was originally derived under the assumption that the total number of mosquitoes was constant. Under our new assumptions it becomes

$$d\hat{y}/dt = acy(1 - \hat{y}) - [\mu_2 + (d\hat{N}/dt)/\hat{N}]\hat{y}. \tag{14.14}$$

The steady annual cycles to which the solutions of this system of eqns (14.2), (14.13), and (14.14) tend are illustrated in Fig. 14.23. Figure 14.23(a) shows first the peak for the mosquito density, $\hat{N}(t)$, then the peak for the total number of infected mosquitoes, $\hat{y}(t)\hat{N}(t)$, and finally (as the total population is declining) the peak for the proportion infected, $\hat{y}(t)$. Figures 14.23(b), (c), and (d) show that the peak for human prevalence, $y(t)$, follows the maximum both for total density, $\hat{N}(t)$, and for the number of infected mosquitoes, $\hat{y}(t)\hat{N}(t)$, but precedes the maximum for the mosquito prevalence, $\hat{y}(t)$. This basic model does not incorporate latent periods, the inclusion of which would accentuate the lags. Latency is clearly important in determining the exact timing of the peaks (Dietz *et al.* 1974), but the relative timing during the transmission season is simply a consequence of the seasonal growth dynamics of the mosquito population.

In summary, the basic model can—with a few refinements—account for the main patterns exhibited within the mosquito population. We now turn to the more important problems presented by infection within the human community,

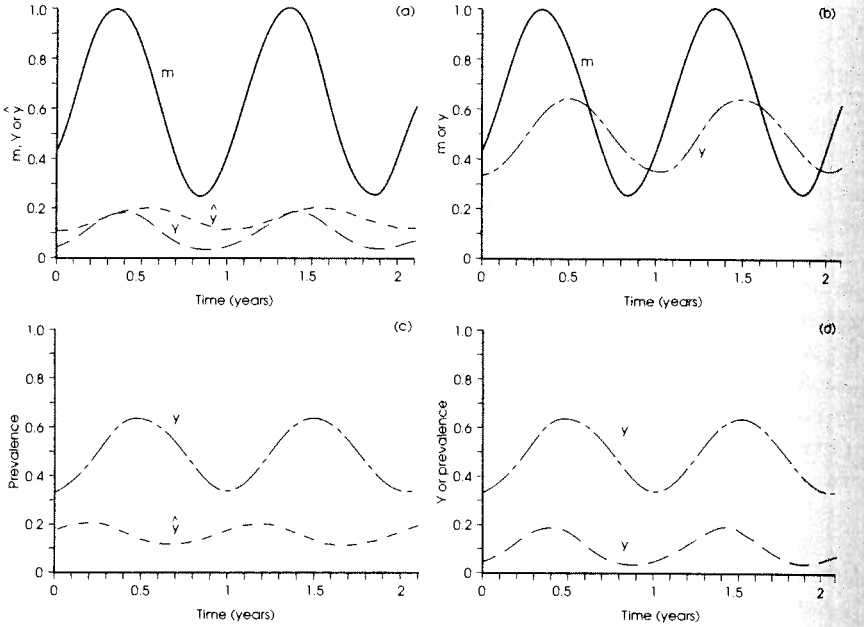


Fig. 14.23. (a) The absolute number of mosquitoes per host, m ($m = \hat{N}/N$), number of infected mosquitoes, Y ($Y = \hat{y}\hat{N}$), and the proportion of mosquitoes infected, $\hat{y}$, are shown as functions of time. These curves are obtained from the basic dynamical model defined by eqns (14.2), (14.13), and (14.14). The rate of emergence is taken to vary sinusoidally, with a 1-year period. The parameters used in these simulations are $a = 20\ \text{yr}^{-1}$, $\mu_2 = 50\ \text{yr}^{-1}$, $\gamma = 4\ \text{yr}^{-1}$, $b = 1$, $N = 20$, and $m(t) = 25 + [15 \sin(2\pi t)]$ (so that $m_{\max} = 40$). The total number, m, and the total number of infected mosquitoes Y are plotted as proportions of $m_{\max}$; the prevalence $\hat{y}$ is by definition a fraction $0 < \hat{y} < 1$, and the time is plotted in years (from Aron and May 1982). (b) The total mosquito population, m, and the proportion of humans infected, y, are plotted as functions of time, with units as for (a). (c) The prevalence of malaria among mosquitoes, $\hat{y}$, and humans, y, as function of time, with units as for (a). (d) The absolute number of infected mosquitoes, Y, and the human prevalence of malaria, y, are shown as functions of time, with units as for (a).

to investigate how various details about the biology of the infection between the malarial parasites and humans can be incorporated.

14.4.3 *Multiple infections in humans*

We have so far assumed that an infected person is not subject to further infection. There is evidence to suggest that this is not the case and that at any one time a given individual may harbour more than one infective inoculation of parasites via multiple infectious bites (Cohen 1973*a*; Molineaux and Gramiccia 1980). This problem is often referred to as superinfection, and it has been considered by a variety of researchers (Macdonald 1957; Bailey 1975; Fine 1975; Aron and May 1982). Superinfection may arise as a consequence of concurrent infections with different species of malaria, or from different genetic strains, or from different inocula of the same strain.

There are several models for superinfection, forming a continuum of descriptions for the effect of a subsequent infection when one is present already. One extreme is the original Ross model, already discussed, in which secondary infections are lost (i.e. superinfection is ignored). The other extreme is Macdonald's (1950, 1957) model, in which successive infections are effectively 'stacked', waiting to express themselves when the previous infection is over. An intermediate version is the model introduced by Dietz (described in Bailey 1975, pp. 317–22) in which infections arrive and run their course totally independently of each other. (Macdonald's version was intended to correspond to the situation described by Dietz, but there was a mathematical misunderstanding; see Fine (1975).)

These various assumptions may be compactly written by replacing eqn (14.2) with the more general form

$$dy/dt = \lambda(1 - y) - py. \tag{14.15}$$

Here λ is the force of infection (the parameter referred to as h or 'happenings' in the paper of Ross (1911)), and is defined, in the notation of the basic model (eqns (14.2) and (14.3)), as

$$\lambda = (ab\hat{N}/N)\hat{y}. \tag{14.16}$$

The quantity p is the rate of recovery to the uninfected state, and is defined variously as

$$\text{Ross:} \quad p = \gamma, \tag{14.17}$$

$$\text{Dietz:} \quad p = \lambda/[\exp(\lambda/\gamma) - 1], \tag{14.18}$$

$$\text{Macdonald:} \quad p = \gamma - \lambda \quad (\gamma > \lambda), \qquad p = 0 \quad (\gamma < \lambda). \tag{14.19}$$

As before γ is the rate of recovery from a single infection.

Contrary to what is sometimes implied in Macdonald's work, the different assumptions about the nature of superinfection make for quantitative, rather than qualitative, differences in the overall dynamic behaviour. This is clearly seen by returning to the phase-plane analysis of Fig. 14.20, and replacing the y isocline (along which $dy/dt = 0$) of the original Ross model by the corresponding y isocline generated by the Dietz and Macdonald formulae (eqns (14.18) and (14.19) respectively). This is done in Fig. 14.24. There is no difference between the models at low prevalence levels, so that the basic reproductive rate, R_0, is the same for all three, and all have the same criterion for the maintenance of infection (i.e. there are no differences at low transmission intensities, where superinfection is rare). On the other hand, the equilibrium values of the

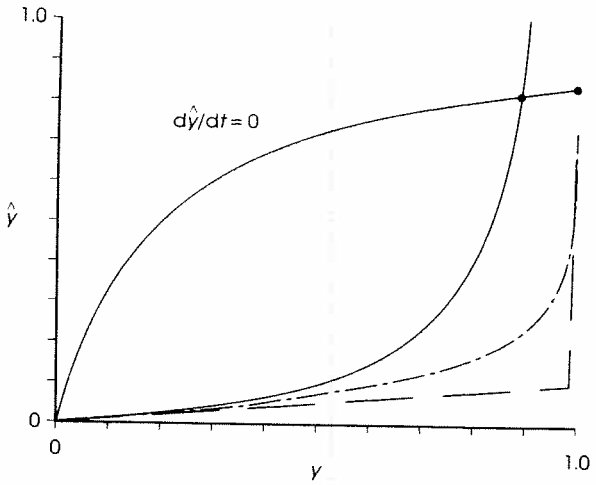


Fig. 14.24. The phase-plane of the dynamical variables y and $\hat{y}$ is shown as in Fig. 14.20. The $\hat{y}$ isocline, along which the proportion of mosquitoes infected is unchanging, is as before. The y isocline, along which the proportion of humans infected is unchanging, is calculated under various assumptions about the nature of superinfection: the full curve, as before, assumes no superinfection (Ross model); the broken curve assumes 'stacked' infections (Macdonald model); the dot-dashed curve corresponds to the Dietz model. At lower prevalence levels the three models are essentially the same, and the qualitative dynamics are essentially similar; the detailed locations of the equilibrium points are different for the three models. (From Aron and May 1982.)

proportions of humans and of mosquitoes infected, y^* and $\hat{y}^*$, do depend on how superinfection is defined. As one moves from the original Ross model, to that of Dietz, to that of Macdonald, both y^* and $\hat{y}^*$ increase somewhat. Thus the details, but not the overall stability properties, are affected by the inclusion of superinfection.

To proceed further in our refinements, with the aim of understanding observed patterns in human communities, we need to consider the question of acquired immunity. First, however, by way of introducing the problem we turn to the treatment of age structure within the human population.

14.4.4 *Age structure*

The basic model of Ross can be easily extended to encompass age structure within the human community. To do this we consider population densities, as opposed to proportions, and define $Y(a, t)$ as the number of infected people of age a at time t. The model is now of the form

$$\partial Y(a,t)/\partial t + \partial Y(a,t)/\partial a = (ab\hat{Y}(t)/N)(N(a) - Y(a,t)) - (\gamma + \mu_1)Y(a,t), \tag{14.20}$$

$$\mathrm{d}\hat{Y}(t)/\mathrm{d}t = (ac\bar{Y}(t)/N)(\hat{N} - \hat{Y}(t)) - \mu_2\hat{Y}(t). \tag{14.21}$$

Here $\hat{Y}(t)$ defines the density of infected mosquitoes, $N(a)$ denotes the density of humans of age a, and N and $\hat{N}$ the total densities of humans and mosquitoes respectively (both assumed to be constant). Human and mosquito mortality are represented by the rates μ_1 and μ_2 as in eqns (14.7) and (14.8). The term $\bar{Y}(t)$ denotes the total density of infected people weighted by the proportional representation of each age class in the community

$$\bar{Y}(t) = \left(\int_0^\infty Y(a,t)\exp(-\mu_1 a)\,\mathrm{d}a\right)\left(\int_0^\infty \exp(-\mu_1 a)\,\mathrm{d}a\right)^{-1}. \tag{14.22}$$

It is here assumed that human mortality is constant and independent of age (Type II survivorship). Thus the total density of humans N is given by $N(0)L$ where $N(0)$ is the cohort size at birth (assumed constant) and L is human life expectancy ($L = 1/\mu_1$).

At equilibrium ($\partial Y(a,t)/\partial t = \mathrm{d}\hat{Y}/\mathrm{d}t = 0$), eqn (14.20) becomes

$$\mathrm{d}y^*/\mathrm{d}a = \lambda(1 - y^*(a)) - (\gamma + \mu_1)y^*(a). \tag{14.23}$$

Here $y^*(a)$ denotes the equilibrium proportion of infected people of age a. The force of infection, λ, is defined as

$$\lambda = (ab\hat{N}/N)\hat{y}^* \tag{14.24}$$

where $\hat{y}^*$ is the equilibrium proportion of infected mosquitoes. The solution of eqn (14.23) is

$$y^*(a) = [\lambda/(\lambda + \gamma + \mu_1)]\{1 - \exp[-(\lambda + \gamma + \mu_1)a]\}, \tag{14.25}$$

given that $y(0) = 0$ (i.e. infants are uninfected at birth). The simple model therefore predicts that the prevalence of infection within the human community rises monotonically with age to a plateau, $\lambda/(\lambda + \gamma + \mu_1)$, in the older individuals. This pattern, however, differs markedly from those observed in human communities with endemic malaria infection (Fig. 14.5). Observed trends are normally convex in form; the prevalence rises rapidly with age in the young infants and children, attains a peak, and declines in the older children to reach a low level in adults. It is clear that the basic model must be modified to encompass some description of the acquisition of immunity to infection. Before turning to this problem, however, it is worth considering the parameter λ, the force of infection, in a bit more detail.

A good estimate of the pristine force of infection can be obtained from the rate of increase of prevalence with age in young children, before acquired

Table 14.7 Estimates of force of infection

Age group	Location	Daily force of infection	Reference
Infants	Nyanza Province, Kenya	0.0084	Pull and Grab (1974)
0–4 years	Maputo, Mozambique	0.001–0.0075[a]	Schapira *et al.* (1990)
5–14 years	Maputo, Mozambique	0.001–0.013[a]	
Infants	Garki, Nigeria	0.0015–0.0323[a]	Bekessy *et al.* (1976)
1–4 years	Garki, Nigeria	0.007–0.0220[a]	
5+ years	Garki, Nigeria	0.0171–0.0233[a]	
0–14 years	Gambela, West Ethiopia	0.0064–0.0255[a]	Krafsur and Armstrong
15+ years	Gambela, West Ethiopia	0.0037–0.0151[a]	(1977)

[a] Range from dry to wet season.

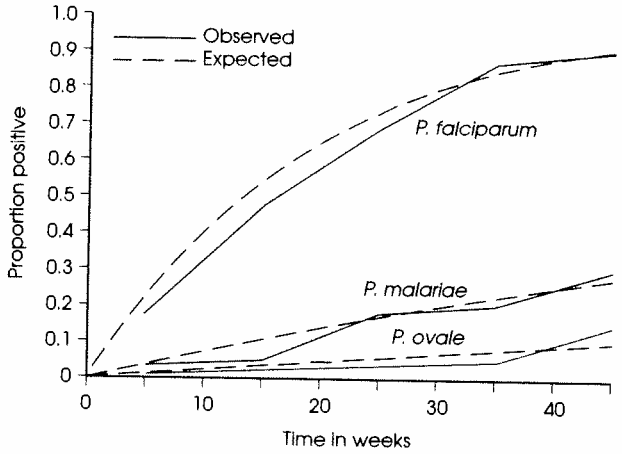


Fig. 14.25. The fit of eqn (14.25) in the main text to the data recorded in Fig. 14.9 for (a) *P. falciparum*, (b) *P. malariae*, and (c) *P. ovale*. The estimated forces of infection (λ) are (a) $\lambda = 2.7\,\mathrm{yr}^{-1}$, (b) $\lambda = 0.37\,\mathrm{yr}^{-1}$, (c) $\lambda = 0.126\,\mathrm{yr}^{-1}$ (for $\gamma = 1\,\mathrm{yr}^{-1}$, $\mu = 0$). The average ages at first infection for the three parasites are approximately (a) 0.37, (b) 2.67, and (c) 7.91 (years).

immunity complicates the interpretation of observed trends. A variety of epidemiological studies have focused on the rate of increase of prevalence over the first few years of life in children born within areas of endemic infection (e.g. Macdonald 1950; Molineaux and Gramiccia 1980). Table 14.7 reveals various estimates of λ that are derived from a wide variety of data sets. Examples of fitting the model defined by eqn (14.25) to certain records of change in prevalence with age in children are displayed in Fig. 14.25. In many instances the model provides a good description of observed trends in children between the ages of 0 and 2 years.

In areas of stable endemic malaria we can express the basic reproductive rate R_0 in terms of the parameter λ, the equilibrium prevalence of sporozoite-infected mosquitoes (the sporozoite rate), $\hat{y}^*$, and certain other parameters via the use of eqns (14.4) and (14.24):

$$R_0 = \lambda ac/\mu_2 \gamma \hat{y}^*. \tag{14.26}$$

To estimate the value of R_0 for a given area, we therefore require a number of separate bits of epidemiological data. The parameters λ and $\hat{y}^*$ may be reliably estimated from data on changes in prevalence with age in humans (as indicated in Fig. 14.25) and by sampling mosquitoes to measure the sporozoite rate (note, however, that this may vary on a seasonal basis; see Fig. 14.23). The remaining parameters, however, are more difficult to determine (i.e. the biting rate, a, the probability that a bite on an infectious person results in a patent infection in the mosquito, c, and mosquito life expectancy, μ_2). As noted in Fig. 14.22, the probability c depends on the density of gametocytes within an individual patient. However, by way of a numerical example suppose $c = 0.5$, $a/\mu_2 = 5$, $\hat{y}^* = 0.05$, $\lambda = 0.005\,\mathrm{day}^{-1}$, and $\gamma = 0.005\,\mathrm{day}^{-1}$. The substitution of these values in eqn (14.26) yields an R_0 value of 50. Some crude estimates of R_0 for different localities and times are recorded in Table 14.8. Note that the

Table 14.8 Estimates of the basic reproductive rate, R_0, of *Plasmodium* spp.

Infectious agent	Location/time period	R_0	Reference
P. falciparum	Northern Nigeria (1970s)	~80	Molineaux and Gramiccia (1980)
P. malariae	Northern Nigeria (1970s)	~16	Molineaux and Gramiccia (1980)

values for areas of stable endemic infection (particularly in Africa) are somewhat higher than those typically estimated for directly transmitted viral infections such as measles (see Table 4.1). This observation is in part corroborated by the observation that the average age at which a child typically first acquires malarial infection in an endemic area is normally much lower (i.e. 2–6 months) than that recorded for viral infections such as measles (i.e. 1–3 years, see Chapter 13). However, it must be remembered that—in contrast to what one might believe from reading some descriptions of the derivation of R_0 for malaria—many uncertainties surround the estimating of the parameters, a, c, and μ_2 in any given locality. The values presented in Table 14.8 are no more than rough approximations.

14.4.5 *Acquired immunity*

Models for the transmission dynamics of malaria have only recently begun to take account of the phenomenon of acquired immunity, despite its obvious relevance as a determinant of observed age-related changes in the prevalence of

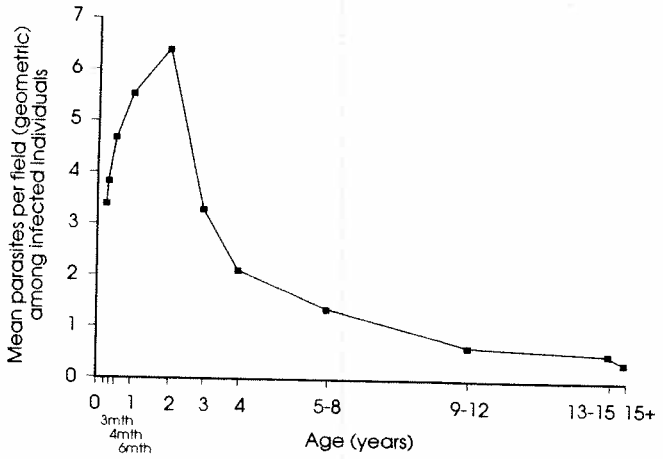


Fig. 14.26. The mean number of parasites per microscope field, according to the age of the human host (from Putnam 1931).

infection. This is in part a consequence of the early focus in malaria models on the vector components of transmission, deriving from the initial aim of global eradication of malaria based on the application of DDT (see Macdonald 1957; Bruce-Chwatt and Glanville 1973; Yekutiel 1980). The failure of this campaign owing to the problems of resistance to insecticide, along with recent advances in immunology and molecular biology, has shifted the focus of research to the mechanisms of immunity in man. Recent work, for example, on the immunogenicity of various sporozoite, merozoite, and gametocyte antigens, plus the use of recombinant DNA technology in the expression of the genes that encode for particular antigens within bacteria, has raised the hope that vaccines to protect against malarial infection will be developed in the coming few years (Zavala *et al.* 1985).

In this subsection we turn to the question of whether enough is understood about immunity to malaria to formulate sensible models for the impact of herd immunity on transmission within a community. The standard characterization of the epidemiology of malaria is, as discussed earlier, based on age–prevalence curves, which show the proportion of each age group whose blood slides contain infected cells. In endemic areas, the prevalence peaks at a very early age and then declines slowly (Fig. 14.5); at the same time the number of infected cells and gametocytes found in those slides positive for parasites decreases relatively quickly with age (Fig. 14.26). Unfortunately, however, the measurement of such patterns does not provide sufficient information with which to unravel the various components of acquired immunity and their dependence on the intensity of transmission. Observed curves can be fitted by a wide variety of models that contain very different assumptions (Dietz *et al.* 1974; Elderkin

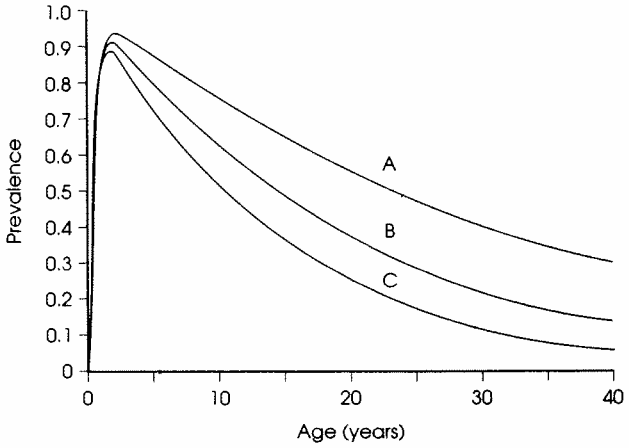


Fig. 14.27. Prevalence of infection versus age according to eqn (14.30), derived from the simple model with lifelong immunity. A single infection rate λ is used with three different recovery rates, γ: $\lambda = 20\,\text{yr}^{-1}$; and A, $\gamma = 0.03\,\text{yr}^{-1}$; B, $\gamma = 0.05\,\text{yr}^{-1}$; C, $\gamma = 0.07\,\text{yr}^{-1}$.

et al. 1977; Aron and May 1982; Aron 1983). However, with this caveat in mind, we start with the simplest possible assumption, namely, that on recovery from first exposure an individual acquires sterile immunity for life (in line with the assumption made in the simple compartmental models for directly transmitted microparasites discussed in earlier chapters).

The age-structured model defined in eqns (14.20)–(14.21) can be simply modified to incorporate an immune class of individuals as follows. We consider the system at equilibrium and define $x^*(a)$, $y^*(a)$, and $z^*(a)$ as the proportion of susceptible, infected, and immune individuals of age a, respectively. The rates of change of these variables, with respect to age, may be expressed as

$$\mathrm{d}x/\mathrm{d}a = -(\lambda + \mu_1)x, \tag{14.27}$$

$$\mathrm{d}y/\mathrm{d}a = \lambda x - (\gamma + \mu_1)y, \tag{14.28}$$

$$\mathrm{d}z/\mathrm{d}a = \gamma y - \mu_1 z. \tag{14.29}$$

The term λ, the force of infection, is as defined in eqn (14.24), γ denotes the recovery rate (where recovery takes an individual into the immune class), and μ_1 represents the rate of human mortality (note that no account is taken of disease-induced mortality). The initial condition is $x(0) = 1$, and it follows that $x(a) + y(a) + z(a) = \exp(-\mu_1 a)$ for all ages a. This set of equations can be integrated to obtain an explicit description of the experiences of a cohort as it ages

$$y(a) = \{\exp[-(\gamma + \mu_1)a] - \exp[-(\lambda + \mu_1)a]\}[\lambda/(\lambda - \gamma)]. \tag{14.30}$$

In Fig. 14.27 we choose $\lambda = 2\,\text{yr}^{-1}$ and γ between 0.07 and $0.03\,\text{yr}^{-1}$ (corresponding to mean durations of infection of 15–30 years), to obtain

age–prevalence curves very similar to those observed (Fig. 14.26). However, although the model can mirror observed trends, the assumptions on which it is based are clearly wrong. The inferred recovery rate (a duration of infection of 15–30 years) is far too slow since the available evidence suggests a duration of infection of roughly 6 months to 1 year for *P. falciparum* (Fig. 14.3), nor is there good evidence for the acquisition of lifelong immunity. The above discussion and Fig. 14.26 are offered in the spirit of a cautionary tale (Aron and May 1982).

If immunity is not lifelong, how is it related to past and present experience of infection? Bekessy *et al.* (1976) have analysed the epidemiology of malaria (mostly *P. falciparum*) in Nigeria, using a study in which individuals are followed over several years (a longitudinal cohort study). They argue that the decline in prevalence with age is primarily due to a decline in the intensity of the parasite burden, coupled with a greater ability of older hosts to suppress parasite population growth once an infection is acquired; in other words the rate of parasite replication within the host is inversely related to the host's accumulated past experience of infection. A marked seasonal pattern in parasitaemia continued even for the adults, indicating that they are still susceptible. Dietz *et al.* (1974) have incorporated those ideas into a model of the epidemiology of malaria. In it, there are two classes of individuals: one class has a slow recovery rate from malaria; the other has a fast recovery rate, and infections only have a 70 per cent chance of being detected (owing to the low densities of parasites in the fast recovery class). Both classes are repeatedly exposed, become infected, and recover, remaining within their own class except for a fixed rate of transition from the relatively susceptible class (low recovery) to the relatively immune class (fast recovery). This model is illustrated schematically in Fig. 14.28. The model gave a good fit to data collected in an extensive study of malaria in northern Nigeria (see Molineaux and Gramiccia 1980), but parameter estimation was based to a large extent on the patterns which the model was intended to reflect. The major deficiency in the model of Dietz *et al.* (1974), however, is its failure to account for the loss of immunity that is known to occur when transmission is significantly reduced. For villages in the same Nigerian study used by Dietz *et al.* (1974), Cornille-Brögger *et al.* (1978) showed that two transmission seasons with massive intervention in the form of drug administration and insecticide spraying were followed, in the next season in which no control was attempted, by a higher than usual prevalence of malaria. Figure 14.29 illustrates the results of these studies, showing the relative rise in prevalence in 1974 for those over 10 years old (younger individuals still received drugs to prevent serious morbidity and mortality). In subsequent years, following the cessation of control, the prevalence of infection within adults settled back to the levels recorded in a set of comparison villages (in which no control was attempted). Although the loss of immunity amongst adults was small and easily recovered in this particular field study, the phenomenon is clearly an important feature of the transmission biology of malaria.

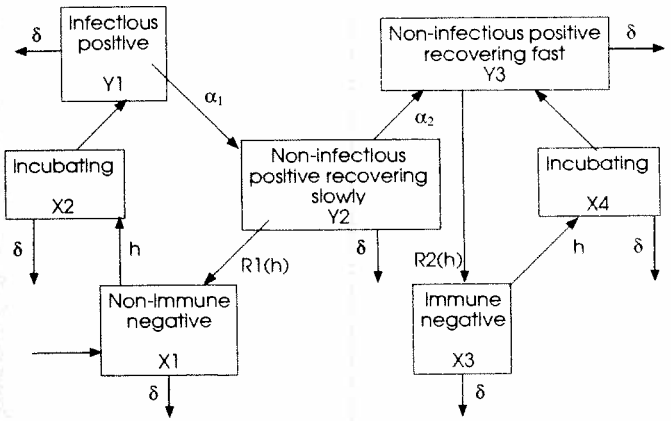


Fig. 14.28. States and transitions of the Dietz model (Dietz *et al.* 1974). Humans are born into the non-immune negative state X1; i.e. passive immunity is ignored. Non-immune negatives are innoculated at a rate h and move to the incubating class X2, remaining for a fixed incubation of N days. After this they become positive and infectious, in class Y1. Infectivity is lost at a rate α_1, while persons move to a positive but non-infectious state Y2. From here a person may either recover from infection and return to the non-immune negative state X1, at a rate $R1(h)$, or become an 'immune positive' at a constant rate α_2. The actual recovery rate $R1(h)$ is a function of a constant, r_1, which is the basic recovery rate of non-immunes, and of h, the effective inoculation rate: as inoculation rate increases the recovery rate decreases, i.e. superinfection prevents recovery and an increasing proportion of Y2 move to Y3. The 'immune positives' in Y3 recover from infection at a rate $R2(h)$, which is a function of r_2, the basic recovery rate of immunes, and of h; r_2 is larger than r_1: immunes tend to recover faster than non-immunes, but superinfection again reduces the recovery rate. If an immune positive (Y3) recovers from infection he or she becomes an immune negative (X3). Immune negatives are successfully inoculated at the same rate (h) as the non-immune negatives, and incubate the infection for the same period of N days (X4) after which they are 'immune positives' (Y3). δ denotes the death rate from each class (from Molineaux and Gramiccia 1980).

Pringle and Avery-Jones (1966) have demonstrated similar effects in African children. The children received antimalarial drugs for a few weeks, and were then taken off the drugs; they then had higher parasitaemias than at the start of the study. In short, it seems that continued exposure to infection helps maintain immunity.

Recently, Aron and May (1982) and Aron (1983) have described a simple way to incorporate this mechanism. Suppose there are three classes of individuals: susceptibles, infecteds, and immunes. Assume that immunity lasts for some fixed period of time, τ, in the absence of re-exposure, but that if a person is further exposed before τ units have elapsed, immunity is sustained and another interval of duration τ without infection is required before immunity is lost. If infection occurs at a per capita rate λ (as a Poisson process), the average

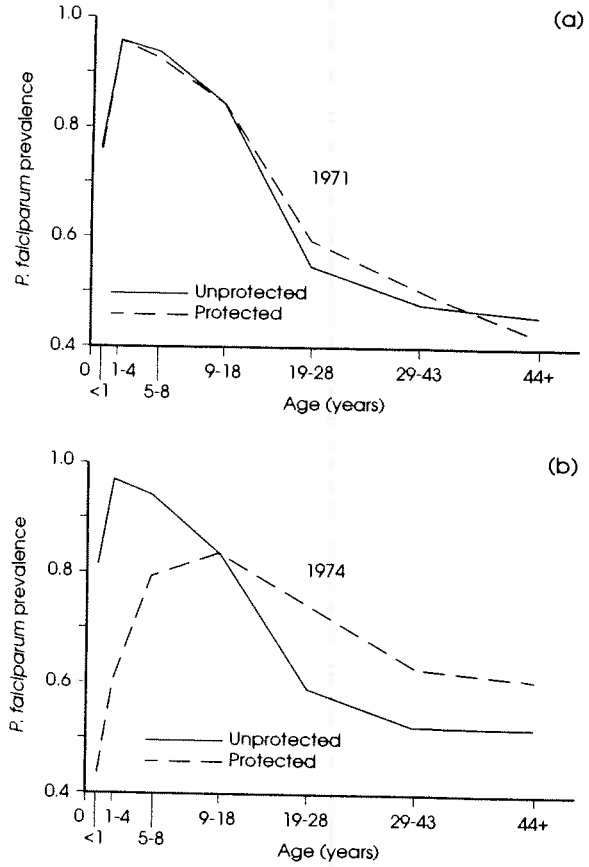


Fig. 14.29. (a) Prevalence of infection versus age in years in an endemic area in 1971 before intervention. There is no difference as yet between the two villages (full and broken curves). In 1972 and 1973 there was massive intervention in the form of drug administration and anti-mosquito spraying in one of the groups, which was subsequently halted for adults in 1974. (b) Prevalence of infection versus age in years in 1974. The adults in the once-protected group (broken curve) show significantly higher prevalences than in the comparative villages (full curve) (from Cornille-Brögger *et al.* 1978).

time spent in the immune state, $T(\lambda, \tau)$, can be calculated as a function of λ (see Aron (1983)):

$$T(\lambda, \tau) = [\exp(\lambda\tau) - 1]/\lambda. \tag{14.31}$$

Hence the average per capita rate of loss of immunity, $v(\lambda, \tau)$, as a function of λ and τ, is simply

$$v(\lambda, \tau) = 1/T(\lambda, \tau). \tag{14.32}$$

Fig. 14.30. This figures shows the rate of loss of immunity, $v(\lambda, \tau)$, as a function of infection rate, λ, for eqn (14.32). In this model, repeated infection helps maintain immunity. The 'immune interval', τ, is taken to be 1 year.

An illustration of the relationship between v and λ as predicted by eqn (14.32) is depicted in Fig. 14.30.

This simple description of immunity as a function of exposure can now be incorporated into the equilibrium age–prevalence model defined in eqns (14.27)–(14.29):

$$dx/da = v(\lambda, \tau)z - (\lambda + \mu_1)x, \tag{14.33}$$

$$dy/da = \lambda x - (\gamma + \mu_1)y, \tag{14.34}$$

$$dz/da = \gamma y - (v(\lambda, \tau) + \mu_1)z. \tag{14.35}$$

The only difference is that now immunity is not permanent. As before, this linear set of differential equations can be integrated to construct age–prevalence curves given the initial condition $x(0) = 1$ (all uninfected at birth).

The patterns predicted by this simple model are illuminating. First, if v is held to be a predetermined constant such that the average duration of immunity is $1/v$, then complex changes in prevalence with age can arise as shown in Fig. 14.31. However, note that the shapes of these curves bear little similarity to those actually observed (Fig. 14.5). If we now employ the function defined in eqns (14.31) and (14.32), where loss of immunity is a function of the rate of exposure to infection, λ, then a different picture emerges as illustrated in Fig. 14.32. The patterns are much closer to those observed for parameter values that are chosen to accord with observations on recovery rates and the duration of immunity.

Although this model represents an advance on the simpler models discussed in the earlier sections, it is still a very crude description of the true complexities

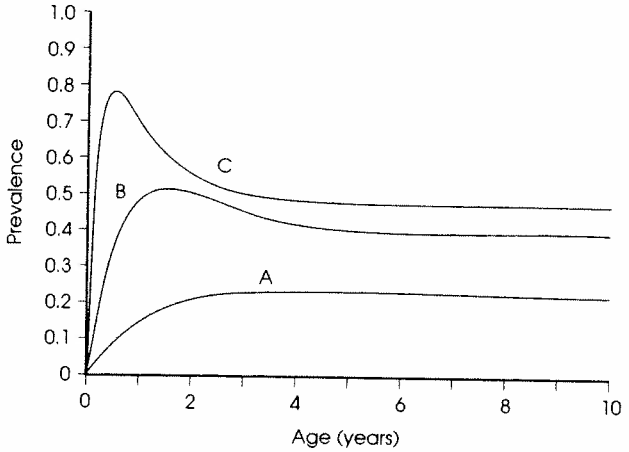


Fig. 14.31. Age structure curves for malaria calculated from the model defined by eqns (14.33)–(14.35), assuming both the intrinsic recovery rate, γ, and the rate of loss of immunity, $v(\lambda, \tau)$, are constants, independent of the transmission rate, λ (specifically $\gamma = 0.5\ \text{yr}^{-1}$, $v(\lambda, \tau) = 0.5\ \text{yr}^{-1}$) and $\lambda = 0.2\ \text{yr}^{-1}$ (A), $1\ \text{yr}^{-1}$ (B), and $5\ \text{yr}^{-1}$ (C).

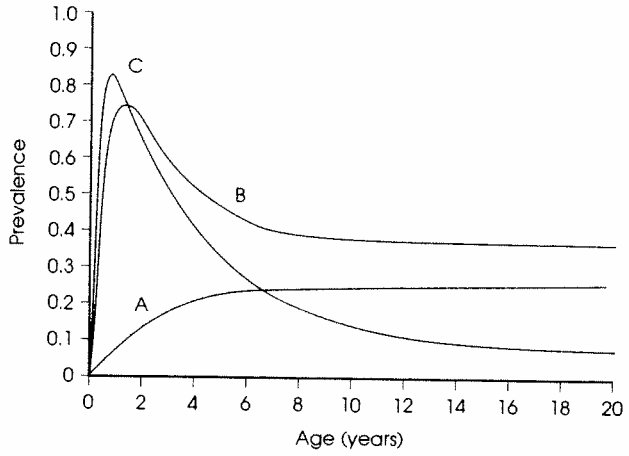


Fig. 14.32. As for Fig. 14.31 except here the rate of loss of immunity $v(\lambda, \tau)$ depends on the transmission rate, λ, as described by eqns (14.31) and (14.32). Specifically, the figure is for $\gamma = 0.25\ \text{yr}^{-1}$ and $\tau = 1.3$ year; the three curves are for the different transmission rates; A, $\lambda = 0.1\ \text{yr}^{-1}$; B, $\lambda = 2\ \text{yr}^{-1}$; C, $\lambda = 4\ \text{yr}^{-1}$.

of immunity to malarial infection. In particular, the classification into three discrete categories—susceptible, infected, and immune—is a poor reflection of the observation that populations of malarial parasites can exist at various densities within individual people. In many respects, the transmission dynamics of malaria depends on the quantitative distribution of parasite abundance within the human community, rather than on mere presence or absence of infection. A related complication arises in the determination of prevalence from blood slides, especially at lower parasite densities, because 'false' negatives become common (Miller 1958; Molineaux and Gramiccia 1980; Aron 1982). This problem can affect the reliability of estimates of infection and recovery rates.

All detailed descriptions of the acquisition and loss of immunity, whether in hospital or in the natural environment, indicate that the phenomenon is gradual. In the studies of Crica *et al.* (1934), in which *P. vivax* infections were administered therapeutically to a group of patients, there was a steady decline in the manifestation of clinical symptoms from the first inoculation to the fifth and last (which induced no clinically measurable symptoms). The gradual acquisition and loss of immunity has been demonstrated in laboratory rodent hosts. For example, Zuckerman (1974) showed that serum from immune rats (used to protect non-immune animals) became more and more effective as the number of infections given to the immune donor rats increased. Furthermore, Sergent and Poncet (1956) have shown loss of immunity in rats to be gradual; the longer the interval to a subsequent infection, the greater was the proportion of rats producing parasitaemias and the greater was the intensity of the parasitaemias.

These observations combine to suggest that an accurate mathematical description will need to abandon the compartmental, or prevalence-based, structure of conventional microparasite models and move toward a more detailed description of the growth and decay of parasite abundance within individuals. This latter approach is conventionally restricted to the description of the transmission dynamics of macroparasites, but many protozoan infections—such as malaria, trypanosomiasis, and leishmaniasis—fall in the buffer zone between the extremes presented by viral infections, where a compartmental framework is a good description of observed events, and helminth parasites, where notice must be taken of parasite abundance within the host.

An earlier attempt to model the malarial parasite population within an individual host and the acquisition of immunity is that of Elderkin *et al.* (1977). The dynamical variables in this model are the population of asexual stages in the human host, the population of gametocyte sexual stages in the blood, and the level of resistance (immunity) of the host. We make no attempt to discuss this model in detail, but simply note that it can generate convex changes in the parasite density within the host as people age. A somewhat simpler approach is to consider a single variable, $M(a)$, denoting the mean number of malarial parasites (asexual and sexual stages) in a person of age a. Suppose that new

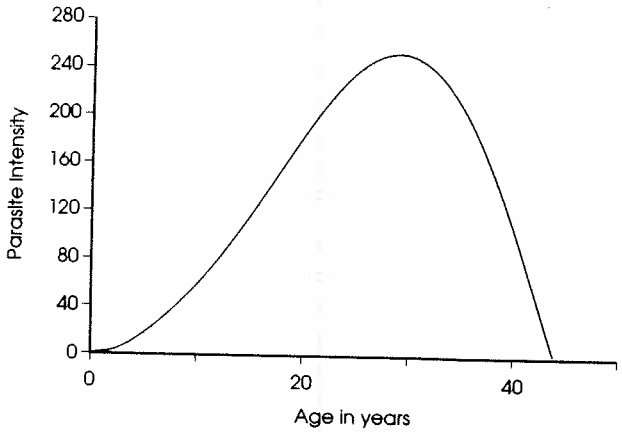


Fig. 14.33. Numerical solution of eqn (14.38) with parameter values $\Lambda = 0.1$, $b = 1.0$, d and $\delta = 0.0003$ (arbitrary time units).

parasites arrive at a per capita rate Λ (via inoculation by the mosquito vector) and that the population within the host has per capita birth and death rates b and d respectively. Further assume that immunity acts to increase the death rate, $d(\bar{M}(a))$, of the parasite (as seems likely from experimental studies) in a manner linearly dependent on the accumulated sum of the hosts' past experience of infection $\bar{M}(a)$; that is,

$$\bar{M}(a) = \int_0^a M(\alpha)\, \mathrm{d}\alpha \tag{14.36}$$

and

$$d(\bar{M}(a)) = d + \delta \bar{M}(a). \tag{14.37}$$

Here d is the death rate in naive hosts and δ measures the severity of the acquired immunological response. We may therefore represent changes in $M(a)$ with respect to age by the simple differential equation

$$\mathrm{d}M(a)/\mathrm{d}a = \Lambda + M(a)[b - d(\bar{M}(a))]. \tag{14.38}$$

As illustrated in Fig. 14.33, this model, with an appropriate choice of parameter values, can generate convex patterns of change in the mean parasite density with host age that are reminiscent of those observed in endemic areas (see Fig. 14.26). A further discussion of this type of model of acquired immunity is developed in Chapter 18 in the context of macroparasites.

In short, this example further illustrates the point that a variety of models for acquired immunity, each containing different assumptions, can generate patterns similar to those observed in areas of endemic infection. It is impossible at present to discriminate among these models with respect to their biological accuracy, since the detailed mechanisms of human immune responses to malaria are not well understood.

Further complications arise if we consider the significance of genetic heterogeneity within both the human and mosquito hosts and within the parasite population. It is well understood that different people exhibit different innate susceptibilities to malaria infection and different abilities to acquire immunity. This is sometimes mediated by factors other than genetic background, such as nutritional status (Scrimshaw *et al.* 1968). However, laboratory studies with rodent malaria models demonstrate well the importance of genetic background as a determinant of innate resistance and the development of specific immunity (Cox 1982). With respect to humans, the sickle cell genetic trait is known to confer a degree of innate resistance with heterozygous individuals (Allison 1964). More broadly, Armstrong (1978) demonstrated that two tribes living adjacently in Ethiopia had significantly different susceptibilities to *P. vivax*. Even within a community, genetic background undoubtedly influences the effectiveness of an individual's immune response to invasion by malarial parasites. The complexity of the issue is further compounded by variation among strains within the parasite population. Recent evidence suggests that *P. falciparum* populations exhibit considerable antigenic variation even within a defined locality (Forsyth *et al.* 1988).

Little is understood about these factors at present, yet they are likely to be of some importance to the development and community-wide use of potential malarial vaccines. The ideal vaccine will probably have to incorporate antigens from different parasite developmental stages and different strains. However, the major problem may concern genetic variability in immunocompetence within the human community. An effective vaccine must be able to convert 'low responders' (the genetically less immunocompetent individuals who suffer most from mortality and morbidity) into 'high responders'.

14.5 Control

The problems outlined above lead us to the issue of community-wide control. Past attempts have been based on chemotherapy and vector control. The successes and failures are well documented in the literature and we do not intend to go into any detail concerning these methods (see Molineaux and Gramiccia 1980). The problems of insecticide and drug resistance are acute at present in many regions of the world and this has added an increased urgency to research on the development of malaria vaccines (Ballou *et al.* 1987).

What can simple theory tell us about the use of vaccines (or other control measures) for the community-wide control of malaria? It is our view that mathematical models of the kind reviewed in this chapter—in which the characterization of acquired immunity is admittedly phenomenological and imperfect—do provide some useful insights. These fall under four general headings.

14.5.1 *Reduction in transmission intensity*

Ideally, control measures should aim to reduce the value of the effective reproductive rate of the parasite, R, below unity. This is irrespective of whether intervention is based on the application of insecticides, the use of antimalarial drugs, mass vaccination, or some combination of these methods. In practice, however, this objective is rarely achieved. Intervention normally results in a reduced transmission efficiency but with the parasite persisting at some lower overall abundance.

In terms of the simple model defined in eqns (14.33)–(14.35), which incorporates a crude description of acquired immunity, a reduction in transmission implies a lowering in the magnitude of the force of infection, λ. On the assumption that acquired immunity plays an important role, a reduction in λ will sometimes result in a decreased prevalence of infection in the younger age classes but an increased abundance of the parasite in the adult groups. Reduced transmission implies less experience of infection in childhood and hence lower immunity to infection as these children move into the adult classes. Prior to control, those that survive childhood will have built up strong acquired immunity due to the intensity of their exposure. The problem is illustrated in Fig. 14.34, where the pattern of age-related change in prevalence, $y^*(a)$, predicted by eqns (14.33)–(14.35) is shown for various values of λ (moving from a high value representing the pre-control situation to a lower value depicting the results of increased intervention). Note that we discussed an empirical example of this phenomenon in an earlier section (see Fig. 14.29).

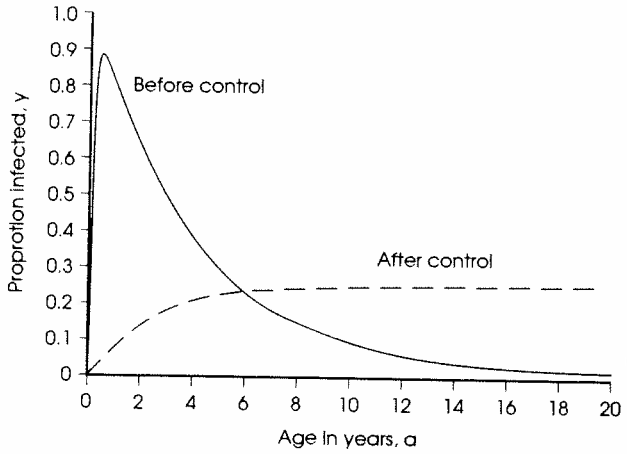


Fig. 14.34. An illustration of the impact of control (a reduction in the force of infection) on the age–prevalence profile of malaria as predicted by eqns (14.33)–(14.35) (parameter values, $\tau = 1.3$ years, $\mu = 0$, $\gamma = 0.25\ \text{yr}^{-1}$). Prior to control $\lambda = 4\ \text{yr}^{-1}$, and after $\lambda = 0.1\ yr^{-1}$.

This problem—whereby control measures can have a perverse outcome—is one we have encountered in earlier chapters where, in the context of mass vaccination against directly transmitted viral infections, it was predicted (and observed) that reduced transmission tends to shift the age distribution of the incidence of infection and increase the average age at first exposure (Chapter 5). In the case of malaria, whether or not this phenomenon is of practical significance depends on the manner in which the risk of mortality and serious morbidity due to infection changes with age. Fortunately (or unfortunately in the pre-control situation), these risks appear to be greatest in infants and young children. Thus even low to moderate reductions in transmission, whether induced by insecticide application or mass vaccination, will tend to reduce the overall incidence of disease in endemic areas. It is still important, however, to recognize the fact that control measures can act to increase the prevalence and intensity of malarial infections in adult age classes over the levels pertaining prior to control.

14.5.2 *Eradication by mass vaccination*

The criterion for eradication by mass vaccination, when and if vaccines become available, remains as defined in Chapter 5 in the context of directly transmitted viral infections. With respect to malaria, the crude estimation procedures outlined earlier suggest that the value of the basic reproductive rate, R_0, is typically much higher in endemic areas than is normally the case for many important childhood viral and bacterial infections (Table 14.8). This implies that the level of vaccination coverage required to eradicate malaria in hyperendemic regions will be very high. To take a simple numerical example, if the value of R_0 is 50 (Table 14.8), then eqn (5.2) indicates that eradication requires approximately 98 per cent of each cohort of children to be effectively immunized soon after birth with a vaccine that gives lifelong protection. In practice, therefore, the goal of eradication is likely to prove extremely difficult to attain. This point is not well appreciated by those who believe that the advent of malarial vaccines heralds the demise of malarial parasites world-wide. A bleaker view is that vaccines will certainly be of benefit to the Western traveller to tropical regions, but may have less impact on the inhabitants of these regions. It is important to remember in this context that the development of cheap, safe, and effective vaccines is only a first step (albeit an essential one) in the community-wide control of an infection. Economic and motivational issues are at least as important as technological ones. For example, a cheap, effective, and safe vaccine for measles has been available since the late 1960s and yet the infection remains one of the major causes of child mortality in the world today (Anderson and May 1985*c*).

14.5.3 *What age to vaccinate?*

The principles involved in this issue are identical to those discussed in Chapter 13. The central issue is that the maximum impact on transmission is achieved

by immunizing as young as is practically possible, taking into account the rate of decay of maternally derived protection and the rate at which children acquire infection prior to intervention. For malaria, maternal antibodies do not appear to provide significant protection to infection. Hence, in principle, vaccination can take place almost immediately after birth. However, weighed against this advantage (by comparison with viral infections such as measles) are the disquieting observations that in endemic areas the average age at first infection is often as low as 3–6 months of age and that morbidity and mortality are most severe in young infants and children. Thus the 'age window' in which vaccines can be administered to best advantage is very small. But, as indicated earlier, low to moderate levels of vaccination at the start of an immunization programme will tend to widen the 'age window' (by lowering the net rate of transmission) provided vaccine is administered well before the average age at first infection pertaining before intervention.

14.5.4 *Reinfection following cessation of control*

A further consequence of high basic reproductive rates, in addition to the requirements of high levels of vaccine coverage for eradication and a narrow age window in which to administer the vaccine, is that the rate of return to the pre-control prevalence of infection will be extremely rapid following a cessation of intervention measures (irrespective of whether they involve insecticides, chemotherapy, or vaccines). The experience gained in past malaria control campaigns clearly supports this prediction. For example, results from the 'Garki' project in northern Nigeria, reported by Molineaux and Gramiccia (1980), show that the prevalence of infection in a series of study villages rapidly returned to its pre-control state (as recorded in 1971) following insecticide spraying and drug administration over a period from April 1972 to October 1973. The resurgence of malaria was monitored in 1974 and 1975; the observed patterns are recorded in Fig. 14.35.

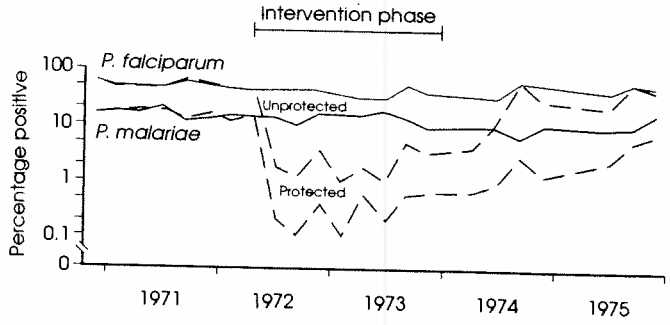


Fig. 14.35. Prevalence of *P. falciparum* and *P. malariae* in an unprotected population and a population protected in 1972–3 by drug administration and antimosquito spraying (Molineaux and Gramiccia 1980).

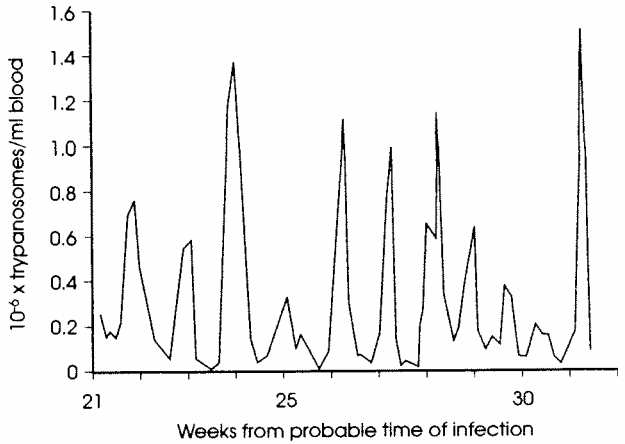


Fig. 14.36. Fluctuation of parasitaemia in a case of human trypanosomiasis (*Trypanosoma gambiense*) (Ross and Thomson 1910).

14.6 Other indirectly transmitted infections

Although much of this chapter has been devoted to malaria, the principles outlined apply equally well to many other important viral and protozoan infections that are transmitted by vectors. In this section we outline a few points of epidemiological interest with respect to these other diseases.

14.6.1 *African trypanosomiasis*

The trypanosome protozoa in Africa cause a number of important diseases in humans. The most notorious is *Trypanosoma brucei gambiense* which is the cause of African sleeping sickness. The parasite is transmitted by tsetse flies of the genus *Glossina*. Control has proved to be very difficult: effective non-toxic drugs are unavailable at present, and vector management is ineffective because of the presence of animal reservoirs of the parasite, the wide distribution of the flies, and the underground habitat of their pupal stages. Parasite populations in humans undergo cycles of 'antigenic variation'. During the course of infection the number of trypanosomes in blood and lymphatic fluids fluctuates in a characteristic oscillatory fashion (Fig. 14.36). Each decline in parasitaemia is a result of antibody-mediated destruction of trypanosomes having a particular surface antigen. The subsequent growth of the population in the next 'epidemic' cycle within the host is due to the emergence of a different antigen type of the parasite (Vickerman 1978; Hoare 1972; Cross 1978). It appears that each parasite is able to express somewhere in the order of 100 different variable surface antigens (called VATs, variable antigen types). This has frustrated all attempts to develop effective vaccines. Antigenic variation within the host is

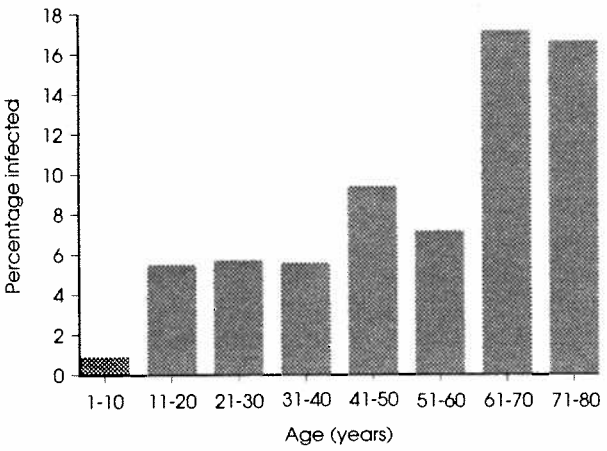


Fig. 14.37. Age–prevalence pattern for human sleeping sickness cases (diagnosed parasitologically) from the Timbo area of Central Nyanza, Kenya (Rogers 1988).

clearly an effective strategy to enhance the parasite's ability to persist, both within an individual host and within the community as a whole.

The principal differences between the transmission dynamics of African trypanosomes and malaria may be summarized as follows:

1. As a result of antigenic variation (the evasion of the host's immunological attack) trypanosome infections tend to be persistent in character such that following a single inoculation an infected person may harbour parasites for many years.

2. In endemic areas, the basic reproductive rate of the parasite appears to be much lower than that typically estimated for *P. falciparum*. As illustrated in Fig. 14.37, the prevalence of trypanosome infection usually rises slowly with host age.

3. Certain species of trypanosomes, such as *T. brucei gambiense*, are a significant cause of mortality. Deaths due to infection, however, more typically occur after childhood since the disease is progressive in character.

4. Reservoirs of infection exist in animal species other than humans, in areas of endemic human infection. In the case of *T. brucei gambiense* these reservoirs are typically pigs and dogs while for *T. brucei rhodesiense* they are often various species of antelopes and wild dogs (Hoare 1972). Reservoirs often play an important role in maintaining transmission in human communities where the 'within human' transmission component of R_0 is less than unity in value (Rogers 1988; Mulligan *et al.* 1988).

5. The insect vector has a much lower reproductive rate and longer life expectancy than the mosquito intermediate hosts of malaria. In current ecological jargon, tsetse flies lie to the *K*-selected end of the life history spectrum among insects (Rogers 1988).

Most of the factors mentioned above create problems in the design of effective control programmes. The only methods currently available are those of vector control by insecticide application, and environmental management to destroy the habitats both of the vector and of the mammalian species that act as reservoir hosts. No detailed study of the transmission dynamics of African trypanosomes has been completed as yet. It is clearly an area that demands greater attention, given the global significance of these parasites as causes of mortality and morbidity (Walsh and Warren 1979; Molineaux 1985).

14.6.2 *Leishmaniasis*

Leishmania species are obligate intracellular protozoan parasites in the mammalian host that are transmitted by the bites of infected sand flies. They are, in a broad sense, the trypanosomes of the New World. Transmission to humans is usually from other infected mammalian species that act as reservoirs of infection. Depending on the species of the parasite, infection can result in cutaneous, mucocutaneous (espundia), or visceral (kala azar) disease. Non-toxic chemotherapeutic agents and vaccines are unavailable at present and vector control can be very difficult due to the behavioural habits of sand flies. In many of its principal features the epidemiology of *Leishmania* species is similar to that of the trypanosome parasites. The infection is persistent in character although the latent period may be long for infections such as *L. donovani* (3–6 months) in contrast to trypanosome infections. If an individual recovers strong immunity is acquired and endemic as opposed to epidemic patterns are more commonly observed within communities. The vector is relatively long-lived and has a low reproductive rate in comparison with species such as mosquitoes. In some cases reservoir hosts facilitate disease persistence within human populations. This class of infections has not received much attention with respect to the quantitative study of transmission dynamics.

14.6.3 *Arboviruses*

Arthropod-borne viruses form an important group of infectious diseases of humans. Roughly 400 arthropod-borne viruses of vertebrates are currently recognized, and about 20 per cent of these are known to infect humans. In contrast to the protozoan vector-borne infections, most viral diseases are of very short duration and if a person recovers long-lasting or lifelong immunity is usually acquired. The two most important groups of viruses are those that cause yellow fever and those that induce dengue fever.

14.6.3.1 *Yellow fever* This infection is caused by viruses that are transmitted by the mosquito *Aedes aegypti*. Two forms are distinguished on the basis of

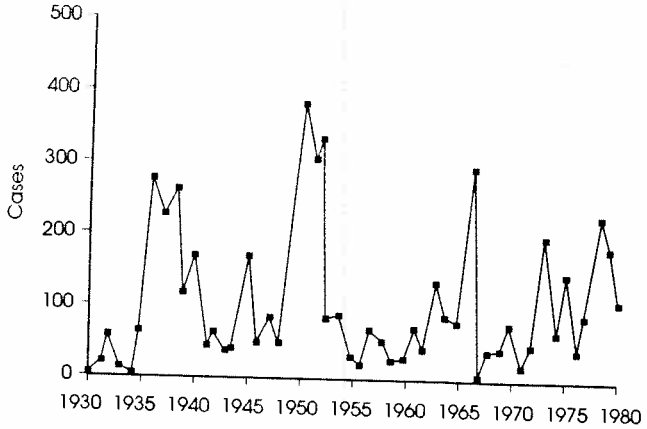


Fig. 14.38. Annual incidence of reported cases of yellow fever in South America (Warren and Mahmoud 1984).

transmission: urban yellow fever in which the virus is spread from person to person by *A. aegypti* strains that breed in urban habitats; and jungle or sylvan yellow fever which is transmitted by forest-dwelling strains of the mosquito between non-human primates and thence to, and sometimes between, people. In past history, yellow fever was one of the great epidemic scourges of humankind until the development and deployment of an effective vaccine in the twentieth century. However, yellow fever persists today in tropical areas of the Americas and Africa although it has not as yet appeared in Asia or the Pacific region (Theiler and Smith 1973).

The epidemiology of yellow fever is markedly different from that described for malaria and other vector-borne protozoas. First, the infection is typically epidemic in character such that the incidence of disease in a defined locality tends to fluctuate greatly from year to year (Fig. 14.38). Second, the latent and infectious periods in humans tend to be short (of the order of a few days; see Table 14.2) while those in the mosquito vector are not dissimilar from protozoan infections such as malaria (Table 14.3). Third, on recovery an individual tends to acquire long-lasting (if not lifelong) immunity to reinfection. Fourth and finally, transmission within human communities may be maintained, in the presence of a high degree of herd immunity, either by reservoir hosts (other primates) or vertical transmission of the virus within mosquito populations.

In light of these observations it is clear that, at least in the case of urban yellow fever, a simple compartmental model should capture the main features of transmission. If we ignore age structure for simplicity, the appropriate set of equations to describe changes in the proportions of infected mosquitoes, $\hat{y}$, and humans, y, and immune people, z, are very similar to those presented in earlier sections for malaria (see eqns (14.2) and (14.3)). Using the same notation as

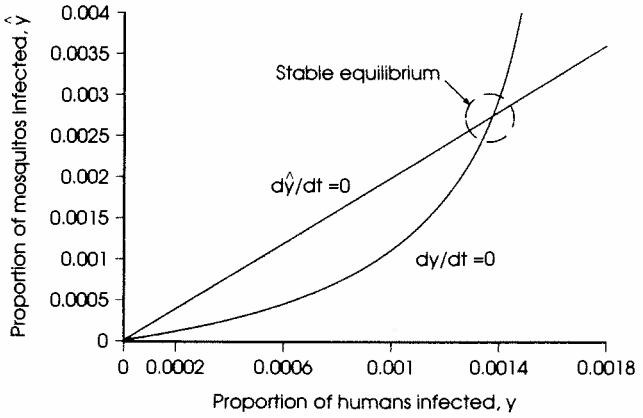


Fig. 14.39. Phase plane of the proportion of infectious mosquitoes, $\hat{y}$, and the proportion of infected humans, y, showing the isoclines $d\hat{y}/dt = 0$ and $dy/dt = 0$ for eqns (14.39)–(14.41). In the case of yellow fever it is assumed that immunity is lifelong. Parameter values $ab\hat{N}/N = 0.1$, $1/\mu_1 = 30$ years, $1/\mu_2 = 10$ days, $1/\gamma = 20$ days, and $ac = 0.2$.

that described for the basic malaria model, an appropriate model is of the form

$$dy/dt = (ab\hat{N}/N)\hat{y}(1 - y - z) - (\gamma + \mu_1)y, \tag{14.39}$$

$$dz/dt = \gamma y - \mu_1 z, \tag{14.40}$$

$$d\hat{y}/dt = acy(1 - \hat{y}) - \mu_2\hat{y}. \tag{14.41}$$

Here μ_1 and μ_2 denote the death rates within human and mosquito populations respectively (note that disease-induced mortality in people is ignored). The properties of this model are broadly similar to those outlined for the basic malaria model. For example, the basic reproductive rate R_0 is as defined in eqn (14.4) with γ replaced by $\gamma + \mu_1$. However, there is one important difference induced by the presence of an immune class. This is best illustrated by a geometrical 'phase-plane' analysis of the dynamical behaviour of eqns (14.39)–(14.41). We consider dynamical changes in three dimensions created by the variables y, z, and $\hat{y}$ by reference to the isoclines obtained by setting $dy/dt = dz/dt = d\hat{y}/dt = 0$. An example is illustrated in Fig. 14.39 for the situation $R_0 > 1$. A stable equilibrium exists, but the dynamical trajectories to this state may be oscillating in character. In other words, the system has a propensity to exhibit weakly dampled oscillations as a direct consequence of the inclusion of an immune class. The properties of the system are very similar to those described earlier (see Chapter 6) for directly transmitted viral and bacterial infections. The phase and amplitude of the epidemic cycles will be dependent on the magnitude of R_0 and the generation time of the virus (the sum of the latent plus infectious periods in both hosts). The model can be easily extended to include age structure as illustrated earlier in eqns (14.20) and (14.21), and by

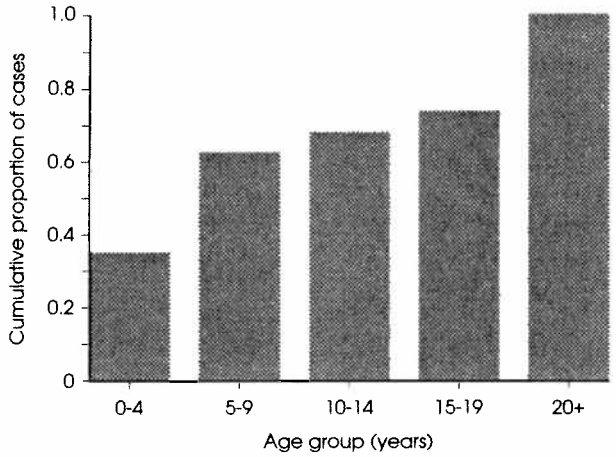


Fig. 14.40. Cumulative proportion by age of individuals who experienced infection by the yellow fever virus in Ghana from 1977–80. Data based on case reports of infection (Agadzi *et al.* 1984).

the equilibrium age distribution model defined in eqns (14.27)–(14.29). This latter set of equations is directly applicable to the study of yellow fever.

The above discussion prompts the question of why yellow fever incidence fluctuates so erratically in endemic areas when infections such as measles tend to exhibit more regular oscillatory patterns. The reason is unclear at present, but a variety of observations provide some clues. First, in endemic urban areas, where vaccination is (or was) low, the proportion seropositive for antibodies to the yellow fever virus tends to rise steadily with age, to approach a plateau in older age classes (Fig. 14.40). This is not dissimilar to measles, although the rate of rise with age is slower for yellow fever (which has a lower R_0 and larger average age at first infection, A). These age–seropositivity curves suggest that either many people acquire inapparent infections (with a mild and short-duration fever) or that case reporting is highly inaccurate. Both are likely to be true, and the former is backed by a body of clinical evidence (Monath 1985).

In rural areas, the erratic patterns of incidence in humans are more easily explained. Human density may often be too low to maintain R_0 above unity in the absence of non-human primate reservoirs and vertical transmission in the mosquito population. Epidemics in human communities will therefore occur at infrequent intervals when herd susceptibility rises to a sufficient level to trigger an outbreak of infections transmitted solely among humans.

14.6.3.2 *Dengue fever* Dengue viruses are vector-transmitted, single-stranded, enveloped RNA viruses of the genus *Togaviridae*. They are transmitted by various species of day-biting *Aedes* mosquitoes (principally *A. aegypti*) and

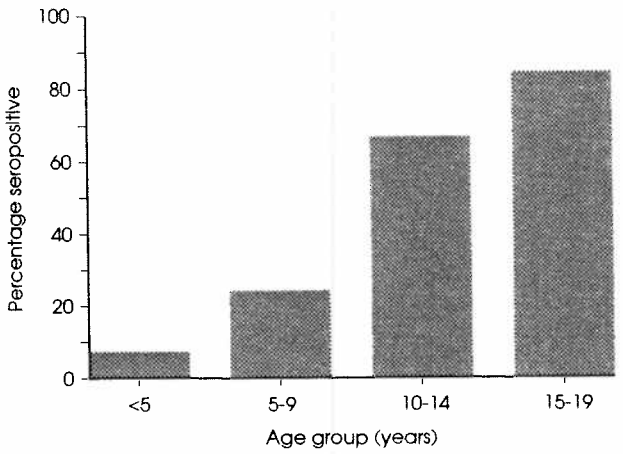


Fig. 14.41. Prevalence of dengue virus antibodies detected by immunoglobulin G enzyme-linked immunosorbent assay in children in Tahiti (April–June 1987) (Chunque *et al.* 1989).

may, in certain areas, also infect non-human primates. As for yellow fever, dengue viruses are transmitted in two basic patterns, either urban or sylvan. They can produce a spectrum of diseases in humans ranging from undifferentiated fever, dengue fever syndrome to dengue haemorrhagic fever. There appear to be four major antigenic types of the virus (labelled types 1 to 4), although evidence exists for extensive genetic heterogeneity within the group.

The epidemiology of dengue virus infection is broadly similar to that described for yellow fever. In brief, latent and infectious periods in humans are of short duration (a few days), immunity or recovery is long lasting, patterns of disease tend to be epidemic in character, non-human primates enhance population persistence, and inapparent infections in humans are common. Serological surveys in areas of endemic infection often reveal high levels of seropositivity in children and young adults, indicating that the virus can have a significant transmission potential (R_0 large) in certain areas (Fig. 14.41). The transmission dynamics of these viruses have been little studied but the model outlined for yellow fever would seem to be appropriate. At present, control is based on reductions in vector abundance. Vaccines are under development. However, an effective vaccine must be able to protect against infection by all four of the major strains of the virus since they often occur together within human communities (Halstead 1984).