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Chapter 6

Understanding the Importance of Asymptomatic and Low-Density Infections for Malaria Elimination

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Additional information is available at the end of the chapter

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Abstract

In recent years, the use of more sensitive diagnostic techniques has demonstrated a significant number of malaria infections at densities beneath the limit of detection of conventional microscopy and rapid diagnostic tests (RDT). These low-density infections are almost always asymptomatic, found in all endemic settings, including those nearing elimination, and in all ages of the population. They typically account for a high proportion of all infections and since they have also been shown to be infectious to mosquitoes, low-density infections are thought to be important contributors to maintaining malaria transmission. However, there is currently no direct evidence that specifically targeting this low-density parasite reservoir will hasten progress towards elimination. In this chapter we review the data to date and identify knowledge gaps. We present potential scenarios for the causes of low-density infections, if and how these might drive transmission, and the likely impact of specifically targeting them.

Keywords: asymptomatic malaria, transmission, longitudinal carriage, malaria elimination, diagnostics

1. Epidemiology and relevance of asymptomatic infections

It has long been acknowledged that not all *Plasmodium falciparum* infections lead to clinical symptoms, and in the vast majority of malaria endemic settings most infections are asymptomatic. In the last two decades data on infection prevalence in endemic populations have been generated using nucleic acid amplification techniques (NAAT). The use of these sensitive diagnostic methods showed that, on average, there are approximately twice the number

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of infections than those identified with more conventional diagnostics, such as microscopy [1] and rapid diagnostic tests (RDT) [2], with most of these previously undetected infections being asymptomatic. Indeed, the association between clinical disease and relatively high parasite levels [3–5] implies that most asymptomatic infections are also low-density, although parasitaemias above the microscopy detection limit are common in seemingly healthy infected individuals in endemic areas [3]. Of particular relevance, in light of the renewed interest in malaria elimination, is that in areas with low levels of transmission, often a high proportion of infections detected during prevalence surveys have sub-patent parasite densities (below the detection threshold of conventional diagnostics) [1].

For malaria elimination, a major consideration is how much the following different types of infections contribution to onwards transmission to mosquitoes: (1) clinical symptomatic and patent, (2) asymptomatic and patent, (3) asymptomatic and sub-patent, and what are the relative proportions of these infections in different endemic settings. Broadly speaking, the probability of a mosquito becoming infected after feeding on an infected human is dependent on the density of gametocytes. At an individual level, this probability of infection is higher from those with higher density symptomatic infections than those individuals with low-density asymptomatic infections [6], provided there has been enough time for gametocytes to fully mature (8–12 days). At a population level, contributions to malaria transmission from each of the three types of infections detailed above may be more balanced as there will be more individuals with low density infections than high density infections. In the context of control and elimination, symptomatic infections often have a very short duration because symptomatic individuals are more likely to seek and receive treatment and have their infections curtailed. This is more pronounced if treatment is given early after establishment of blood stage infection as gametocytes will be at relatively low densities and may not reach highly infectious levels.

Much of the data on asymptomatic infections is from community cross-sectional surveys. However, these snapshots are less informative on the dynamics of parasitaemia over time in individual infections. For example, an individual with a sub-patent infection today has several different potential infection outcomes (**Figure 1**). S/he may have been recently infected and will develop patent infection and clinical symptoms shortly afterwards, or alternatively may become a chronic parasite carrier, remaining asymptomatic for weeks or months. Conversely, individuals with sub-patent infections identified in cross-sectional surveys may also be at the tail end of an infection and will only remain minimally infectious for a short period of time (**Figure 1**). The contributions to onwards transmission from sub-patent infections that are only briefly asymptomatic [7] (all symptomatic infections invariably have a pre-clinical incubation period) and those that are chronic are likely to be very different. In community mass treatment campaigns that aim to interrupt transmission, clearing the infections of individuals who would otherwise go on develop symptoms, seek and obtain effective treatment a few days later, will reduce morbidity but is likely to have a smaller impact on reducing onwards transmission than treating infections in individuals who remain asymptomatic for several months. Estimations of the duration of malaria infections are necessary to understand the consequences of imperfect coverage during these interventions. However, quantifying infection duration in endemic settings is complicated because individuals are frequently superinfected with different falciparum clones, which means that periods of continuous parasite

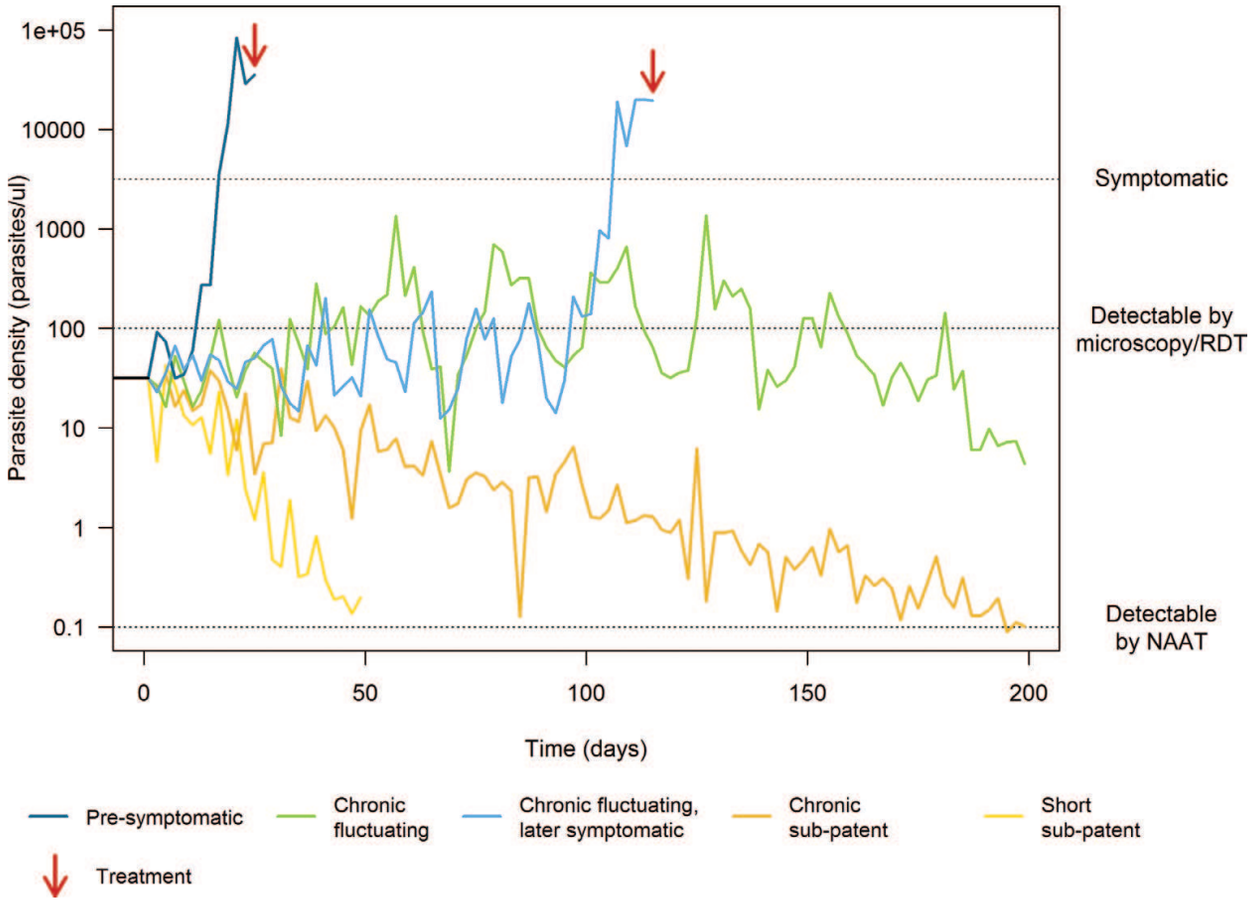


Figure 1. Hypothesised infection trajectories for sub-patent infections. An individual that has low-density asymptomatic infection on a given day can have several potential outcomes: s/he could continue to have long- (orange curve) or short-lasting (yellow curve) low-density infection, with limited infectiousness to mosquitoes and never developing symptoms or seeking treatment. The same individual could also be very recently infected and in the pre-symptomatic stage (dark blue line), or experience a slower increase in parasite density to a level where symptoms develop (light blue line). Another possible outcome is that parasitaemia fluctuates between detectable and undetectable levels by microscopy (green line). Any of these scenarios could be perturbed by re-infection, which could result in either continued asymptomatic infection or development of symptoms. RDT, rapid diagnostic test; NAAT, nucleic acid amplification techniques.

carriage often represent overlapping infections with different clones. A longitudinal study in Ghana using *msp*-2 genotyping to distinguish parasite strains showed that naturally occurring infections last on average 5–6 months [8]. In Myanmar, in an area with transmission approaching elimination levels and consequently low probability of super-infection, falciparum carriage of at least 6–9 months was observed [9]. A study in Cambodia, which followed 24 adults with asymptomatic falciparum infections monthly, found that 13% carried parasites for 2–4 months, whereas the remaining 87% had cleared their parasitaemia after 1 month [10]. Finally, in a recent cohort study in Vietnam, nearly 10% of infected individuals carried parasites for 4 months or longer [11]. These studies vary in design such that a mean duration is hard to estimate, however, the data demonstrate that chronic carriage occurs in a wide range of endemicities, although its frequency and duration is likely context-specific.

Identifying the factors that moderate parasite growth to make an infection asymptomatic, (and untreated [3]) rather than symptomatic, is necessary to better understand the likelihood

of transmission from these infections. This will allow an assessment of whether specific individuals with asymptomatic infections need to be targeted and, if so, how this might be done, for example by enhanced coverage efforts or more sensitive infection detection tools targeted at those individuals who have a higher probability of being chronically infected.

In Sections 2 and 3, we consider factors that influence the establishment of asymptomatic infections and their parasite and gametocyte carriage levels. Specifically, we discuss how different factors might relate to the different archetypes of parasite dynamics described in **Figure 1**: chronic infections with fluctuating patent and sub-patent levels; chronic sub-patent infections; clinical episodes with short incubation period; clinical episodes with long incubation period; and short asymptomatic infections. Additionally, we discuss how blood sampling for parasite detection can influence estimates of prevalence of sub-microscopic infections. In Section 4, we use malariotherapy data and validated mathematical models to assess the benefits of targeting the asymptomatic reservoir of parasites.

2. Human factors influencing the duration of infection

The development of asymptomatic and low-density infections is intimately related to an individual's tolerance to parasites [12]. Several host characteristics have been linked to differential clinical expression of malaria infection, as well as to modulation of parasite levels, including genetic factors [13], acquired immunity [14, 15], co-infections with non-falciparum malaria parasites [16], iron status [17], among others. In this section, we discuss two widely prevalent factors that are likely to influence the frequencies of asymptomatic and low-density infections in various settings: haemoglobinopathies, which are genetically determined and consequently whose effects on parasites might remain unchanged with decreases in transmission, and acquired immunity, that varies with cumulative exposure to parasites and will wane as exposure drops or ceases.

Both haemoglobin S (HbS) and haemoglobin C (HbC) mutations are protective against clinical malaria [18], and evidence from a longitudinal study performed in Uganda [19] suggests that HbS reduces progression of infection to disease. This protective effect suggests that these mutations are associated with chronic infections or clinical episodes with delayed onset (**Figure 1**; light blue, green or orange line). Data also suggest that the parasite densities observed in individuals with sickle cell trait [20] are lower compared to densities in HbAA individuals and thus presumably more likely to be sub-patent and not necessarily detected in population surveys. Given the high prevalence of haemoglobinopathies in many malaria endemic countries, particularly those in Africa for HbS [21, 22], and the potential for carriage of sub-patent infections, the contribution of this group of individuals to the transmission reservoir should be considered. Determining how often parasite densities in heterozygous individuals are below the lower limit of detection of standard diagnostics would be informative. This is particularly relevant as haemoglobinopathies have been associated with increased gametocyte positivity and duration of gametocyte carriage [19, 23–25], which could amplify the infectivity of asymptomatic individuals with these mutations. Unlike naturally acquired immunity, these genetic traits will persist for several generations even after reductions in

malaria transmission and they have the potential to influence transmission phenotypes in the whole spectrum of endemicities, including in areas approaching malaria elimination.

Another cause of variation in the risk of symptoms and in parasite burden is acquired immunity against asexual blood stage parasites, which develops with cumulative exposure and consequently age. Asymptomatic adults have lower parasitaemias compared to children [4], and a higher proportion of their infections are sub-patent [26]. Adults are also less likely to develop symptoms, especially in highly endemic areas, and when they do, the parasite densities associated with fever are on average lower than the corresponding densities in children [27]. On the other hand, estimates based on clone-specific carriage show that in highly endemic areas, asymptomatic infection duration is higher in schoolchildren compared to adults [8] though the differential detectability of clones may affect observations. Together, these studies suggest that infections in adults most commonly correspond to the archetype parasite dynamics of short duration asymptomatic infection or chronic infections with sub-patent carriage (**Figure 1**, yellow and orange lines). In settings where transmission intensity approaches elimination levels, depending on how fast transmission decreases, acquired immunity in adults would still be effective against parasitaemia and symptoms, while in young children with limited cumulative exposure to falciparum parasites, this might not be the case. In this scenario, the epidemiological differences between these demographic groups could be enhanced. Interestingly, in an area of Papua New Guinea with recent declines in transmission, reductions in parasite prevalence have been associated with an increase in the proportion of infections that are sub-patent [28], indicative, perhaps of persisting immune responses that control parasitaemia in a setting where the incidence of super infection is reduced.

Short-term changes in immunity might also be relevant. For example, recent malaria infection might modulate immune responses to subsequent infections [29], which suggests that dynamics of parasitaemia might differ at the start *versus* peak of transmission season, and so might the proportion of infected individuals that remain asymptomatic. Indeed, several epidemiological studies using different methodologies have shown that the risk of clinical symptoms during infection varies during a transmission season: Mueller and colleagues [30] observed that after adjusting for the incidence of new infections, defined by molecular identification of individual clones, the risk of clinical malaria per infection was higher at the beginning of the transmission season. In Mali, the ratio of asymptomatic to symptomatic infections was higher during the low transmission season compared to the rainy season [31]. Whether this is due to modulation of host immune responses or to changes in parasite phenotype, it may result in longer infections at the end of the transmission season that would be advantageous for falciparum parasite populations to persist over the often long dry seasons. Furthermore, short-term immunological changes might also directly affect infectivity of asymptomatic infections: in Burkina Faso, experimental mosquito infections indicate that short-lived immunity that reduces transmission is boosted after season-long exposure to parasites [32].

Of note, high-density infections in the absence of symptoms have been described, in particular in young children [3, 33, 34]. The relevance of these infections to transmission is unknown, although it could be anticipated that unless commitment to sexual development is reduced, these infections will produce high numbers of gametocytes and be potentially highly infectious.

3. Parasite factors associated with infection duration

After inoculation of sporozoites and the subsequent release of merozoites from the liver, there is a period of time when parasites are present in the blood at concentrations undetectable by conventional diagnostics. In many individuals, parasites then multiply to reach detectable densities, however in other individuals, parasites may remain at low densities that are undetectable. Human challenge studies on non-immune individuals in which parasites are monitored both by molecular methods and by microscopy have estimated that infections are detectable by PCR an average of 3.7 days (range 2–4 days) [35] or 3.1 days (range 0–4) [36] before being detectable by microscopy. Controlled human infections also suggest that the parasite stages that precede blood invasion might influence asexual blood stage dynamics. For example, Churcher and colleagues [37] observed that the inoculum size (the estimated number of sporozoites injected by infected *Anopheles* mosquitoes) influences the time it takes for infections to become patent: individuals receiving five bites from mosquitoes with more than 1000 sporozoites have detectable parasitaemia at least 2 days earlier than those volunteers infected by mosquitoes with 11–101 sporozoites. Quantification of sporozoite counts in wild-caught mosquitoes is necessary to confirm the relevance of this finding in natural settings. In Papua New Guinea, it was estimated that infected malaria vectors had on average (geometric mean) 4000 sporozoites [38], which is of the same order of magnitude as sporozoite counts in mosquitoes used in controlled infections.

Microscopy has limited sensitivity to quantify low parasite densities and this will affect its utility for studying any chronicity in infection dynamics. Histidine rich protein 2 (HRP-2), a protein the parasite secretes in the plasma, is considered to be a more accurate measure of total falciparum parasite burden [39], however, this measure does not distinguish between monoclonal and multiclonal infections. Molecular tools are more sensitive and allow discrimination of different parasite genotypes. They have been used to assess the effects of super-infection and exposure to different parasite clones on clinical malaria risk. A study that involved daily blood sampling of children with initially asymptomatic infections [40] suggests that development of symptoms is often associated with appearance of a new parasite strain in the blood and increases in parasite levels. Correspondingly, recent data from Papua New Guinea [16] showed that incidence of infections by new clones correlates with clinical malaria risk. This indicates that clinical malaria is often associated with new infection, presumably by a parasite clone with a previously unencountered antigenic profile.

Consistent with this, genetic analysis of malaria parasite populations in Zambia [41] found that in some settings individuals with symptomatic infections had different parasite strains compared to asymptomatic individuals. One hypothesis for this is that symptomatic infections originated from imported or recently introduced strains and that immunity to these strains is insufficient. This indicates that the rate of importation may play a role in the proportion of infections that are asymptomatic and symptomatic, especially in areas approaching elimination. An infection with a clone to which immunity has been acquired might lead to infections with shorter duration (e.g., **Figure 1**, yellow line).

3.1. Gametocytes in asymptomatic infections

Gametocytes derive from a small percentage of asexual parasites that commit to sexual development; therefore, asymptomatic infections with low asexual levels may also have low

gametocyte densities. Data from epidemiological studies confirm that most asymptomatic infections with patent or sub-patent asexual stage parasite levels have sub-patent gametocytaemia [42], only detectable by RNA-based molecular methods. However, a few asymptomatic individuals with low-density infections have relatively high gametocyte densities, which could be related to symptomless fluctuations in parasitaemia that result in higher gametocytaemia a few days later. The rate of commitment of asexually replicating parasites to sexual development is another factor that influences gametocyte levels in malaria infections. Adults, who on average carry lower asexual stage parasite densities, have a higher sexual to asexual density ratio [43]. This could be related to an unequal increase in clearance rates of asexual and sexual parasites with age, or potentially to changes in commitment to gametocytogenesis [43]. Consistent with the latter, parasite investment in transmission stages has been shown to vary in areas with different transmission levels, being higher in settings with lower endemicity. Recent data suggest that parasite variations in commitment to gametocytes are epigenetically imprinted and higher in parasites in lower endemicity settings [44].

As articulated above, the importance of asymptomatic infections for malaria transmission does not lie in their average sexual stage parasite densities but in the durations of gametocyte carriage and infectiousness over time. A mathematical model [45] fitted to both asexual parasite and gametocyte malariotherapy data estimated infectivity over the course of an infection based on gametocyte density data. This analysis concluded that the majority of infectivity was usually concentrated early in infection, although some patients were significantly infectious later on. However, in this model, it was assumed relatively low infectivity of low gametocyte densities compared with other analyses [46]. While these data are extremely detailed, it is not known whether these dynamics are similar to those in naturally infected individuals who have immunity. Furthermore, specific *P. falciparum* strains were selected for malariotherapy because they were 'benign' and may not exhibit the same behaviour in terms of parasite multiplication rates and gametocyte commitment as parasites in endemic areas.

Although asymptomatic infections do not prompt treatment-seeking behaviour, during community mass treatment campaigns that involve treatment regardless of symptomatology (e.g., mass drug administration (MDA) or mass screening and treatment), these infections are cleared with antimalarials. In a meta-analysis of trials with gametocyte density data [47], the combinations artesunate-mefloquine and artemether-lumefantrine were more effective in preventing the appearance of gametocytes and in clearing existing sexual stage parasites compared to dihydroartemisinin-piperaquine. The choice of drugs to be used during control interventions thus may be important to limit residual transmission from these infections. In Section 4, we discuss the impact of different interventions that target asymptomatic and symptomatic infections.

3.2. Underestimations of parasitaemia linked to sampling

Two variables linked to blood sampling for parasite detection can influence prevalence and density estimates: volume and timing. Even sensitive molecular assays will not detect low parasite densities in samples if nucleic acids are isolated from small blood volumes. High-volume PCR has been used in epidemiological studies in Southeast Asia to circumvent

this problem and less than 30% of all falciparum infections are estimated to be missed by this method [48]. The timing of blood sampling in parasitological surveys might also affect parasite detection and quantification because asexual falciparum parasites do not circulate continuously; sequestration of falciparum schizonts starts 12-18 hours after merozoite invasion and during this period they might not be detectable. An intensive longitudinal study in Tanzania showed that periodic changes in parasite densities are common. The periodicity of clone-specific detectability indicates that in natural infections, synchronised sequestration of clonal parasite populations occurs [49]. A study [50] that collected samples on two consecutive days found a prevalence disparity of approximately 25% between the two samples. Periodic changes in parasite levels could have a direct impact on the selection of diagnostics, for example by favouring assays that detect more persistent markers, such as HRP-2.

The detection of either asexual or sexual stage parasites is sufficient to establish the diagnosis of infection. Although gametocytes are not known to periodically sequester, there is evidence of periodic variation in gametocyte levels [51] in peripheral blood. For several decades now [52], accumulation of mature gametocytes in the skin [53] has been hypothesised as a possible mechanism of transmission enhancement. If confirmed, this would imply that subpatent gametocytaemias in peripheral blood might be associated with higher-than-expected infectivity.

4. Contribution of low-density asymptomatic infections to transmission

In the previous sections, we discussed factors influencing the duration and average density of individual infections. In this section, our goal is to understand the significance and contribution of low-density asymptomatic infections to local transmission. This question is particularly important in areas where control efforts have pushed transmission towards near elimination levels – in this case it has been hypothesised that chronic low density asymptomatic infections could maintain local transmission.

4.1. Should we detect and treat low-density asymptomatic infections?

Since identifying the reservoir of low-density infections, there has been interest in developing more sensitive rapid diagnostics in order to detect and treat these infections. However, the benefit of treating such infections, both at the individual level and in terms of preventing onward transmission to others, remains unclear. The impact of treating a low-density infection depends not only on its current infectiousness to mosquitoes, but the future course of infection and infectiousness that is prevented (**Figures 1** and **2**). If low-density infections most commonly represent the tail end of an infection, which will clear rapidly without treatment, then the benefit of treatment would be small (**Figure 2**, yellow bar). However, if such infections commonly become chronic and lead to future periods of higher parasite densities, infectiousness, and possibly also symptoms, the benefit of treating such infections would be greater (**Figure 2**, green and light blue bars). Consistent with this second scenario, longitudinal data

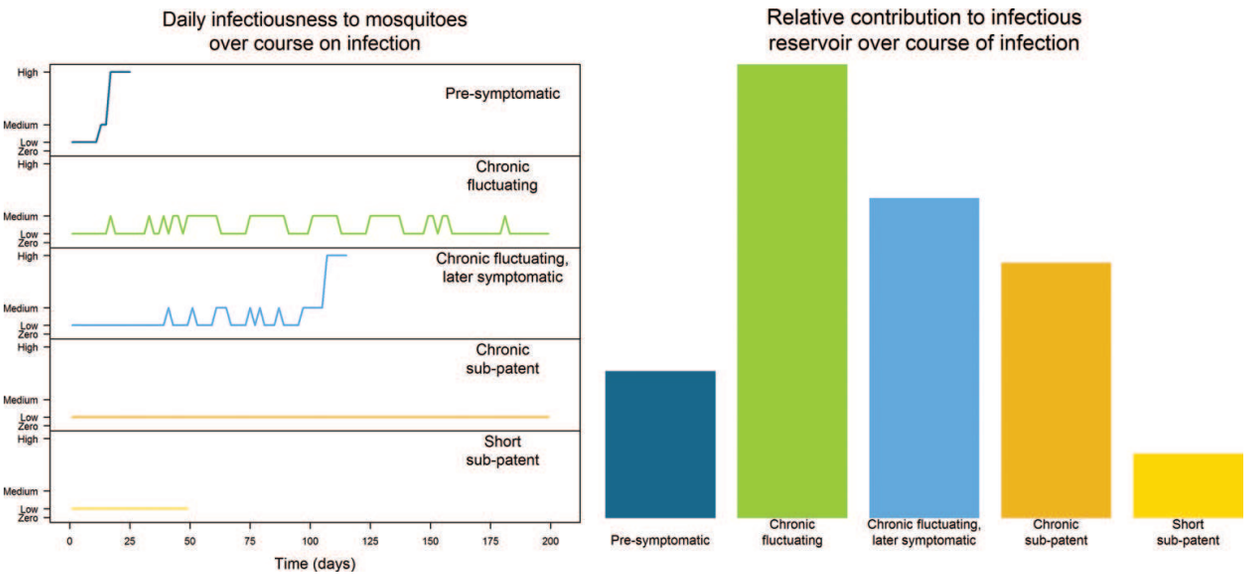


Figure 2. Estimated infectiousness to mosquitoes over course of infection and cumulative relative contribution to onwards infectiousness for each type of infection. The infectiousness of each parasite density trajectory from **Figure 1** is estimated by assuming that individuals with very high parasite densities (associated with being febrile) are three times as infectious as individuals with microscopy-detectable asymptomatic infection, who are then in turn three times as infectious as individuals with sub-microscopic asymptomatic infection [32, 56]. The cumulative infectivity of an individual is simply the area under the infectiousness curve (left panel). This area under the curve of each type of infection is compared in the right panel.

from Vietnam suggest that chronic sub-patent infections can lead to high parasitaemias, 5–6 orders of magnitude higher [11].

The relative proportions of low density infections which go on to rapidly clear *versus* those which become higher density infections are unknown and likely depends on many of the factors highlighted in Sections 2 and 3, such as age, immunity and host genetics. Studying variations in detectability over the course of a single naturally acquired infection is difficult for a few reasons: (i) super- and co-infections: in high transmission settings, most individuals are infected with more than one parasite clone [54] and standard techniques do not indicate the density of each parasite genotype (therefore the density of older *versus* newer infections cannot be distinguished); (ii) even using molecular methods, parasite densities often fluctuate below detection limits before the end of an infection and it is difficult to distinguish this from clearance of infection; (iii) long follow up is needed: even in endemic areas where individuals have immunity, specific parasite genotypes have been shown to persist for more than 6 months [55]. Here, we use a simple modelling framework to explore how the duration and infectiousness of an infection affect the impact of different intervention strategies.

4.2. Model framework

Four archetypal parasite density trajectories are identified from the malaria therapy data [57, 58] to represent broadly four potential outcomes of a new infection (**Figure 3**): (1) initially symptomatic before becoming asymptomatic and fluctuating between patent and sub-patent levels for a long time (~300 days); (2) initially symptomatic before becoming asymptomatic and fluctuating

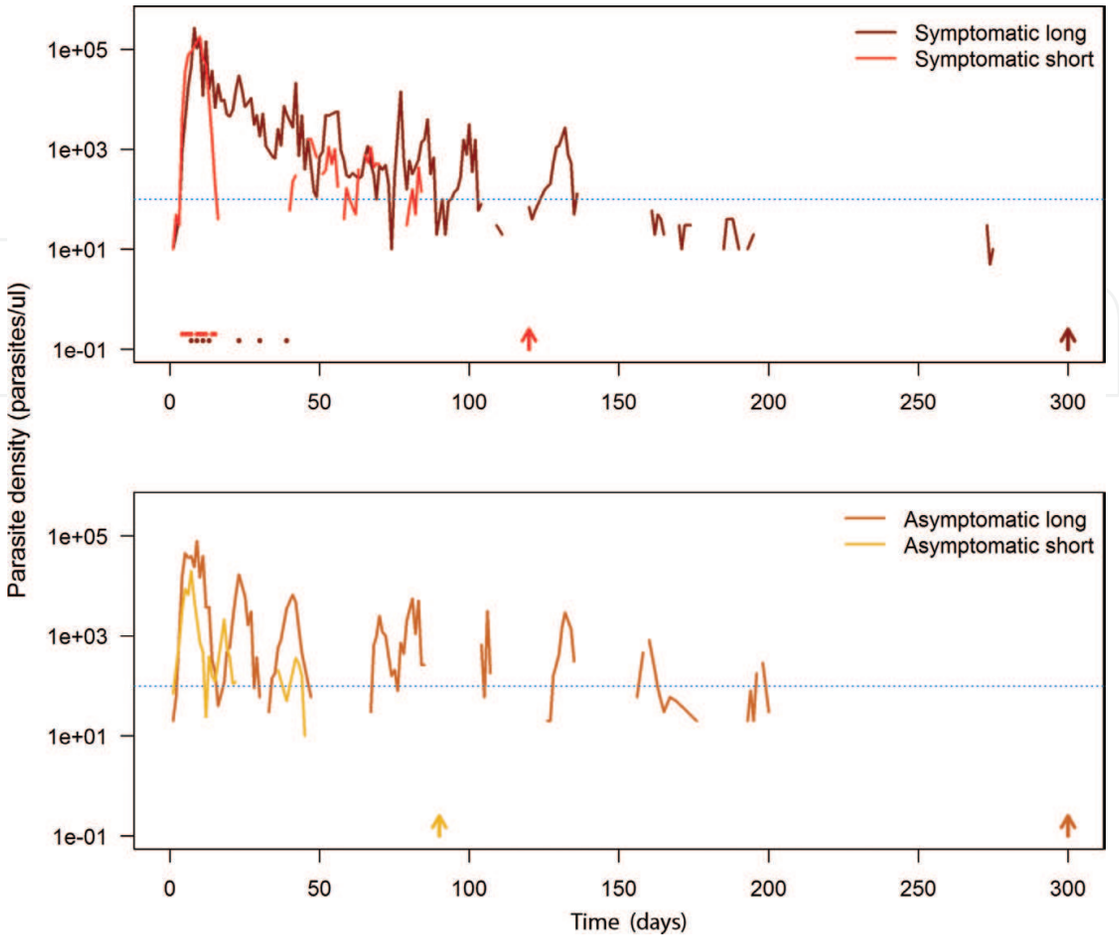


Figure 3. Parasite density trajectories from four infected individuals. The arrows represent the estimated time to clear infection (assuming a period of sub-patent infection after the last patent day of infection). The upper panel shows two symptomatic patients (red points indicate the days on which the patients were febrile) and the lower panel shows asymptomatic patients. The horizontal dotted line indicates the limit of detection of field microscopy (100 parasites/μl).

between patent and sub-patent levels for a short time (~120 days); (3) always asymptomatic and fluctuating between patent and sub-patent densities for a long time (~300 days); and (4) always asymptomatic and fluctuating between patent and sub-patent for a short time (~90 days). Note how these relate to the hypothesised profiles in **Figure 1**.

An age-structured population of individuals is simulated whereby individuals have a daily probability of acquiring a new infection. Upon being infected, an individual's probability of developing symptoms is based on their age and the intensity of transmission (fitted estimates taken from [56]) (**Table 1**). In a single simulation, infections are assumed to be either all long (300 days) or all short (120 or 90 days). Infected individuals will follow one of the parasite density trajectories shown in **Figure 3** unless they are treated or re-infected. Febrile individuals have a 50% probability of receiving treatment. Treated individuals are assumed to clear their asexual parasites after being febrile for 3 days, they then become non-infectious after 6 days. These individuals are also assumed to be protected from reinfection for 14 days after treatment.

The model is simulated with either high transmission (20% slide prevalence) or low transmission (5% slide prevalence) and the daily probability of infection is fitted to achieve these prevalence levels. Infected individuals can be reinfected (unless they received treatment in the

	Age range (in years)		
	0–5	**5–15**	**15+**
High transmission (20% slide prevalence)	66%	52%	38%
Low transmission (5% slide prevalence)	78%	70%	59%

Table 1. Probability of developing symptoms upon being successfully inoculated (estimates from [56]).

last 14 days) at any time and will start at the beginning of a new parasite density trajectory selected based on their age-specific probability of developing symptoms. The impact of two interventions is simulated: increasing treatment coverage among febrile individuals to 90% or delivering a single round of MDA to a random 80% of the population. The effect of each intervention is assessed by calculating the percentage reduction in the combined onwards infectiousness of the whole population in the following year, which depends on whether they are in a patent and symptomatic, patent and asymptomatic or sub-patent state. Parasite density is translated to infectiousness according to assumptions described in **Figure 2**. After an intervention the infection risk is reduced proportionally with the reduction in the proportion of the population that are infected to account for the population-level impact of these interventions on transmission.

MDA is predicted to be more effective at reducing the infectious reservoir than increasing treatment coverage among febrile individuals in low transmission settings with both short and long infection durations and high transmission settings with long infection durations only (**Figure 4**). In these scenarios the rebound of infection is slow, meaning over the course of a year, MDA prevents a higher number of infected/infectious days than increasing treatment coverage of febrile individuals. In high transmission settings with a short duration of infection, a higher force of infection is needed to achieve a given prevalence. Therefore, the effect of any intervention is reduced because the population become reinfected quicker. In this scenario, increasing treatment coverage is more effective because it is a sustained intervention. It is important to note that the outcome metric considered here is the reduction in the infectious reservoir—increasing treatment coverage is likely to always have the greatest impact on reducing malaria morbidity and mortality in all transmission scenarios. The model simply illustrates how our uncertainties about the duration of untreated infection affect estimates of intervention impact.

5. Conclusions

Since asymptomatically infected individuals do not actively seek antimalarial treatment, their infections may last longer than symptomatic episodes. In this chapter, we discussed human and parasite factors that influence the dynamics of parasitaemia and the duration of gametocyte circulation in these infections. These factors result in a range of infection profiles, the relative combinations of which in a population will define not only the composition of the infectious reservoir but the likelihood of success of intervention measures. For example, our calculations suggest that MDA is most effective if infections have long durations. In a high transmission setting, MDA might have been expected to be more effective than increasing

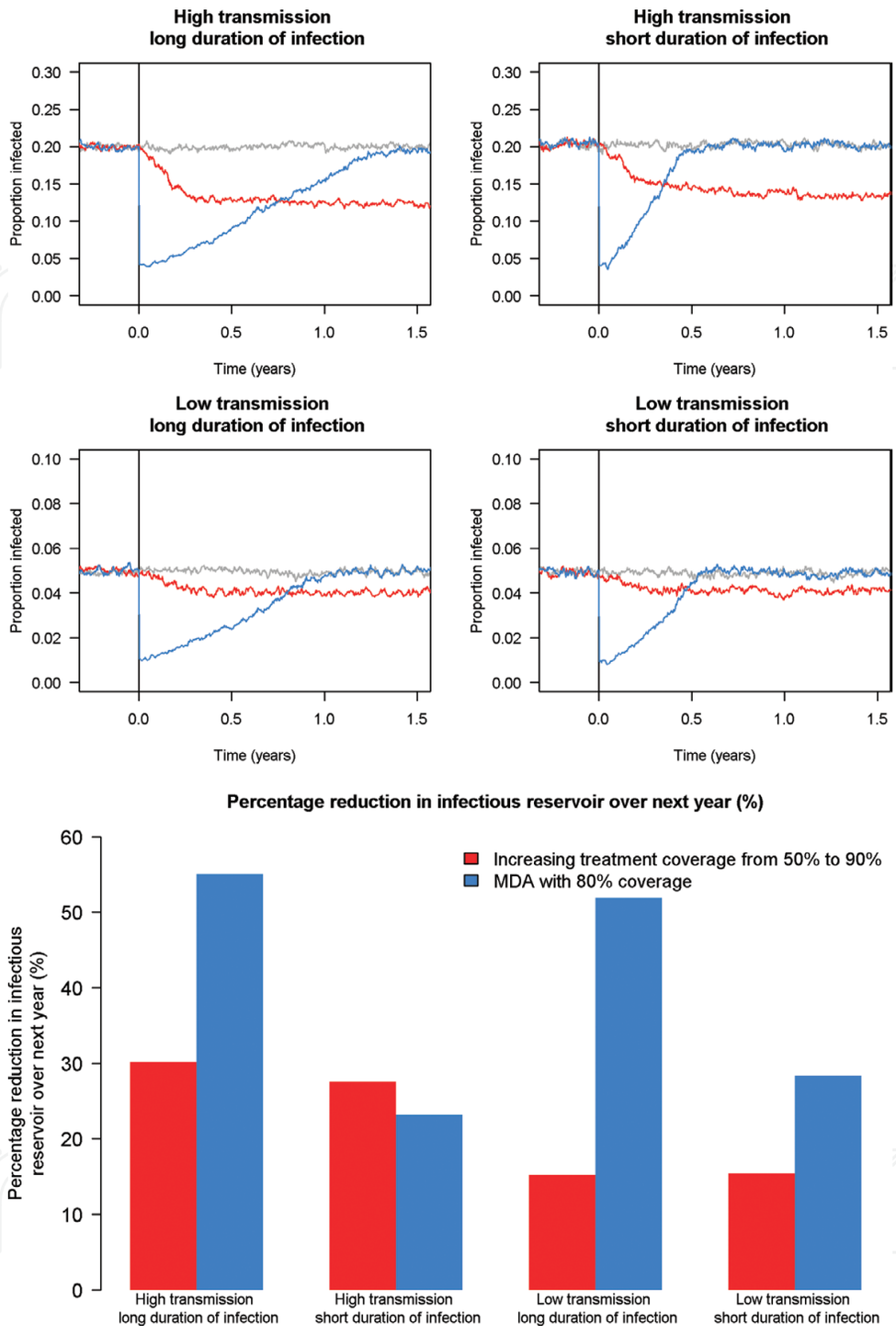


Figure 4. Simulated impact of increasing treatment coverage or mass drug administration (MDA) on the proportion of mosquitoes infected by a population: influence of transmission setting and infection duration. The grey lines represent continuing 50% treatment coverage and no MDA, and the blue and red lines as shown in the legend.

treatment coverage, because higher immunity reduces the probability of developing symptoms and the proportion of infections getting treated. However, when transmission is high, the reduction in prevalence after an MDA is temporary, due to the drug half-life and imperfect coverage levels, and individuals are likely to become reinfected quickly, therefore in the

absence of repeated rounds of MDA, increasing treatment coverage may in fact be more effective in the long term (**Figure 4**). However, the model assumes no seasonality, when in reality many malaria endemic regions transmission is highly seasonal; this could underestimate the impact of MDA. As discussed above, seasonal changes in infection duration represent another aspect of the epidemiology of asymptomatic infections that could be explored to target interventions. Indeed, where transmission is seasonal, infections persisting during the dry season correspond to long-term asymptomatic carriage since incidence of new infections is thought to be negligible. This means that during this period, infections are likely to be missed by passive surveillance, while active approaches, such as MDA, might be more efficacious.

Determining the optimal control strategy, and moreover, whether asymptomatic/sub-patent infections actually need to be identified and treated, will require careful analysis of local epidemiological data. The three key metrics that need to be determined are: (1) the proportion of individuals that develop symptoms and seek treatment, (2) the distribution of durations of asymptomatic infections, and (3) the relative infectivity of different infections. These factors are in turn driven by the complex interplay of host immunological factors, such as strain-specific immunity, intrinsic parasite growth factors and population characteristics (e.g. prevalence of HbAA *versus* HbAS, variation in demographic risk within a community). The relative high prevalence of asymptomatic and low-density infections in areas with low transmission and high treatment coverage might indicate that either these infections are contributing towards transmission and enabling malaria to persist or that they reflect the tail end of infections with transmission maintained by the few highly infectious symptomatic cases. This will vary in different settings and whilst the rapid identification and treatment of symptomatic malaria infections remains key to all control approaches, a better understanding of the nature of asymptomatic infections will determine if and what additional measures are required for malaria elimination.

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List of abbreviations

HbAA	haemoglobin A (homozygous)
HbAS	haemoglobin AS (heterozygous)
HbC	haemoglobin C
HbS	haemoglobin S

HRP-2	histidine-rich protein 2
MDA	mass drug administration
msp-2	merozoite surface protein 2
NAAT	nucleic acid amplification techniques
PCR	polymerase chain reaction
RDT	rapid diagnostic test
RNA	ribonucleic acid

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