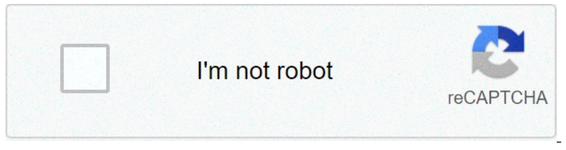

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Simple life cycle of plasmodium

Browse posted on 18.06.2015, 03:56 by Sandra K. Nilsson, Lauren M. Childs, Caroline Buckee, Matthias MartiThe malaria parasite is transmitted to the human host when an infected female Anopheles mosquito takes a blood meal and simultaneously injects a small number of sporozoites into the skin. After reaching the liver, the sporozoites invade hepatocytes in which they develop into a liver schizont and replicate asexually. After about seven days of liver stage development, each infected hepatocyte releases up to 40,000 merozoites that enter the peripheral blood stream. Once in the blood stream, merozoites quickly invade circulating red blood cells (RBCs), thereby initiating the repeated asexual replication cycle. Over the course of 48 hours, the parasite progresses through the ring and the trophozoite stages before finally replicating into 8–32 daughter merozoites at the schizont stage (schizogony). At this point, the parasitized RBC (pRBC) ruptures and releases merozoites into circulation, commencing another round of asexual replication. Mature asexual stages that display increased stiffness, trophozoites and schizonts, adhere to the vasculature in various organs, which allows them to avoid splenic clearance. During each cycle, a small subset of parasites divert from asexual replication and instead produce sexual progeny that differentiate the following cycle into male and female sexual forms, known as gametocytes. A subset of parasites (see possible scenarios in Fig 4) leave the peripheral circulation and enter the extravascular space of the bone marrow, where gametocytes mature and progress through stages I–V over the course of eight to ten days (gametocytogenesis). Although evidence suggests that the bone marrow is the primary location of gametocyte maturation, some immature gametocytes have been observed elsewhere in the human body, such as in the spleen. By stage V, male and female gametocytes re-enter peripheral circulation, in which they become competent for infection to mosquitoes. Once ingested by a mosquito, male and female gametocytes rapidly mature into gametes (gametogenesis). Within the midgut, the male gametocyte divides into up to eight flagellated microgametes (exflagellation), whereas the female gametocyte develops into a single macrogamete. Fertilization of a macrogamete by a microgamete results in the formation of a zygote, which undergoes meiosis and develops into an invasive ookinete that penetrates the mosquito gut wall. The ookinete forms an oocyst within which the parasite asexually replicates, forming several thousand sporozoites (sporogony). Upon oocyst rupture, these sporozoites migrate to the salivary glands, where they can be transmitted back to the human host during a blood meal. Asexual parasites (in RBCs) are represented in pale yellow, sexual parasites in green.figshare. credit for all your research. The natural history of malaria involves cyclical infection of humans and female Anopheles mosquitoes. In humans, the parasites grow and multiply first in the liver cells and then in the red cells of the blood. In the blood, successive broods of parasites grow inside the red cells and destroy them, releasing daughter parasites (“merozoites”) that continue the cycle by invading other red cells. The blood stage parasites are those that cause the symptoms of malaria. When certain forms of blood stage parasites (gametocytes, which occur in male and female forms) are ingested during blood feeding by a female Anopheles mosquito, they mate in the gut of the mosquito and begin a cycle of growth and multiplication in the mosquito. After 10-18 days, a form of the parasite called a sporozoite migrates to the mosquito’s salivary glands. When the Anopheles mosquito takes a blood meal on another human, anticoagulant saliva is injected together with the sporozoites, which migrate to the liver, thereby beginning a new cycle. Thus the infected mosquito carries the disease from one human to another (acting as a “vector”), while infected humans transmit the parasite to the mosquito, In contrast to the human host, the mosquito vector does not suffer from the presence of the parasites. The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female Anopheles mosquito inoculates sporozoites into the human host . Sporozoites infect liver cells and mature into schizonts , which rupture and release merozoites . (Of note, in P. vivax and P. ovale a dormant stage [hypnozoites] can persist in the liver (if untreated) and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). Merozoites infect red blood cells . The ring stage trophozoites mature into schizonts, which rupture releasing merozoites . Some parasites differentiate into sexual erythrocytic stages (gametocytes) . Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal . The parasites’ multiplication in the mosquito is known as the sporogonic cycle . While in the mosquito’s stomach, the microgametes penetrate the macrogametes generating zygotes . The zygotes in turn become motile and elongated (ookinetes) which invade the midgut wall of the mosquito where they develop into oocysts . The oocysts grow, rupture, and release sporozoites, which make their way to the mosquito’s salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle. More on: Anopheles Mosquitoes More on: Malaria Parasites Human Factors And Malaria Biologic characteristics and behavioral traits can influence an individual’s risk of developing malaria and, on a larger scale, the intensity of transmission in a population. More on: Human Factors and Malaria For malaria transmission to occur, conditions must be such so that all three components of the malaria life cycle are present: Anopheles mosquitoes, which able to feed on humans humans, and in which the parasites can complete the “invertebrate host” half of their life cycle Humans. who can be bitten by Anopheles mosquitoes, and in whom the parasites can complete the “vertebrate host” half of their life cycle Malaria parasites. ecology.html-Untitled_f63c1 In rare cases malaria parasites can be transmitted from one person to another without requiring passage through a mosquito (from mother to child in "congenital malaria" or through transfusion, organ transplantation, or shared needles.) Climate Climate is a key determinant of both the geographic distribution and the seasonality of malaria. Without sufficient rainfall, mosquitoes cannot survive, and if not sufficiently warm, parasites cannot survive in the mosquito. Anopheles lay their eggs in a variety of fresh or brackish bodies of water, with different species having different preferences. Eggs hatch within a few days, with resulting larvae spending 9-12 days to develop into adults in tropical areas. If larval habitats dry up before the process is completed, the larvae die; if rains are excessive, they may be flushed and destroyed. Life is precarious for mosquito larvae, with most perishing before becoming adults. Life is usually short for adult mosquitoes as well, with temperature and humidity affecting longevity. Only older females can transmit malaria, as they must live long enough for sporozoites to develop and move to the salivary glands. This process takes a minimum of nine days when temperatures are warm (30°C or 86°F) and will take much longer at cooler temperatures. If temperatures are too cool (15°C or 59°F for Plasmodium vivax, 20°C or 68°F for P. falciparum), development cannot be completed and malaria cannot be transmitted. Thus, malaria transmission is much more intense in warm and humid areas, with transmission possible in temperate areas only during summer months. In warm climates people are more likely to sleep unprotected outdoors, thereby increasing exposure to night-biting Anopheles mosquitoes. During harvest seasons, agricultural workers might sleep in the fields or nearby locales, without protection against mosquito bites. Anopheles Mosquitoes The types (species) of Anopheles present in an area at a given time will influence the intensity of malaria transmission. Not all Anopheles are equally efficient vectors for transmitting malaria from one person to another. Those species that are most prone to bite humans are the most dangerous, as bites inflicted on animals that cannot be infected with human malaria break the chain of transmission. If the mosquito regularly bites humans, the chain of transmission is unbroken and more people will become infected. Some species are biologically unable to sustain development of human malaria parasites, while others are readily infected and produce large numbers of sporozoites (the parasite stage that is infective to humans). Many of the most dangerous species bite human indoors. For these species insecticide treated mosquito nets and indoor residual spray (whereby the inner walls of dwellings are coated with a long-lasting insecticide) are effective interventions. Both of these interventions require attention to insecticide resistance, which will evolve if the same insecticide is used continuously in the same area. More on: Anopheles Mosquitoes Humans Biologic characteristics (inborn and acquired) and behavioral traits can influence an individual’s malaria risk and, on a larger scale, the overall malaria ecology. More on: Human Factors And Malaria Parasites Characteristics of the malaria parasite can influence the occurrence of malaria and its impact on human populations, for example: Areas where P. falciparum predominates (such as Africa south of the Sahara) will suffer more disease and death than areas where other species, which tend to cause less severe manifestations, predominate P. vivax and P. ovale have stages (“hypnozoites”) that can remain dormant in the liver cells for extended periods of time (months to years) before reactivating and invading the blood. Such relapses can result in resumption of transmission after apparently successful control efforts, or can introduce malaria in an area that was malaria-free P. falciparum (and to a lesser extent P. vivax) have developed strains that are resistant to antimalarial drugs. Such strains are not uniformly distributed. Constant monitoring of the susceptibility of these two parasite species to drugs used locally is critical to ensure effective treatment and successful control efforts. Travelers to malaria-risk areas should use for prevention only those drugs that will be protective in the areas to be visited. Plasmodium falciparum predominates in Africa south of the Sahara, one reason why malaria is so severe in that area. Animal Reservoirs A certain species of malaria called P. knowlesi has recently been recognized to be a cause of significant numbers of human infections. P. knowlesi is a species that naturally infects macaques living in Southeast Asia. Humans living in close proximity to populations of these macaques may be at risk of infection with this zoonotic parasite. Areas Where Malaria Is No Longer Endemic Malaria transmission has been eliminated in many countries of the world, including the United States. However, in many of these countries (including the United States) Anopheles mosquitoes are still present. Also, cases of malaria still occur in non-endemic countries, mostly in returning travelers or immigrants (“imported malaria”). Thus the potential for reintroduction of active transmission of malaria exists in many non-endemic parts of the world. All patients must be diagnosed and treated promptly for their own benefit but also to prevent the reintroduction of malaria. Biologic characteristics present from birth can protect against certain types of malaria. Two genetic factors, both associated with human red blood cells, have been shown to be epidemiologically important. Persons who have the sickle cell trait (heterozygotes for the abnormal hemoglobin gene HbS) are relatively protected against P. falciparum malaria and thus enjoy a biologic advantage. Because P. falciparum malaria has been a leading cause of death in Africa since remote times, the sickle cell trait is now more frequently found in Africa and in persons of African ancestry than in other population groups. In general, the prevalence of hemoglobin-related disorders and other blood cell dyscrasias, such as Hemoglobin C, the thalassemias and G6PD deficiency, are more prevalent in malaria endemic areas and are thought to provide protection from malarial disease. Persons who are negative for the Duffy blood group have red blood cells that are resistant to infection by P. vivax. Since the majority of Africans are Duffy negative, P. vivax is rare in Africa south of the Sahara, especially West Africa. In that area, the niche of P. vivax has been taken over by P. ovale, a very similar parasite that does infect Duffy-negative persons. Other genetic factors related to red blood cells also influence malaria, but to a lesser extent. Various genetic determinants (such as the “HLA complex,” which plays a role in control of immune responses) may equally influence an individual’s risk of developing severe malaria. More on: Sickle Cell and Malaria Acquired Immunity Acquired immunity greatly influences how malaria affects an individual and a community. After repeated attacks of malaria a person may develop a partially protective immunity. Such “semi-immune” persons often can still be infected by malaria parasites but may not develop severe disease, and, in fact, frequently lack any typical malaria symptoms. In areas with high P. falciparum transmission (most of Africa south of the Sahara), newborns will be protected during the first few months of life presumably by maternal antibodies transferred to them through the placenta. As these antibodies decrease with time, these young children become vulnerable to disease and death by malaria. If they survive repeated infections to an older age (2-5 years) they will have reached a protective semi-immune status. Thus in high transmission areas, young children are a major risk group and are targeted preferentially by malaria control interventions. In areas with lower transmission (such as Asia and Latin America), infections are less frequent and a larger proportion of the older children and adults have no protective immunity. In such areas, malaria disease can be found in all age groups, and epidemics can occur. Anemia in young children in Asembo Bay, a highly endemic area in western Kenya. Anemia occurs most between the ages of 6 and 24 months. After 24 months, it decreases because the children have built up their acquired immunity against malaria (and its consequence, anemia). Mother and her newborn in Jabalpur Hospital, State of Madhya Pradesh, India. The mother had malaria, with infection of the placenta. Pregnancy and Malaria Pregnancy decreases immunity against many infectious diseases. Women who have developed protective immunity against P. falciparum tend to lose this protection when they become pregnant (especially during the first and second pregnancies). Malaria during pregnancy is harmful not only to the mothers but also to the unborn children. The latter are at greater risk of being delivered prematurely or with low birth weight, with consequently decreased chances of survival during the early months of life. For this reason pregnant women are also targeted (in addition to young children) for protection by malaria control programs in endemic countries. More on: Malaria During Pregnancy Behavioral Factors Human behavior, often dictated by social and economic reasons, can influence the risk of malaria for individuals and communities. For example: Poor rural populations in malaria-endemic areas often cannot afford the housing and bed nets that would protect them from exposure to mosquitoes. These persons often lack the knowledge to recognize malaria and to treat it promptly and correctly. Often, cultural beliefs result in use of traditional, ineffective methods of treatment. Travelers from non-endemic areas may choose not to use insect repellent or medicines to prevent malaria. Reasons may include cost, inconvenience, or a lack of knowledge. Human activities can create breeding sites for larvae (standing water in irrigation ditches, burrow pits) Agricultural work such as harvesting (also influenced by climate) may force increased nighttime exposure to mosquito bites Raising domestic animals near the household may provide alternate sources of blood meals for Anopheles mosquitoes and thus decrease human exposure War, migrations (voluntary or forced) and tourism may expose non-immune individuals to an environment with high malaria transmission. Human behavior in endemic countries also determines in part how successful malaria control activities will be in their efforts to decrease transmission. The governments of malaria-endemic countries often lack financial resources. As a consequence, health workers in the public sector are often underpaid and overworked. They lack equipment, drugs, training, and supervision. The local populations are aware of such situations when they occur, and cease relying on the public sector health facilities. Conversely, the private sector suffers from its own problems. Regulatory measures often do not exist or are not enforced. This encourages private consultations by unlicensed, costly health providers, and the anarchic prescription and sale of drugs (some of which are counterfeit products). Correcting this situation is a tremendous challenge that must be addressed if malaria control and ultimately elimination is to be successful. The sickle cell gene is caused by a single amino acid mutation (valine instead of glutamate at the 6th position) in the beta chain of the hemoglobin gene. Inheritance of this mutated gene from both parents leads to sickle cell disease and people with this disease have shorter life expectancy. On the contrary, individuals who are carriers for the sickle cell disease (with one sickle gene and one normal hemoglobin gene, also known as sickle cell trait) have some protective advantage against malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas. CDC’s birth cohort studies (Asembo Bay Cohort Project in western Kenya) conducted in collaboration with the Kenya Medical Research Institute allowed an investigation into this issue. It was found that that the sickle cell trait provides 60% protection against overall mortality. Most of this protection occurs between 2-16 months of life, before the onset of clinical immunity in areas with intense transmission of malaria. Graph of survival curves (“survival function estimates”) of children without any sickle cell genes (HbAA), children with sickle cell trait (HbAS), and children with sickle cell disease (HbSS). Those who had the sickle cell trait (HbAS) had a slight survival advantage over those without any sickle cell genes (HbAA), with children with sickle cell disease (HbSS) faring the worst. Reference: Protective Effects of the Sickle Cell Gene Against Malaria Morbidity and Mortality. Aidoo M, Terlouw DJ, Kolczak MS, McElroy PD, ter Kuile FO, Kariuki S, Nahlen BL, Lal AA, Udhayakumar V. Lancet 2002; 359:1311-1312. Malaria is transmitted to humans by female mosquitoes of the genus Anopheles. Female mosquitoes take blood meals for egg production, and these blood meals are the link between the human and the mosquito hosts in the parasite life cycle. The successful development of the malaria parasite in the mosquito (from the “gametocyte” stage to the “sporozoite” stage) depends on several factors. The most important is ambient temperature and humidity (higher temperatures accelerate the parasite growth in the mosquito) and whether the Anopheles survives long enough to allow the parasite to complete its cycle in the mosquito host (“sporogonic” or “extrinsic” cycle, duration 9 to 18 days). In contrast to the human host, the mosquito host does not suffer noticeably from the presence of the parasites. Diagram of Adult Female Mosquito Map of the world showing the distribution of predominant malaria vectors Anopheles freeborni mosquito pumping blood Larger Picture Sequential images of the mosquito taking its blood meal There are approximately 3,500 species of mosquitoes grouped into 41 genera. Human malaria is transmitted only by females of the genus Anopheles. Of the approximately 430 Anopheles species, only 30-40 transmit malaria (i.e., are “vectors”) in nature. The rest either bite humans infrequently or cannot sustain development of malaria parasites. Geographic Distribution Anophelines are found worldwide except Antarctica. Malaria is transmitted by different Anopheles species in different geographic regions. Within geographic regions, different environments support a different species. Anophelines that can transmit malaria are found not only in malaria-endemic areas, but also in areas where malaria has been eliminated. These areas are thus at risk of re-introduction of the disease. Life Stages Like all mosquitoes, anopheles mosquitoes go through four stages in their life cycle: egg, larva, pupa, and adult. The first three stages are aquatic and last 7-14 days, depending on the species and the ambient temperature. The biting female Anopheles mosquito may carry malaria. Male mosquitoes do not bite so cannot transmit malaria or other diseases. The adult females are generally short-lived, with only a small proportion living long enough (more than 10 days in tropical regions) to transmit malaria. Adult females lay 50-200 eggs per oviposition. Eggs are laid singly directly on water and are unique in having floats on either side. Eggs are not resistant to drying and hatch within 2-3 days, although hatching may take up to 2-3 weeks in colder climates. Larvae Mosquito larvae have a well-developed head with mouth brushes used for feeding, a large thorax, and a segmented abdomen. They have no legs. In contrast to other mosquitoes, Anopheles larvae lack a respiratory siphon and for this reason position themselves so that their body is parallel to the surface of the water. Top: Anopheles Egg; note the lateral floats. Bottom: Anopheles eggs are laid singly. Larvae breathe through spiracles located on the 8th abdominal segment and therefore must come to the surface frequently. The larvae spend most of their time feeding on algae, bacteria, and other microorganisms in the surface microlayer. They do so by rotating their head 180 degrees and feeding from below the microlayer. Larvae dive below the surface only when disturbed. Larvae swim either by jerky movements of the entire body or through propulsion with the mouth brushes. Larvae develop through 4 stages, or instars, after which they metamorphose into pupae. At the end of each instar, the larvae molt, shedding their exoskeleton, or skin, to allow for further growth. Anopheles Larva. Note the position, parallel to the water surface. The larvae occur in a wide range of habitats but most species prefer clean, unpolluted water. Larvae of Anopheles mosquitoes have been found in fresh- or salt-water marshes, mangrove swamps, rice fields, grassy ditches, the edges of streams and rivers, and small, temporary rain pools. Many species prefer habitats with vegetation. Others prefer habitats that have none. Some breed in open, sun-lit pools while others are found only in shaded breeding sites in forests. A few species breed in tree holes or the leaf axils of some plants. The pupa is comma-shaped when viewed from the side. This is a transitional stage between larva and adult. The pupae does not feed, but undergoes radical metamorphosis. The head and thorax are merged into a cephalothorax with the abdomen curving around underneath. As with the larvae, pupae must come to the surface frequently to breathe, which they do through a pair of respiratory trumpets on the cephalothorax. After a few days as a pupa, the dorsal surface of the cephalothorax splits and the adult mosquito emerges onto the surface of the water. The duration from egg to adult varies considerably among species and is strongly influenced by ambient temperature. Mosquitoes can develop from egg to adult in as little as 7 days but usually take 10-14 days in tropical conditions. Anopheles Pupa Anopheles Adults. Note (bottom row) the typical resting position. Like all mosquitoes, adult anopheles have slender bodies with 3 sections: head, thorax and abdomen. The head is specialized for acquiring sensory information and for feeding. The head contains the eyes and a pair of long, many-segmented antennae. The antennae are important for detecting host odors as well as odors of aquatic larval habitats where females lay eggs. The head also has an elongate, forward-projecting proboscis used for feeding, and two sensory palps. The thorax is specialized for locomotion. Three pairs of legs and a single pair of wings are attached to the thorax. The abdomen is specialized for food digestion and egg development. This segmented body part expands considerably when a female takes a blood meal. The blood is digested over time serving as a source of protein for the production of eggs, which gradually fill the abdomen. Anopheles mosquitoes can be distinguished from other mosquitoes by the palps, which are as long as the proboscis, and by the presence of discrete blocks of black and white scales on the wings. Adult Anopheles can also be identified by their typical resting position: males and females rest with their abdomens sticking up in the air rather than parallel to the surface on which they are resting. Adult mosquitoes usually mate within a few days after emerging from the pupal stage. In some species, the males form large swarms, usually around dusk, and the females fly into the swarms to mate. The mating habitats of many species remain unknown. Males live for about a week, feeding on nectar and other sources of sugar. Females will also feed on sugar sources for energy but usually require a blood meal for the development of eggs. After obtaining a full blood meal, the female will rest for a few days while the blood is digested and eggs are developed. This process depends on the temperature but usually takes 2-3 days in tropical conditions. Once the eggs are fully developed, the female lays them then seeks blood to sustain another batch of eggs. The cycle repeats itself until the female dies. Females can survive up to a month (or longer in captivity) but most do not live longer than 1-2 weeks in nature. Their chances of survival depend on temperature and humidity, but also upon their ability to successfully obtain a blood meal while avoiding host defenses. Female Anopheles dirus feeding Understanding the biology and behavior of Anopheles mosquitoes can aid in designing appropriate control strategies. Factors that affect a mosquito’s ability to transmit malaria include its innate susceptibility to Plasmodium, its host choice, and its longevity. Long-lived species that prefer human blood and support parasite development are the most dangerous. Factors that should be taken into consideration when designing a control program include the susceptibility of malaria mosquitoes to insecticides and the preferred feeding and resting location of adult mosquitoes. More on: How to Reduce Malaria’s Impact Preferred Sources for Blood Meals One important behavioral factor is the degree to which an Anopheles species prefers to feed on humans (anthropophily) or animals such as cattle (zoophily). Anthrophilic Anopheles are more likely to transmit the malaria parasites from one person to another. Most Anopheles mosquitoes are not exclusively anthropophilic or zoophilic; many are opportunistic and feed upon whatever host is available. However, the primary malaria vectors in Africa, An. gambiae and An. funestus, are strongly anthropophilic and, consequently, are two of the most efficient malaria vectors in the world. Life Span Once ingested by a mosquito, malaria parasites must undergo development within the mosquito before they are infectious to humans. The time required for development in the mosquito (the extrinsic incubation period) takes 9 days or longer, depending on the parasite species and the temperature. If a mosquito does not survive longer than the extrinsic incubation period, then she will not be able to transmit any malaria parasites. It is not possible to measure directly the life span of mosquitoes in nature, but many studies have indirectly measured longevity by examination of their reproductive status or via marking, releasing, and recapturing adult mosquitoes. The majority of mosquitoes do not live long enough to transmit malaria, but some may live as long as three weeks in nature. Though evidence suggests that mortality rate increases with age, most workers estimate longevity in terms of the probability that a mosquito will live one day. Usually these estimates range from a low of 0.7 to a high of 0.9. If survivorship is 90% daily, then a substantial proportion of the population would live longer than 2 weeks and would be capable of transmitting malaria. Any control measure that reduces the average lifespan of the mosquito population will reduce transmission potential. Insecticides thus need not kill the mosquitoes outright, but may be effective by limiting their lifespan. Patterns of Feeding and Resting Most Anopheles mosquitoes are crepuscular (active at dusk or dawn) or nocturnal (active at night). Some Anopheles mosquitoes feed indoors (endophagic) while others feed outdoors (exophagic). After blood feeding, some Anopheles mosquitoes prefer to rest indoors (endophilic) while others prefer to rest outdoors (exophilic). Biting by nocturnal, endophagic Anopheles mosquitoes can be markedly reduced through the use of insecticide-treated bed nets (ITNs) or through improved housing construction to prevent mosquito entry (e.g., window screens). Endophilic mosquitoes are readily controlled by indoor spraying of residual insecticides. In contrast, exophagic/exophilic vectors are best controlled through source reduction (destruction of larval habitats). Insecticide Resistance Insecticide-based control measures (e.g., indoor spraying with insecticides, ITNs) are the principal way to kill mosquitoes that bite indoors. However, after prolonged exposure to an insecticide over several generations, mosquitoes, like other insects, may develop resistance, a capacity to survive contact with an insecticide. Since mosquitoes can have many generations per year, high levels of resistance can arise very quickly. Resistance of mosquitoes to some insecticides has been documented within a few years after the insecticides were introduced. There are over 125 mosquito species with documented resistance to one or more insecticides. The development of resistance to insecticides used for indoor residual spraying was a major impediment during the Global Malaria Eradication Campaign. Judicious use of insecticides for mosquito control can limit the development and spread of resistance, particularly via rotation of different classes of insecticides used for control. Monitoring of resistance is essential to alert control programs to switch to more effective insecticides. Susceptibility/Refractoriness Some Anopheles species are poor vectors of malaria, as the parasites do not develop well (or at all) within them. There is also variation within species. In the laboratory, it has been possible to select for strains of An. gambiae that are refractory to infection by malaria parasites. These refractory strains have an immune response that encapsulates and kills the parasites after they have invaded the mosquito’s stomach wall. Scientists are studying the genetic mechanism for this response. It is hoped that some day, genetically modified mosquitoes that are refractory to malaria can replace wild mosquitoes, thereby limiting or eliminating malaria transmission. Malaria parasites are micro-organisms that belong to the genus Plasmodium. There are more than 100 species of Plasmodium, which can infect many animal species such as reptiles, birds, and various mammals. Four species of Plasmodium have long been recognized to infect humans in nature. In addition there is one species that naturally infects macaques which has recently been recognized to be a cause of zoonotic malaria in humans. (There are some additional species which can, exceptionally or under experimental conditions, infect humans.) Ring-form trophozoites of P. falciparum in a thin blood smear. Ring-form trophozoites of P. vivax in a thin blood smear. Trophozoites of P. ovale in a thin blood smear. Band-form trophozoites of P. malariae in a thin blood smear. Schizont and ring-form trophozoite of P. knowlesi in a thin blood smear. (All photos courtesy of DPDx) The species infecting humans are the following: P. falciparum, which is found worldwide in tropical and subtropical areas, and especially in Africa where this species predominates. P. falciparum can cause severe malaria because it multiples rapidly in the blood, and can thus cause severe blood loss (anemia). In addition, the infected parasites can clog small blood vessels. When this occurs in the brain, cerebral malaria results, a complication that can be fatal. P. vivax, which is found mostly in Asia, Latin America, and in some parts of Africa. Because of the population densities especially in Asia it is probably the most prevalent human malaria parasite. P. vivax (as well as P. ovale) has dormant liver stages (“hypnozoites”) that can activate and invade the blood (“relapse”) several months or years after the infecting mosquito bite. P. ovale is found mostly in Africa (especially West Africa) and the islands of the western Pacific. It is biologically and morphologically very similar to P. vivax. However, differently from P. vivax, it can infect individuals who are negative for the Duffy blood group, which is the case for many residents of sub-Saharan Africa. This explains the greater prevalence of P. ovale (rather than P. vivax) in most of Africa. P. malariae, found worldwide, is the only human malaria parasite species that has a quartan cycle (three-day cycle). (The three other species have a tertian, two-day cycle.) If untreated, P. malariae causes a long-lasting, chronic infection that in some cases can last a lifetime. In some chronically infected patients P. malariae can cause serious complications such as the nephrotic syndrome. P. knowlesi is found throughout Southeast Asia as a natural pathogen of long-tailed and pig-tailed macaques. It has recently been shown to be a significant cause of zoonotic malaria in that region, particularly in Malaysia. P. knowlesi has a 24-hour replication cycle and so can rapidly progress from an uncomplicated to a severe infection; fatal cases have been reported.