life-threatening, particularly in young children *[254]*. Recurrent vivax malaria is an important impediment to human and economic development in affected populations. In areas where *P. falciparum* and *P. vivax* co-exist, intensive malaria control often has a greater effect on *P. falciparum*, as *P. vivax,* is more resilient to interventions.

Although *P. vivax* has been considered to be a benign form of malaria, it may sometimes cause severe disease *[255]*. The major complication is anaemia in young children. In Papua province, Indonesia *[255]*, and in Papua New Guinea *[256]*, where malaria transmission is intense, *P. vivax* is an important cause of malaria morbidity and mortality, particularly in young infants and children. Occasionally, older patients develop vital organ involvement similar to that in severe and complicated *P. falciparum* malaria *[257][258]*. During pregnancy, infection with *P. vivax*, as with *P. falciparum*, increases the risk for abortion and reduces birth weight *[259][207]*. In primigravidae, the reduction in birth weight is approximately two thirds that associated with *P. falciparum.* In one large series, this effect increased with successive pregnancies *[259]*.

P. knowlesi is a zoonosis that normally affects long- and pig-tailed macaque monkeys. It has a daily asexual cycle, resulting in a rapid replication rate and high parasitaemia. *P. knowlesi* may cause a fulminant disease similar to severe falciparum malaria (with the exception of coma, which does not occur) *[260][261]*. Co-infection with other species is common.

Diagnosis
Diagnosis of *P. vivax*, *P. ovale*, and *P. malariae* malaria is based on microscopy. *P. knowlesi* is frequently misdiagnosed under the microscope, as the young ring forms are similar to those of *P. falciparum*, the late trophozoites are similar to those of *P. malariae*, and parasite development is asynchronous. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of *P. vivax* malaria; however, they are relatively insensitive for detecting *P. malariae* and *P. ovale* parasitaemia. Rapid diagnostic antigen tests for human *Plasmodium* species show poor sensitivity for *P. knowlesi* infections in humans with low parasitaemia *[262]*.

Treatment
The objectives of treatment of vivax malaria are twofold: to cure the acute blood stage infection and to clear hypnozoites from the liver to prevent future relapses. This is known as “radical cure”.

In areas with chloroquine-sensitive *P. vivax*
For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. In the past, the initial 10 mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. As residual chloroquine suppresses the first relapse of tropical *P. vivax* (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.

ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT. The exception is artesunate + SP, where resistance significantly compromises its efficacy. Although good efficacy of artesunate + SP was reported in one study in Afghanistan, in several other areas (such as South-East Asia) *P. vivax* has become resistant to SP more rapidly than *P. falciparum.* The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. A similar temporal pattern of recurrence with each of the drugs is seen in the *P. vivax* infections that follow up to one third of acute falciparum malaria infections in South-East Asia.

In areas with chloroquine-resistant *P. vivax*
ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.

In the systematic review of ACTs for treating *P. vivax* malaria, dihydroartemisinin + piperaquine provided a longer prophylactic effect than ACTs with shorter half-lives (artemether + lumefantrine, artesunate + amodiaquine), with significantly fewer recurrent parasitaemias during 9 weeks of follow-up (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants). The half-life of mefloquine is similar to that of piperaquine, but use of dihydroartemisinin + piperaquine in *P. vivax* mono-infections has not been compared directly in trials with use of artesunate + mefloquine.

Uncomplicated *P. ovale*, *P. malariae* or *P. knowlesi* malaria
Resistance of *P. ovale, P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.