

## **Malaria vectors not only cause problems in rural endemic areas but also can bring malaria into the cities**

*Malaria vectors breeding and biting pattern determine where one gets malaria, but cases might occur in very unlikely places, and a migrating vector threatens African cities with *Pl. falciparum**

'Better to warn tourists about a real danger in the tropics, namely traffic accidents instead of malaria.' That provocative joke was voiced by a very respected Professor of Tropical Medicine from Liverpool, a guest at the Faculty of Tropical Medicine at the Mahidol University in Bangkok, Thailand, at the time of the Vietnam War. Nowadays, the professor's suggestion would be more than justified, at least as far as the malaria situation in Thailand is concerned. A study from the United Kingdom stated that the risk of UK travelers to Thailand to fetch malaria is one in 12.254. Another study in 2005 calculated the risk of getting malaria in Thailand to be one in 50.000 (1, 2). Between 2000 and 2005, the Faculty of Tropical Medicine hospital treated 21 tourists, from whom only 3 got malaria in Thailand (3). All in all, 13 death was due to malaria in Thailand in 2019, while 37 provinces of Thailand were malaria free. WHO selected the country as one of the few countries with the potential to eliminate malaria by 2025 (4).

### In commemoration of Khunying Tranakchit Harinasuta (1918 – 1999)

These remarkable accomplishments were attained despite multidrug-resistant malaria being present for decades. Among those making this possible, the Faculty of Tropical Medicine of the Mahidol University in Bangkok should be mentioned too, and here also Khunying Professor Tranakchit Harinasuta (1918 – 1999), that time the director of the hospital of the faculty, who was the first to report the appearance of chloroquine-resistant *Falciparum* malaria in Thailand (5).

### Malaria cases in Berlin, Germany

Despite the favorable developments, the country's malaria situation must still be monitored. In neighboring states, malaria still is quite present, and a rebound of the disease in Thailand cannot be excluded (6).

The disease even tends to appear in non-endemic areas. In 2019 nine confirmed cases acquired malaria within the European Union, namely in Greece, Spain, France, and Germany (7). A curious example of an unexpected appearance of malaria was observed in one of the districts of Berlin, the capital of Germany. However, the episode happened at the end of the second World War in 1946 (BE 2489). A prisoner of war (POW) camp with about 1.000 German soldiers was set up close to a lake in the North of the city during a hot summer month. The windows of the barracks were broken. The health condition of the prisoners was terrible, as were the hygienic conditions. The unwashed clothes stuck closely to the men's skin in the hot, humid weather. Dozens of soldiers were suffering day by day from fever attacks. Children and women suddenly started developing feverish conditions in the area surrounding the camp. Finally, the disease was recognized as being malaria caused by *Plasmodium vivax*. *Pl. vivax* seldomly is a deadly

infection but can trigger, even over the years, attacks of recurrent malaria fever. Among the detained soldiers were those who cached malaria while fighting in Southeast Europe and Africa. In the sweltering and humid climate, mosquitos around the lake and nearby rivers multiplied tremendously. Among them are also Anopheles mosquitos, able to transmit the disease not only within the camp but also to the population around the camp. About 300 persons were affected, but fortunately, nobody died. Finally, the epidemic was brought to an end by insect spraying (8).

#### How malaria cases in unlikely areas can happen

Cases occurring nowadays in non-endemic areas might be infected by a much more dangerous parasite, instead of *Pl. vivax*, but with *Pl. falciparum*. Death caused by *Pl. falciparum* can occur within hours. A telling case of a *Pl. falciparum* patient who 'not been to an endemic area for more than a decade' was reported from Berlin in 2007 (9). Fortunately, the patient appeared in a competent treatment center and recovered within days.

Finally, the transmission mode for that specific case could not be established. Various opportunities for local transmission must be considered, including an infected vector causing 'airport' or 'port' malaria, which found its way into the non-endemic area or could be carried within the baggage of a traveler (10-13). In this case, none of these routes of transmission could be verified. Potential vectors are available in Germany and have already caused isolated malaria cases (10, 14). A probable vector could be determined in the patient's surroundings (10, 14). However, the mosquito species identified as *An. maculipennis* s.l. could neither be verified nor denied being the vector for infecting the case. In addition, fluids from a parasitemia patient can cause secondary infections through accidental needlesticks or incorrect use of medical instruments such as blood glucose meters or multidose drug vials (15-18). Such a nosocomial transmission was also ruled out. However, the patient was a medical doctor and consultant in an obstetric ward and saw a patient who returned from a month-long visit to the Ivory Coast, West Africa. The traveler from West Africa later also developed malaria.

#### Vector habits determine the malaria situation in endemic areas

Yet, for malaria transmission, not only is a certain Anopheles species' capability to transmit the parasite important but also factors contributing to the 'complex vector system,' including specific breeding and biting habits. Tourists coming to Thailand are reminded that in the forested area near the border, staying in the jungle at dusk and dawn during the rainy season bears a certain risk of catching malaria (19). The recommendations are based on preferred places for the dominant vectors in Thailand to breed and the time the mosquitos are most active in pestering humans and sometimes animals.

The malaria situation in Thailand might be partly dissimilar from those in neighboring countries and other countries within the Asia-Pacific region (20). There are 19 dominant vector species with very different breeding and attacking behaviors and 'entomological complexity' not found elsewhere in other territories. The three main vectors for Southeast Asia mainland are subspecies of the *Dirus*-, *Minimus*- and *Sundaicus* Complex. For Thailand, the first two groups are of importance, but altogether eight Anopheles species are present in Thailand. The two main malaria vectors are *An. dirus* and *An. baimaii*. The vectors prefer to breed in and close to the

forest in rainwater pools and puddles. *An. minimus* species are found in forested hill areas, and breeding places are slow-running streams with grassy margins and partially shaded (6). Since most tourists stay in places like Bangkok, Pattaya, and Phuket, they don't fall victim to any of the four present malaria parasites, especially not to *Pl. vivax* or *Pl. falciparum*. Not being a tourist, one must be a little more careful while staying in the forest for gem mining or working in rubber plantations. In Thailand's endemic area, one should avoid sleeping in the jungle. As a villager in the endemic area, you might not enter the forest too early in the morning or overnight and try to be back home not too late in the evening. In case your home is quite close to the forest, you better follow the advice of the village health volunteers and sleep under impregnated mosquito nets.

### Malaria is a severe problem in Africa

However, the risk of becoming infected with one of the malaria parasites in Thailand might be much lower than being involved in a traffic accident. Such a statement is not valid for many countries in Africa, especially not for countries in sub-Saharan Africa. In the year 2021, it is estimated that 247 million malaria cases occurred in 84 malaria-endemic countries. Due to the interruption of control measures because of the Covid-19 pandemic, the number of malaria cases increased from 2020 for two million to 247 million in 2021. Mortality decreased from 2000 to 2019 but increased by 10%, compared with 2019, to 619.000 in 2021. Ninety-six percent of deaths occur in 29 countries, with Nigeria, the Democratic Republic of the Congo, Niger, and Tanzania very much affected. Approximately 76% of deaths are children below five years old (21).

### *An. gambiae* is the most dangerous animal in the world

The dominant parasite is the most dangerous *Pl. falciparum*, transmitted by highly efficient *An. gambiae* and *An. arabiensis*. In coastal areas, *An. menus* and *An. melas* breed in partly salty water. Together with another three dominant vectors, malaria-transmitting species in Africa are not as numerous as in the Asia-Pacific region (22), but the mosquito *An. gambiae* is considered the most dangerous animal in the world (23). Of the two major mosquito groups in Africa, *An. gambiae* prefers breeding in a humid environment, while *An. arabiensis* also breed under dryer conditions. Both vector groups were found to adjust genetically to environmental changes such as tree cover and change into croplands (24). Most malaria vectors in Africa breed in various natural- and man-made water collections. Some of the vectors living in 'sympatry,' in that *An. coluzzii* is more widespread during the dry seasons, while *An. gambiae* is less frequently identified. During the rainy season, the availability of the two vectors interchange in that *An. gambiae* dominates, contrary to *An. coluzzii*. Both vectors also bite inside the houses (25) and attack during dusk, night, and dawn. For biting *An. arabiensis*, *An. gambiae* and *An. funestus* prefer the ground level and attack their victims' lower legs, ankles, and feet (26).

### A sudden malaria outbreak in the urban area

Up to a decade ago, malaria in Africa basically was spreading in rural areas, and malaria control concentrates on indoor residual spraying and insecticide-treated bed nets. However, the whole scenario of the malaria problem in Africa might drastically change in the future. The world was

starting to realize such a thread through a meeting of the Society of Tropical Medicine and Hygiene (ASTMH) in Seattle in the autumn of 2022. One contribution to the conference reported a 40-fold rise in malaria cases in Djibouti since 2013. The significance of this alarming information is due to the circumstance that Djibouti is a small country in the Horn of Africa, which managed up to 2012 to diminish malaria cases to a minimum, so only 27 malaria cases occurred in 2012 but increased to 1238 cases in 2013 and about 73.000 cases 2021. Dire Dawa, a city in eastern Ethiopia with about 500.000 inhabitants, formerly got about 200 cases a year. Yet, during the dry season between January and May 2022, about 2.400 cases were reported within the community (27, 28).

### *An. stephensi*, the new migrant on the march

The dynamic of the malaria outbreaks mentioned here is unusual for Africa. They predominantly occurred during the dry season and not in the rural areas, and they are probably mainly caused by *Anopheles stephensi*, a formerly unknown vector to Africa. The first report about the invasion of *An. stephensi* into the Horn of Africa was published in 2014 (29). The vector most probably jumped to Africa from South Asia and the Arab Peninsula by shipping containers. *An. stephensi* is known as an urban vector with breeding preferences in clean, artificial water, which transmit *Pl. vivax* and *Pl. falciparum* and is also active during the dry season (20, 28, 29). A sophisticated molecular investigation could demonstrate that those staying with malaria patients had a high risk of being infected with *Pl. falciparum* as well. Breeding places of the vector were located close to their living quarters, and almost all adult mosquitos trapped belonged to the vector *An. stephensi* (30).

In the meantime, the vector also was detected in Ethiopia and Sudan (23). African experts mentioned the findings of the new vector in over 80% of households in Kenia, and others suspect that *An. stephensi* might 'spread faster than researchers realize. A member of the Liverpool Institute of Tropical Medicine, with experience in *An. stephensi* in Sudan and Ethiopia is more careful in her judgments since malaria cases in the area did not increase even though *An. stephensi* was found (28, 31). Thus, the claim, based on some computer modeling, that 126 million people in Africa's cities are at risk should be taken with caution (23). That doesn't mean serious attention shouldn't be given to this new development which might turn malaria control measures into a new dimension. Fighting malaria vectors in rural areas is mainly based on indoor spraying and impregnated bed nets, but it might not work very well in crowded urban settings. *An. stephensi* strains are less resistant to insecticides. The vector tends to rest in barns and sheds and not so much in human homes and bites people outside.

### What sounds like *Aedes*, acts like *Aedes*, but is not *Aedes*

A viewpoint recently emphasized the new thread for Africa in Lancet with the headline 'What sounds like *Aedes*, acts like *Aedes*, but is not *Aedes*?' (32). Thailand is aware of the urban vectors *Aedes* as a public health problem. Dengue fever, a hemorrhagic virus spread by the vectors *Aedes aegypti* and *Aedes albopictus*, is a public health problem here. The disease is connected to a complex epidemiologic pattern. Thousands of people could be infected, out of which more than 80% are without symptoms. Of the remaining 10%, 10% have severe clinical

symptoms with dengue hemorrhagic fever. The mortality and mortality still are high enough to demand serious control attempts (33). Dengue, chikungunya, Zika, and yellow fever are transmitted by *Aedes* mosquitos all over the tropics. The mosquitos are invasive urban living and spread during the last five decades into 129 tropical countries (32). The prospect that *Anopheles stephensi* will spread as easily as *Aedes*, causing not only *Pl. vivax* malaria but also the most dangerous *Pl. falciparum* malaria, is a very uncomfortable vision. Because of the rapid unplanned urbanization where the mosquito can breed in the man-made water container, and poor hygienic systems, the thread should be taken seriously for Africa.

### Conclusion for Thailand

*An. stephensi* is widespread in India and the Persian Gulf and might have found its way to the Horn of Africa. *An. stephensi* is also identified in various countries in Southeast Asia, and in Figure 1 of the publication of Sinka et al. (2020), three spots, two of them close to the border of Myanmar, are recorded (23). A laboratory investigation published in 1974 positively tested the efficiency of *An. stephensi* and *An. gambiae* as vectors of the drug-resistant *Pl. falciparum* from Thailand (34). At least theoretically, *An. stephensi* might once try to create problems for Thailand as well.

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