Simian malaria: a narrative review on emergence, epidemiology and threat to global malaria elimination

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Simian malaria from wild non-human primate populations is increasingly recognised as a public health threat and is now the main cause of human malaria in Malaysia and some regions of Brazil. In 2022, Malaysia became the first country not to achieve malaria elimination due to zoonotic simian malaria. We review the global distribution and drivers of simian malaria and identify priorities for diagnosis, treatment, surveillance, and control. Environmental change is driving closer interactions between humans and wildlife, with malaria parasites from non-human primates spilling over into human populations and human malaria parasites spilling back into wild non-human primate populations. These complex transmission cycles require new molecular and epidemiological approaches to track parasite spread. Current methods of malaria control are ineffective, with wildlife reservoirs and primarily outdoor-biting mosquito vectors urgently requiring the development of novel control strategies. Without these, simian malaria has the potential to undermine malaria elimination globally.

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Introduction

Malaria remains a major cause of morbidity and mortality globally and is a focus for disease control and elimination programmes.[1] All human malaria cases are caused by infections with apicomplexan parasites in the genus *Plasmodium* transmitted by *Anopheles* spp mosquitoes.[2] Over 250 malaria parasite species have been described, infecting a wide diversity of animals, including birds, bats, ungulates, reptiles, rodents, and notably non-human primates.[3] However, of these, only five malaria parasite species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale wallikeri*, and *Plasmodium ovale curtisi*, are fully adapted to humans. Although these parasites are likely to have zoonotic origins in ape populations, transmission is now entirely sustained by human populations.[2]

Additionally, multiple simian malaria parasite species circulating in non-human primate populations can cause malaria in humans (table 1). In the 1930s, experimental transmission studies showed that *Plasmodium knowlesi*, a simian malaria parasite typically carried by long-tailed and pig-tailed macaques (*Macaca fascicularis* and *Macaca nemestrina*) in southeast Asia, could infect and cause clinical malaria in humans.[27] In the mid-20th century, the zoonotic potential of the simian malaria parasites *Plasmodium cynomolgi* and *Plasmodium inui*, also found in macaques, and *Plasmodium eylesi*, found in the Malaysian gibbon species *Hylobates lar*, was shown both through experimental studies and accidental laboratory infections.[28–33] During the same time period, within South and central America, the zoonotic malaria parasites *Plasmodium simium* and *Plasmodium brasilianum* were isolated from platyrrhine (New World) monkeys and natural infections were identified in humans.[34,35] Multiple malaria parasite species were identified in wild non-human primates in Africa, with *Plasmodium schwetzi*, a simian malaria parasite found in chimpanzees (*Pan troglodytes*) and gorillas (*Gorilla gorilla*), experimentally shown to be capable of infecting humans.[32,36] Human malaria parasites also circulate within African wild ape populations with evidence of genetically distinct *P vivax* populations in humans and non-human primates and vector-borne transmission of *P vivax* from a chimpanzee to a human described.[37] The importance of non-human

Key messages

- Wild non-human pimates harbour diverse parasites capable of causing human malaria cases, with the highest reported burdens from *Plasmodium knowlesi* in Malaysia and *Plasmodium simium* in Brazil in rapidly changing landscapes.
- Simian malaria can have complex transmission cycles with spillover from non-human primates to humans, spillback of human malarias to wild non-human primates, and sylvatic circulation between non-human primate populations.
- Host switching and cross-species malaria transmission is determined by the ability of parasites to invade red blood cells, immunity, and the proximity of human and non-human primate populations with suitable vectors to transmit parasites between populations.
- Most simian malaria species from non-human primates are only identifiable by using molecular methods and are frequently misdiagnosed; new low-cost, accurate diagnostic tools are urgently needed for surveillance.
- Conventional antimalarial treatments are effective against zoonotic malaria in humans; however, treatment of cases and distribution of insecticide-treated nets has little efficacy on transmission of simian malaria with wildlife reservoirs and outdoor-biting mosquito vectors and there are no effective control measures currently available.
- WHO now only recognises malaria elimination in countries with negligible risks of zoonotic malaria, making zoonotic simian malaria a critical barrier to malaria elimination globally.

	Non-human primate host species	*Anopheles* vector	Human Infections	Geographical distribution
Plasmodium coatneyi[4]	*Macaca fascicularis*, *Macaca nemestrina*, and *Presbytis melalophos*	*Anopheles balabacensis*, *An hackeri*, and *An introlatus*	Natural infection first recorded in 2021;[5] failed laboratory infection[6]	Thailand, Cambodia, Viet Nam, Laos, and Malaysia
Plasmodium cynomolgi[7]	*M fascicularis*, *M nemestrina*, and *Presbytis cristatus*	*Anopheles latens*, *An balabacensis*, *An introlatus*, and *An hackeri*	Natural infection first recorded in 2014;[8] accidental laboratory infection[9]	Thailand, Indonesia, the Philippines, Cambodia, Laos, Viet Nam, Sri Lanka, Singapore, and Malaysia
Plasmodium eylesi[10]	*Hylobates lar*	Unknown	Laboratory human infection unconfirmed[6]	Malaysia
Plasmodium fieldi[11]	*M fascicularis* and *M nemestrina*	*An hackeri* and *An introlatus*, and *An latens*	Laboratory trials with infected mosquitoes on humans failed to infect[6]	Thailand, Indonesia, Viet Nam, the Philippines, Singapore, and Malaysia
Plasmodium hylobati[12]	*Hylobates moloch*	Unknown	Infection trial on humans failed[6]	Indonesia and Malaysia
Plasmodium inui[13]	*M fascicularis*, *M nemestrina*, *Presbytis cristatus*, *Presbytis obscurus*, and others	*An hackeri*, *An balabacensis*, *Anopheles cracens*, *An introlatus*, and *An latens*	Natural infection first recorded in 1966;[14] laboratory infection successful[15]	Thailand, Indonesia, the Philippines, Taiwan, Cambodia, Viet Nam, Singapore, and Malaysia
Plasmodium jefferyi[16]	*H lar*	Natural vector unknown	Infection trial on humans failed[6]	Malaysia
Plasmodium knowlesi[17]	*M fascicularis*, *M nemestrina*, and *Presbytis melalophos*	*An hackeri*, *An latens*, *Anopheles vagus*, *Anopheles sinensis*, *An introlatus*, *Anopheles maculatus*, *Anopheles kochi*, *An balabacensis*, *Anopheles quadrimaculatus*, and *Anopheles dirus*	First natural infection recorded in 1965;[18] laboratory infection successful[19]	Indonesia, Thailand, the Philippines, Laos, Myanmar, Viet Nam, Cambodia, Brunei, India, Singapore, and Malaysia
Plasmodium pitheci[13]	*Pongo pygmaeus*	Unknown	Unknown	Malaysia
Plasmodium youngi[20]	*Symphalangus syndactylus*, *H lar*	Unknown	Unknown	Malaysia
Plasmodium brasilianum[21]	*Alouatta belzebul*, *Alouatta caraya*, *Alouatta guariba*, *Alouatta palliata*, *Alouatta seniculus straminea*, *Ateles fusciceps*, *Ateles geoffroyi*, *Ateles paniscus paniscus*, *Ateles paniscus chamek*, *Aotus nigriceps*, *Brachyteles arachnoides*, *Cacajao calvus*, *Callithrix geoffroyi*, *Plecturocebus brunneus*, *Plecturocebus cupreus*, *Plecturocebus moloch*, *Plecturocebus ornatus*, *Cheracebus torquatus*, *Cebus albifrons*, *Sapajus apella*, *Cebus capucinus*, *Chiropotes albinasus*, *Chiropotes chiropotes*, *Chiropotes satanas*, *Lagothrix lagothricha*, *Lagotrix poeppigii*, *Leontopithecus chrysomelas*, *Leontopithecus rosalia*, *Mico humeralifer*, *Pithecia irrorata*, *Pithecia monachus*, *Pithecia pithecia*, *Saguinus geoffroyi*, *Saguinus bicolor*, *Saguinus martinsi*, *Saguinus midas*, *Saimiri boliviensis*, *Saimiri sciureus*, and *Saimiri ustus*	*Anopheles cruzii* in slopes and *Anopheles aquasalis* on the plains of Atlantic forest; the vector species is unknown in the Amazon and central America, but local *Kerteszia* species (eg, *Anopheles lepidotus* and *An neivai*) might play a role as vectors	Natural infection in humans in the Yanomami Indigenous Reserve, Roraima State, Brazil;[22] experimental infection in humans was shown involving naturally infected *Ateles geoffroyi* from Panama as simian reservoir, caged colony of *Anopheles freeborni* as anopheline vectors and nine human volunteers as human hosts[23]	Brazil, Colombia, Costa Rica, France, Panama, Peru, and Venezuela
Plasmodium simium[24]	*Alouatta fusca*, *A guariba*, *Alouatta clamitans*, *B arachnoides*	*An cruzii*	Natural infection in man was shown in the 1960's;[25] after 50 years, it has been discovered that most, if not all, autochthonous cases of malaria in Atlantic forest are due to *P simium*, and not *Plasmodium vivax*[26]	Brazil

Table 1: **Simian malaria species identified in non-human primates in southeast Asia and South America**

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primates in malaria transmission cycles in Africa remains largely unknown due to diagnostic limitations and circulation of human parasites in wild non-human primates.[2]

More than 30 species of primate malaria parasite have been identified; however, only a minority of these species can infect humans.[19] Whereas close to 400 primate species are known and less than a third of these have been screened for malaria, with highly variable sampling efforts, resulting in major gaps in our understanding of circulating simian malaria parasites.[38] Known simian malarias have been classified into stages of adaptation to humans, ranging from parasites only found in animal populations (eg, the orangutan malaria *Plasmodium pitheci*), parasites that can spill over from animals to humans and from humans to animals (eg, *P knowlesi*) to parasites fully adapted and transmissible within human populations (eg, *P falciparum*).[39,40] This stage of emergence is determined by both biological and ecological factors. Malaria parasites need to invade red blood cells to sustain infections; differences in parasite binding affinities to human red blood cell receptors determine their ability to replicate within human and non-human primate hosts.[19,41] Immune evasion pathways, cross-immunity

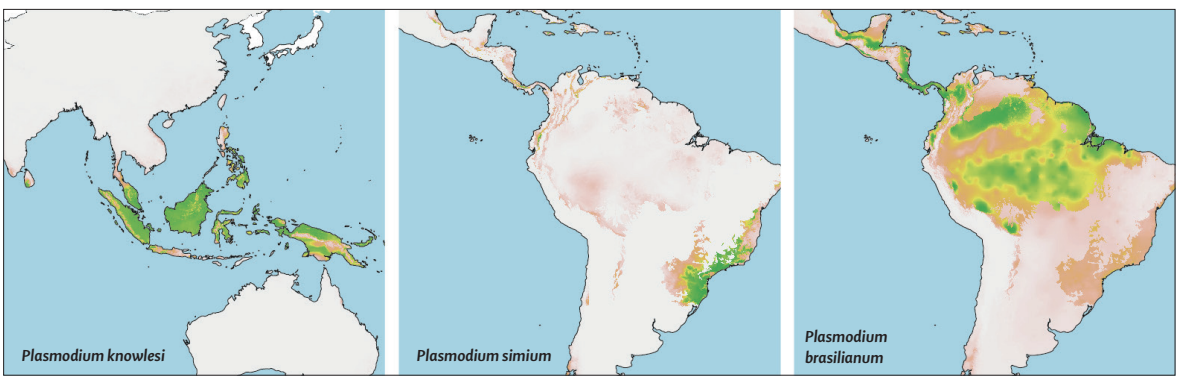

Figure: **Environmental suitability of *Plasmodium knowlesi*, *Plasmodium simium*, and *Plasmodium brasilianum***
The maps reflect models of the probability of a specific simian malaria parasite being reported in a location ranging from green (highly likely) to white (highly unlikely). Additional details on models and datasets are available in the appendix pp 1–2.

See Online for appendix

from previous exposure to other malaria species and the range of genetic diversity in pathogens also influence whether a parasite can replicate within specific hosts.[19] Additionally, the likelihood of transmission is determined by the probability of exposure to a parasite. Transmission of parasites between non-human primates and humans requires shared mosquito vectors to transmit parasites, and spatial and temporal overlap between human, vector, and non-human primate populations.[42] The proximity between these different populations depends on environmental and ecological factors, such as land cover, urbanisation, and behaviour and movement patterns of both humans and non-human primates.[43] Increased contact between humans, vectors, and wildlife can facilitate not only spillover of malaria from non-human primates to humans but also spillback of human malarias into wild primate populations, creating new reservoirs for malaria parasites.[44]

Although isolated human cases of zoonotic malaria were reported throughout the 20th century, the first evidence of zoonotic malaria as a major public health issue occurred when a large cluster of human *P knowlesi* cases were reported in Malaysian Borneo in 2004.[45] Since then, *P knowlesi* has been identified in humans across southeast Asia.[46,47] Increased applications of improved molecular diagnostics have identified multiple natural human infections with other simian malaria parasites including *P simium*, *P brasilianum*, *P cynomolgi*, *Plasmodium coatenyi*, and *P inui* (figure; table 1). Concerningly, many of these cases occurred in settings nearing elimination of transmission of the five main species of human malaria. For example, outbreaks of *P simium* were reported in the Atlantic Forest (Brazil), an area where human malaria was eliminated 50 years ago.[48] Similarly, following an extensive malaria elimination programme, no local transmission of human malaria parasites has been reported in Malaysia since 2018, but thousands of clinical cases of *P knowlesi* are reported every year.[47] In 2022, WHO defined malaria elimination certification as requiring the elimination of the main human malaria parasite species with negligible risk to humans from other *Plasmodium* species.[49,50] This resulted in Malaysia becoming the first country not to be certified for malaria elimination due to zoonotic simian malaria species and prompts major questions about the feasibility of malaria elimination in other countries reporting zoonotic malaria cases.

Simian malaria poses new challenges to malaria surveillance and control. Standard malaria interventions, such as insecticide-treated bednets and improved testing and treatment programmes, are less effective when there is a wildlife reservoir. Although wider environmental changes threaten to create new opportunities for cross-species malaria transmission, there remain critical knowledge gaps on the distributions of non-human primates, the types of parasites they harbour, and their susceptibility to human malaria parasites. The complexity of sylvatic and human transmission cycles necessitates new molecular and epidemiological tools to understand parasite flow and detect changing risks. Whereas simian malaria poses global threats, the highest human burdens of zoonotic malaria cases currently reported are *P knowlesi* in Malaysian Borneo, and *P simium* and *P brasilianum* in the Brazilian Atlantic Forest. Innovative One Health control measures are urgently needed to manage simian malaria risks to achieve global malaria elimination goals.

Emergence of *P knowlesi* and other simian malarias in southeast Asia

The rapid rise of *P knowlesi* cases in Malaysia exemplifies how spillover of malaria from wildlife reservoirs can undermine malaria elimination. Across the Asia-Pacific region, human malaria cases have declined due to effective preventive measures and control activities.[51] Malaysia was recognised by WHO as a country likely to achieve malaria elimination by 2020 and reported no indigenous human malaria cases since 2018.[47,52] Since the initial identification of large numbers of human *P knowlesi* cases in Malaysian Borneo, molecular diagnostics have identified increasing numbers of

	Year	Cumulative number of cases
Brunei		
Plasmodium knowlesi	2007–17	73[55]
Cambodia		
P knowlesi	2007–20	8[56-58]
Plasmodium cynomolgi	2013–16	13[58]
China (Yunnan province)		
P knowlesi	2008–12	2[59]
India		
P knowlesi	2004–18	60[60,61]
Indonesia		
P knowlesi	2008–19	547[61-74]*
Laos		
P knowlesi	2010–16	10[75,76]
Malaysia		
P knowlesi	2008–21	29 370[77-79]†
P cynomolgi	2011–17	18[80,81-83]
Plasmodium inui	2011–20	5[83,84]
Plasmodium coatneyi	2011–14	3[83]
Plasmodium simiovale	2011–14	2[83]
P inui-like	2011–14	3[83]
Myanmar		
P knowlesi	2008–13	49[85-87]
Philippines		
P knowlesi	2006–18	8[88-91]
Singapore		
P knowlesi	2007–08	6[92-93]
Thailand		
P knowlesi	2016–22	327[94]‡
P cynomolgi	1996–2021	33[95-97]
P inui	1996–2016	19[97]
P fieldi	1996–2016	3[97]
Viet Nam		
P knowlesi	2004–2010	38[76,98-100]

*Duplicate reports of the same case were combined and counted as a single record accordingly. †Consisted of only case data reported by the Ministry of Health Malaysia. ‡Consisted of only case data reported by the Ministry of Public Health, Thailand.

Table 2: **Cumulative cases of natural zoonotic malaria infection in humans by countries in Asia**

P knowlesi cases in Malaysia, especially in indigenous populations in peninsular Malaysia and Malaysian Borneo.[45,47,53,54] Human *P knowlesi* cases have been identified across Asia, with increases in both the incidence and total numbers of infections reported, with over 30 000 human *P knowlesi* cases diagnosed since 2004 (table 2).[46,101,102]

Southeast Asia harbours a wide diversity of non-human primates, including 57 species of monkeys, 18 gibbon species and three ape species.[103] The predominant natural reservoirs of *P knowlesi*, long-tailed macaques (*M fascicularis*) and southern pig-tailed macaques (*M nemestrina*), are highly sympatric and widely distributed across southeast Asia.[104–106] *P knowlesi* was also reported in other less common non-human primate species, including banded leaf monkey (*Presbytis melalophos*), stump-tailed macaque (*Macaca arctoides*), and dusky leaf monkey (*Semnopithecus obscurus* or *Trachypithecus obscurus*).[107–109] *P knowlesi* prevalence in non-human primates is highly heterogeneous, with mean infection rates ranging from 0% to 81% in endemic regions.[110] Genetic evidence suggests *P knowlesi* evolved from an ancestral parasite population that predates human settlement in southeast Asia, with separate parasite subpopulations linked with long-tailed and pig-tailed macaque populations.[105,111] There are multiple *Plasmodium* species commonly identified within non-human primate populations in this region.[112] In addition to *P knowlesi*, cases of *P cynomolgi* and *P inui* naturally transmitted to humans have been recorded.[53,113] Subsequently, increased surveillance efforts detected *P cynomolgi* and *P inui* infections in other settings in southeast Asia.[114–121] High throughput sequencing has further identified other simian malaria parasites in humans, including *P coatneyi*, *P fieldi*, and *P simiovale* (table 2).[53,120]

Increased incidence of human *P knowlesi* cases is strongly associated with deforestation and other land cover changes.[122] Investigations of the initial cluster of *P knowlesi* cases reported in Sarawak, Malaysian Borneo, found the main vector in the area, *Anopheles latens*, preferred biting humans in farms and forest edges.[123] Similarly, in Sabah, Malaysia, the incriminated vector of *P knowlesi*, *Anopheles balabacensis* is mainly abundant near villages, plantations and forest fringes.[124–126] In Viet Nam, *Anopheles dirus* preferentially fed on humans and macaques in forests and forest fringes.[127,128] Mixed infections have been reported in mosquito vectors, including co-infections of *P knowlesi* and human malarias, and co-infections with multiple species of simian malaria are widely reported in non-human primates.[129–132] Human movement and residence near forest edges is associated with increased exposure to infectious mosquito bites.[133–135] Expansion of these habitats might lead to increased and sustained transmission.

Zoonotic malaria cases have been predominantly reported in adult men, many with occupational activities in forest or plantation areas.[42,134] The clinical spectrum of human *P knowlesi* malaria ranges from asymptomatic to severe and fatal disease.[136–142] In contrast to falciparum and vivax malaria where severe disease and death are predominantly seen in children, less than 10% of *P knowlesi* infections are reported in children, with no severe or fatal cases of *P knowlesi* malaria.[143–145] However, 6–9% of symptomatic adults progress to develop severe disease, mainly manifesting as acute kidney injury, jaundice, and hyperparasitaemia.[143,146,147] Higher parasitaemia and older age are risk factors for severe *P knowlesi* malaria whereas female gender, age above

45 years and the presence of comorbidities are risk factors for fatal knowlesi malaria.[143,148,149] Analysis of human knowlesi cases in Peninsular and Bornean Malaysia from 2013 to 2017 showed average case fatality rates of 1·20% (24 deaths of 3665 people with malaria), and 0·15% (22 deaths of 12 835 people with malaria) respectively.[150] Accurate diagnosis and timely administration of intravenous treatment are crucial in preventing fatal outcomes.[140,149]

Complexity and diversity of zoonotic malaria transmission in South America

Human and platyrrhine simian *Plasmodium* transmission outside the Amazon region mainly occurs in forest remnants across Serra do Mar (Atlantic Forest, Brazil). Malaria occurs either as isolated cases or sporadic outbreaks, with fewer than 100 human cases of suspected simian malaria reported annually in Brazil.[48,151] Complex cycles involving humans, platyrrhines, and *Anopheles* (*Kerteszia*) maintain endemic dispersions of *P vivax*, *P malariae*, *P brasilianum*, and *P simium*.[48,152,153] *Anopheles cruzii*, *Anopheles bellator*, and *Anopheles homunculus* are important vectors where bromeliad phytotelmata are abundant.[154–156] Forest loss decreases the abundance of the dominant vector *An cruzii*, while forest fragmentation increases its human biting rate, leading to increased exposure of the local human population to the risk of *Plasmodium* infection.[157]

Platyrrhine are human plasmodia reservoirs of zoonotic malaria in Brazil, and elsewhere in South America and central America.[158–160] Despite evidence of elevated concentrations of antibodies to malaria detected in multiple platyrrhine species, only the howler monkey, *Alouatta clamitans*, is incriminated as the primary reservoir of zoonotic malaria species in Serra do Mar.[158,161,162] From surveys of six non-human primate species in this region, only howler monkeys were infected with *Plasmodium*, with the highest *P simium* prevalence (71%) reported in Serra do Mar.[158] Most zoonotic malaria cases are reported in Serra do Mar; however, platyrrhine can harbor *P vivax* and *P falciparum* in the Amazon rainforest.[162–164] DNA of *P malariae* or *P brasilianum*, and *P vivax* or *P simium* were identified by PCR in simian blood samples, whereas *P falciparum* was detected in fecal samples of *Alouatta seniculus* in Colombia, and *Leontocebus lagonotus* in Ecuador.[160,165] In contrast to *P knowlesi*, genetic evidence suggests *P simium* and *P brasilianum* originated in humans, with spillback to wild non-human primates.[166]

P brasilianum is an important simian malaria parasite that can infect humans in central and South America.[167] It infects all families of New World monkeys found in the Serra do Mar and the Amazon rainforest (Brazil), as well as Colombia, Costa Rica, French Guiana, Panama, Peru, and Venezuela.[168,169] The genetic similarities shared with *P malariae* limits true estimates of *P brasilianum* prevalence in simians and humans in South America.[170,171] Closely related to *P vivax*, the first human infection by *P simium* was reported in the 1960s.[35] Since then, zoonotic malaria cases, likely misidentified as *P vivax* by microscopy, are reported annually; these are not always confirmed by molecular methods but the absence of circulating *P vivax* and existing molecular work suggests most or all cases are zoonotic.[48,172] Co-infections of *P vivax* or *P simium*, and *P malariae* or *P brasilianum* in humans add complexity to the transmission scenario and hamper identification and enumeration of *Plasmodium* species.[153] A *P falciparum*-like parasite that was found in Serra do Mar and asymptomatic co-infected humans further complicate the surveillance of zoonotic malaria.[153,173] Novel approaches are needed to detect low parasite density and identify species accurately to improve surveillance and understanding of zoonotic malaria potential.

Key challenges in the diagnosis and detection of simian malarias

A critical barrier to understanding changing simian malaria risks globally is the identification of specific parasites; all zoonotic simian malaria parasites appear microscopically similar to human malaria parasites and require molecular confirmation.[32,48,174,175] Initial PCR methods used for *P knowlesi* targeted the small subunit rRNA gene; however, primers cross-reacted with *P vivax*.[176] Nested PCR and real-time PCR approaches targeting the 18S RNA, plasmepsin and cytochrome b genes of *Plasmodium* parasites improve sensitivity, but also increase diagnostic costs.[177–179] Alternative, lower cost, potentially field-deployable isothermal nucleic acid amplification methods, such as loop-mediated isothermal amplification and recombinase polymerase amplification, have been developed.[180,181] Commercially available kits are sufficiently sensitive and specific for clinical detection of *Plasmodium*, but fail to discriminate *Plasmodium* species.[182,183] Additionally, no reliable rapid immunochromatographic tests for zoonotic malaria parasites are available. For *P knowlesi*, multiple studies showed commercially available rapid diagnostic tests based on parasite lactate dehydrogenase and aldolase are not sensitive and specific enough.[184–186] All evidence to date suggests that simian malarias respond to standard antimalarial drugs and a less specific diagnostic could guide treatment; however, there is a real need for species-specific diagnostics for surveillance.

Development of non-invasive methods is also critical to identify malaria parasites in non-human primates in the field. Simian blood collection requires a complex protocol with animal trapping and sedation, which can cause injuries or death, and induce behaviour change that ultimately hampers surveillance activities. Promising outcomes were shown with non-invasive methods and diagnostics from simian faeces samples in southeast Asia.[187] This approach had an important contribution in unravelling evolutionary relationships in phylogenetic studies on the subgenus *Laverania* in Africa.[2]

Notwithstanding, novel field and laboratory protocols should be considered for surveillance and screening of zoonotic malaria in distinct simian populations, including endangered forest-specialist and generalist species.[188] Novel protocols for screening of simian and human malarias among non-human primates are needed to assess risks of spillover and spillback.[173]

Molecular epidemiology to track zoonotic malaria emergence

Molecular epidemiological approaches to understand host genetic variants and the pathogen genotypes is likely to prove instrumental in improving understanding of transmission, infection prevalence, and prevention. Genetic polymorphisms of *P knowlesi* infections in humans showed transmission from different local parasite reservoir hosts rather than a single clonal outbreak.[45] Multiple genome analysis also revealed population subdivisions of *P knowlesi* based on the geographical region and macaque host species.[111] Additionally, high parasite diversity and positive natural selection was identified in different loci across *P knowlesi* subpopulations.[189] In contrast, *P simium* might have evolved as a lineage of *P vivax* that switched from humans to platyrrhine simians, as supported by phylogenetic analysis showing *P simium* as a monophyletic lineage within the *P vivax* South American clade.[166,190] Differences in the genes coding Duffy-binding and reticulocyte-binding proteins of *P simium* and *P vivax* could explain recent events of zoonotic malaria in Brazil.[166]

Analysis of *P knowlesi* isolates from clinical cases has not detected drug resistance mutations, suggesting limited selective pressure and onward transmission from humans.[111,191] Although there is currently no evidence of circulating simian malaria parasites in wild non-human primates with drug resistance, documented malaria transmission from humans to non-human primates highlights the potential for wild non-human primates to become a reservoir of drug-resistant malaria.[44] Genetic analysis aligned with measurement of species-specific immune responses could also inform how multiclonal and multispecies infection persist and impact onward transmission.

Simian malaria risks in changing environments

The interactions between humans and non-human primates are strongly associated with environmental change, with human malaria risks in both Brazil and Malaysia closely linked with forest fragmentation.[122,192,193] Deforestation can break up forest habitats into smaller patches and create new ecotones, edge habitats with increased contact from previously separated populations.[194,195] Forest edges are associated with higher densities of the main *P knowlesi* vectors and human movement into these habitats, resulting in increased *P knowlesi* exposure risks.[43,131,196] Changes in vegetation and resulting microclimates can create new breeding sites for mosquito vectors and increase or decrease the suitability for different vector species.[125,156] Land use also interacts with wider climate changes and interannual variability in rainfall to impact vector and wildlife ecology.[43] Similarly, the availability of food sources, roosting locations, and predators in changing landscapes alters wild non-human primate distribution, behaviour, and contact with people.[43,197–199] Infection rates of these non-human primates vary substantially by geographic region and habitat type.[110,200] Changing host availability can also influence vector biting patterns; in Brazil, canopy-dwelling vectors increasingly bite humans within these edge habitats.[152,157,201] Highly plastic vector species biting both humans and non-human primates in disturbed habitats are one of the key drivers of simian malaria risks globally. Current epicentres of zoonotic malaria outbreaks have some of the highest rates of environmental change globally; there remain key questions on how future environmental changes could drive new simian malaria risks.

Mathematical modelling as a tool to understand simian malaria transmission

In the absence of key data from varied ecologies, a mathematical modelling approach permits simulations and hypothesis testing.[202] Varying rates of anthropophilicity of mosquito vectors identified evolutionary conditions, which would drive non-zoonotic *P knowlesi* transmission.[202] Further model developments account for variation in the transmission dynamics into distinct landscape sites (forest, farm, and villages) and the effect of malaria control and interventions (rapid treatment or insecticide-treated nets), showing the need for control measures targeted for different environments.[203] Spatially explicit models support empirical observations that *P knowlesi* infections in humans are more likely to occur in the habitat edges of ecotones, particularly in the interfaces of houses and secondary forest, where pathogen–vector–people interaction intensifies transmission dynamics.[43] Model simulations showed that sustained human-to-human transmission can occur when macaques have frequent dispersal through anthropogenic–forest habitats and conventional malaria control measures are partly effective; however, modelling suggests non-zoonotic *P knowlesi* transmission remains highly unlikely.[203] Subsequently, model-based inference methods surveillance data of over 25 000 cases were used to estimate individual case reproductive numbers, assessing the likelihood of two human cases being within the same transmission chain.[204,205] Outputs suggest increases in *P knowlesi* are largely driven by zoonotic spillover, with no evidence for sustained non-zoonotic transmission; these approaches can be applied to monitor future changes in transmission patterns if the parasite becomes increasingly adapted to humans.[102]

Models have examined effects of biodiversity on the likelihood of the emergence of *P vivax* in an isolated island in the Brazilian Atlantic coast.[206] The density of non-transmitting animal hosts to this parasite and abundance of competing non-vector mosquitoes were identified as mechanisms likely to explain the absence of malaria on that island.[206] The model was extended when *P simium* was implicated to include simians as reservoirs,[48,152] with results showing that an increase in human infections is possible only if non-human primates are present.[152] This finding provides further evidence that *P simium* transmission to humans is more likely in the forest edges, where biodiversity effects are lower, vector and non-human primates are present, and vector canopy–ground displacement is greater.[152,206] By contrast to *P knowlesi*, there is evidence of non-zoonotic transmission of *P simium* and *P brasilianum*, and models have been used to identify where sustained transmission could occur.[152] Modelling of zoonotic malaria in Malaysia and in the Atlantic Forest can advance the knowledge of complex transmission scenarios and evaluate novel methods of surveillance, control, and prevention.

Need for innovative control strategies for zoonotic simian malaria

Understanding zoonotic and non-zoonotic malaria transmission patterns has critical implications for design of control measures. Control of simian malaria vectors poses many challenges as these vectors are exophilic, exophagic, and crepuscular feeders. Studies in both Malaysian Borneo and Myanmar evaluated outdoor residual spray as a possible solution to control *P knowlesi* vectors.[207–209] Despite some promising results, the effectiveness of outdoor residual spray is still debatable as environmental factors can diminish its efficacy rapidly and the effects on non-target beneficial insects can be detrimental. Attractive targeted sugar baits were used in Mali to reduce mosquito biting and were associated with a 30% reduction in prevalence of human malaria cases.[210] This method seems to have less impact on the non-target insects, which are important for the ecosystem.[211] Field trials are needed before mass deployment of this innovative control method in the specific forest fringe environments associated with simian malaria.

Personal protective equipment, such as insecticide-treated clothing and topical repellent, has been advocated, but might not be financially feasible for rural populations.[212] Wristbands and anklets impregnated with DEET (N,N-diethyl-meta-toluamide) could be an alternative solution.[213] Past studies showed effectiveness and reduced human malaria cases.[214] Alternatively, chemoprophylaxis can be targeted to high-risk populations. In Cambodia, a randomised controlled trial showed antimalarial chemoprophylaxis with artemether-lumefantrine substantially reduced the risk of human malaria among forest workers and that this benefit should extend to simian malarias.[215]

Search strategy and selection criteria

We developed a list of key priorities for simian malaria surveillance and control based on expert consultations with researchers, policy makers, and practitioners working on zoonotic malaria. Case studies on simian malaria in Malaysia and Brazil were separately developed by researchers based in these locations. We identified previous systematic reviews on simian malaria, including reviews conducted by study authors. Relevant papers were manually identified from these reviews. We additionally searched PubMed and Web of Science for articles published up to Jan 31, 2023, with the terms: "malaria", "zoonotic malaria", "simian malaria", AND "*Plasmodium*" in combination with "non-human primate", "vectors", "*Anopheles*", "humans", "theoretical models", "molecular", "treatment", "control", "surveillance", OR "diagnosis", AND "global", OR "specific country", OR "region names". We reviewed articles, relevant referenced articles, peer-reviewed literature, and policy documents identified by experts in the field. No language restrictions were applied. For the purposes of this Review, we included articles on simian malaria with evidence of transmission or infections in both humans and non-human primates. From the assembled reference database, we individually reviewed all references for relevance to the priorities identified. Updating previous systematic reviews with more recent literature, we additionally assembled a spatially referenced database of published locations of human cases of *Plasmodium knowlesi*, *Plasmodium simium*, or *Plasmodium brasilianum* to model the distribution of case occurrence (appendix pp 1–2).

However, the presence of a large, untreated wildlife reservoir remains the major hurdle in control strategies against the zoonotic simian malaria. Treatment of reservoirs with antimalarials, endectocides, or both, could be used to control zoonotic malaria.[216] The mosquito vectors are killed when it feeds on the host blood containing the endectocides (such as ivermectin), eventually interrupting the transmission chain.[217] However, further investigations are warranted especially on the feasibility of large-scale drug administration to wild non-human primates, despite successful examples of oral-baited treatment of wildlife reservoirs.[218] Additional studies are required to assess possible evolution of drug resistance, logistical feasibility, and viability under deployed field-conditions and effectiveness of ivermectin as an endectocides on wild non-human primates.

In reality, due to the complex dynamics of zoonotic malaria transmission and the different expertise required, integrated control strategies that incorporate multisectoral collaboration (ie, health, forestry, conservation, and education) at both national and international levels will be necessary. Specific attention should be given to the role of environmental factors, such as

forest conservation and monitoring of the anthropogenic changes to land use in reducing the incidence of zoonotic malaria including improving public awareness of risk.

Simian malaria: a critical threat to malaria elimination

With no currently available effective interventions, zoonotic simian malaria is a major barrier to malaria elimination, particularly in southeast Asia and South America. Spillover of simian malaria is primarily reported in locations undergoing rapid deforestation with highly sympatric wild non-human primate populations and vectors biting both humans and non-human primates at forest fringes. These spillover events have the potential to lead to future chains of non-zoonotic transmission depending on the species of parasite and vector adaptation to humans.[40] This transmission is particularly a threat when human malaria species have been transmitted back into wild non-human primate populations; in these cases, wild non-human primate populations can become the last reservoir of malaria in otherwise malaria-free regions as has been seen in the Brazilian Atlantic Forest.[48] There is a critical need to improve diagnostics and surveillance approaches to address these simian malaria threats. Cross-sectoral cooperation and integrated One Health solutions are essential to identify sustainable land management methods and interventions to support human and wildlife health. Without developing novel control strategies for zoonotic malaria, global malaria elimination goals cannot be achieved.

Contributors

KMF, GZL, IV, THC, KA, AMRdCD, CD, MAMS, and YLL conceived this Review. THC, GZL, AMRdCD, and MAMS designed and drafted the table. GZL conducted spatial analysis. KMF wrote the first draft of the manuscript. All authors conducted literature searches, contributed to, and reviewed the final manuscript draft.

Declaration of interests

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