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Primate malaria: An emerging challenge of zoonotic malaria in Indonesia

Meyby Eka Putri Lempang [a], Farahana Kresno Dewayanti [b], Lepa Syahrani [b], Dendi Hadi Permana [b], Ratmawati Malaka [c], Puji Budi Setia Asih [b], Din Syafruddin [b,d,*]

[a] Doctoral Program, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[b] Eijkman Institute for Molecular Biology, National Research and Innovation Agency, Jakarta, Indonesia
[c] Faculty of Animal Husbandry, Hasanuddin University, Makassar, Indonesia
[d] Department of Parasitology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

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ABSTRACT

The emergence of zoonotic malaria in different parts of the world, including Indonesia poses a challenge to the current malaria control and elimination program that target global malaria elimination at 2030. The reported cases in human include *Plasmodium knowlesi, P. cynomolgi* and *P. inui,* in South and Southeast Asian region and *P. brazilianum* and *P. simium* in Latin America. All are naturally found in the Old and New-world monkeys, macaques spp. This review focuses on the currently available data that may represent primate malaria as an emerging challenge of zoonotic malaria in Indonesia, the distribution of non-human primates and the malaria parasites it carries, changes in land use and deforestation that impact the habitat and intensifies interaction between the non-human primate and the human which facilitate spill-over of the pathogens. Although available data in Indonesia is very limited, a growing body of evidence indicate that the challenge of zoonotic malaria is immense and alerts to the need to conduct mitigation efforts through multidisciplinary approach involving environmental management, non-human primates conservation, disease management and vector control.

1. Introduction

Malaria still poses a public health challenge in many countries around the world, including Indonesia. The objectives of malaria control programmes range from reducing the disease burden and maintaining it at a reasonably low level, to eliminate the disease from a defined geographical area, and ultimately eradicating the disease globally [1]. Currently, there are 241 million malaria cases in 2020 distributed in 85 malaria endemic countries (including the territory of French Guiana), increasing from 227 million in 2019, with the most of this increase coming from countries in the WHO Africa, South Asia, and Southeast Asian regions [2]. In Indonesia, since the adoption of malaria elimination program in 2009, the incidence of malaria continuously decreases in the western parts of the country and as of 2020, over 300 Districts and municipalities have been declared to be malaria free (Fig. 1.). However, in Sumatra and Kalimantan (Indonesian part of Borneo), a new challenge has emerged with the rise of zoonotic malaria [3,4]. Human infection with various primate malaria such as *Plasmodium knowlesi*, *P cynomolgi*, and *P inui* have been tracked in various sites in Malaysia. It is highly possible that this phenomenon may also be happening in various locations in Indonesia where the non-human primate is endemic.

Malaria is a blood protozoan parasitic disease caused by genus *Plasmodium* spp., and transmitted to a wide variety of vertebrates by insect. It is believed that approximately 250 *Plasmodium* parasites parasitizes different animal species, including birds, reptiles, snakes, and mammals [5–7]. Of these, 27 *Plasmodium* species have been documented to infect a wide variety of non-human primates around the world, including apes, gibbons, and New and Old-World monkeys [8].

Humans have been infected with various *Plasmodium* species such as *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Some monkey malaria parasites have been experimentally transmitted to humans in the past through the bites of infected mosquitoes. They include *P. cynomolgi* [9,10], *P. knowlesi* [11,12], and *P. inui* [12] from Old World monkeys, *P. brasilianum* [13] and *P. simium* [13,14] from New World monkeys, and *P. schwetzi* (now regarded to be either *P. vivax* or *P. ovale*-like parasites) from chimpanzees [15].

The first zoonotic malaria report in 1964 was caused by *P. knowlesi* [16]. In 1971, another case report of *P. knowlesi* infected human from the same location in Peninsular Malaysia was published [17,18]. Until recently, many cases of natural human infection by *P. knowlesi* in

* Corresponding author at: Eijkman Institute for Molecular Biology, National Research and Innovation Agency, Jakarta, Indonesia.
E-mail address: din@eijkman.go.id (D. Syafruddin).

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Southeast Asia including Indonesia [19–21], Thailand [22–24], Malaysia [18,25], Philippines [26,27], Singapore [28], Brunei Darussalam [29], Laos [30], Myanmar [31], Cambodia [32], Vietnam [33], have been documented but so far no report from Timor Leste. Between 2004 and 2016, Malaysia Borneo reported 4553 cases and had the highest number of cases of *P. knowlesi* in humans, followed by Indonesia with 465 cases, and Peninsular Malaysia with 203 cases, a polymerase chain reaction (PCR) was used to confirm all of the cases [34]. The occurrence of zoonotic malaria has therefore hampered malaria control and elimination program that focuses to reduce the burden of human malaria in the region.

The non-human primate malaria parasites (NHPMPs) could potentially be a new challenge of malaria elimination in human in many parts of the world where the primate and human are sympatric [20]. Human natural infection with *P. brazilianum* and *P. simium* have been documented in Brazil, while *P. knowlesi, P. cynomolgi* and *P. inui* have been reported in Southeast Asia [9,10,12–14,16–18]. Noteworthy, researchers from India also reported the occurrence of *P. falciparum* infection in *Macaca mullata* and*M. radiata* [35]. Different to other *Plasmodium* (Table 1), *P. knowlesi* has a 24-h erythrocytic cycle (quotidian) and can cause both symptomatic and asymptomatic infections in humans [36–38]. Three predominant natural host of *P. knowlesi* is *Macaca fascicularis*, *Macaca nemestrina*, and *M. leonina* [39–42]. Not only *P. knowlesi*, but also *P. cynomolgi, P. inui, P. coatneyi, P. inui–like, and P. simiovale* caused infection in human [43–45].

The archipelago of Indonesia stretches along the equatorial line, connecting the Asia mainland and Australia, and consists of 17,504 islands [46]. Indonesia uniquely has the second largest biodiversity in the world. There are 61 species of primates identified in Indonesia [47]. Sulawesi and Mentawai Islands particularly have endemic primate species [48,49]. *Plasmodium pitheci* was discovered to infect orangutans in 1907, as was *Plasmodium inui*, which parasitized Java monkeys [50].

This review will explore all malarial parasite species across humans and the non-human primate natural hosts, the habitat distribution of non-human primate, and the mosquito vector associated with the zoonotic malaria across a wide geographic and environmental region of Indonesia. Dramatic changes of land use, deforestation within the last 3 decades has intensified interaction between non-human primate with human being. It is, therefore, anticipated that the more interaction between human and non-human primate will facilitate the spill-over of many pathogens from human and non-human primate (Anthropozoonotic infection) or vice versa either through mosquito or direct transmission.

2. Non-human primate in Indonesia

Indonesia is home for a large number of primates species and occupies the third rank in the world after Brazil (116 species) and Madagascar (98 species) [47]. About 5 families from 11 genera and 61 species of primates have been documented, 38 species of which are endemic in Indonesia [51–53]. All primates distributed across archipelago based on genus from north Kalimantan to coast of Java and from the western part of Sumatra to east Timor (Table 2) [54–58]. Most primates in Sumatra, Kalimantan, and Java have similar genus with the types of primates in Asia, such as slow loris (*Nycticebus*), lutung (*Trachypithecus*), langur (Presbytis), monkey (*Macaca*), gibbon (*Hylobates*) [47,57]. But, orangutan (*Pongo*), proboscis (*Nasalis*), tarsies (*Tarsius*), and pig tailed langur (*Simias*) are not found in any others area in Asia [59].

Primate species that are endemic in the Mentawai islands include the Mentawai pig tailed macaque *M. pangenesis* and the Mentawai langur (*Presbytis potenziana*) are only exclusively found in this island [47]. Previously, Sulawesi Island was known to be the home of seven macaque species [58,60,61], but recent finding revealed additional one new species [51] and at least nine species of tarsier [47]. Five species are protected and endangered; the black macaque (*M. nigra*), the moor macaque (*M. maura*), heck's macaque (*Macaca hecki*), the booted macaque (*Macaca ochreata*), and the tonkean macaque (*Macaca tonkeana*) [47,51]. The distribution of tarsiers; Dian's tarsier, *Tarsius dentatus*, and the Sulawesi mountain tarsier observed in Lore Lindu National Park, the province of Central Sulawesi. Orangutan is the only great ape in Indonesia, consisting of three species, such as Sumatran orangutan (*Pongo abelii*), Bornean orangutan (*P. pygmaeus*), and Tapanuli orangutan (*Pongo tapanuliensis*) [47].

3. Distribution of *Plasmodium* sp. among non-human primate in Indonesia

Until recently, very few studies have explored the malaria incidence among the non-human primate in Indonesia. Previously, studies conducted in various localities in Asia reported 7 species such as *P. coatneyi*, *P. cynomolgi*, *P. fieldi*, *P. inui*, *P. knowlesi*, *P. fragile*, and *P. simiovale* that

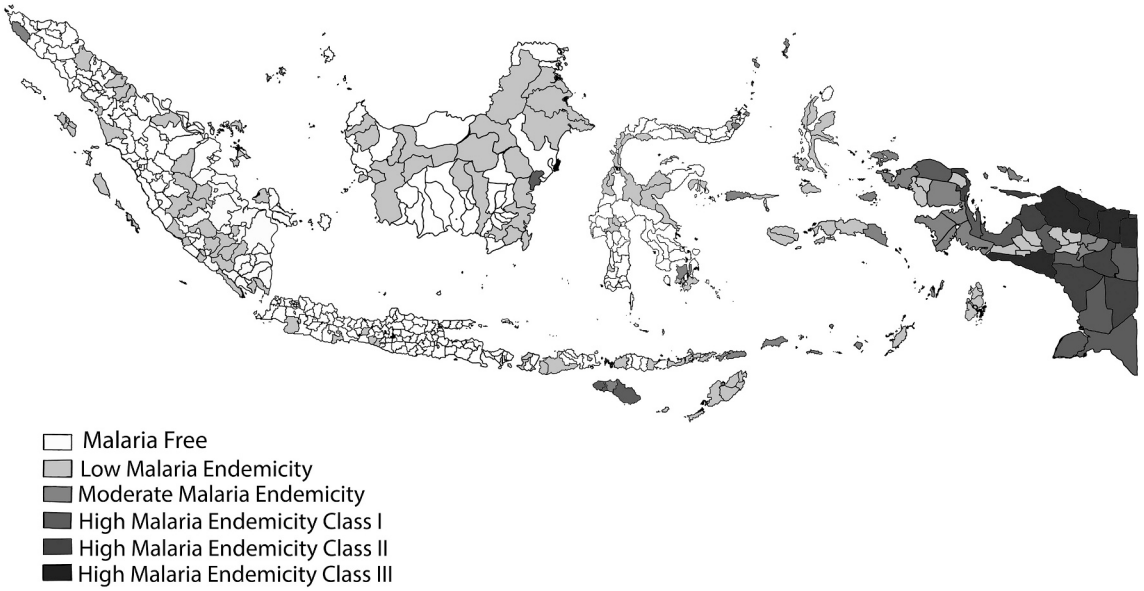

Fig. 1. Malaria Free Areas in Indonesia. The figure was originally obtained from http://www.naturalearthdata.com, and modified according to data from Ministry of Health, Republic of Indonesia, 2022.

Table 1
Plasmodium species that infect human and non-human primate worldwide [43].

	Vivax-type parasites	Ovale-type parasites	Malariae-type parasites	Falciparium-type parasites	Other-type parasites
Human	*P. vivax*	*P.ovale*	*P. malariae*	*P. falciparum*	*P. knowlesi*
Macaque	*P. cynomolgi*	*P. fieldi* *P. simiovale*	*P. inui*	*P. coatneyi* *P. fragile*	
Gibbon	*P. eylesi* *P. hylobati* *Pithecophaga jefferyi* *P. youngi*				
Orangutan	*P. pitheci*				
Chimpanzee	*P. schwetzi*		*Prosevania rodhaini*		
Cacajao			*P. brasilianum*		
Howler monkey	*P.simium*				
Mangabey	*P. gonderi*				
Erythrocytic cycle parasite invasion	48 h (Tertian)	48 h (Tertian)	72 (Quartan)	48 h (Tertian)	24 h (Quotidian)

infect non-human primate such as long tailed macaque (*M. fascicularis*) and leaf monkey. In particular, *Plasmodium fragile* was only reported in India and Sri Lanka, whereas *P. simiovale* was found only in Sri Lanka [52]. Macaques could be infected with a single, double, or even triple *Plasmodium* infections [53,59,62]. The presence of multiple *Plasmodium* infections in vertebrate hosts indicates a high malaria transmission intensity [63].

Plasmodium pitheci was discovered in Borneo's orangutan in 1907 [50]. At the same time, *Plasmodium inui* was discovered in Sumatra and Borneo (now called Kalimantan island) in Javanese monkeys or cynomolgus macaque (*M. fascularis and M. nemestrina*) [50]. Almost a century later, study to explore malaria parasite incidence among the non-human primate in Indonesia found *P. cyonomolgi*, *P. inui*, and *P. fieldi* infection in macaques from Southern Sumatra [64] using paired fecal and blood samples for molecular detection. Subsequently, a study involving 70 wild macaques from South Sumatra and Bintan island reported 92.8% parasite rate using nested PCR assays. They reported 48 macaques had single infection of *P. cynomolgi*, three macaques had single infection of *P. inui*, and one macaque infected with *P. coatneyi* and the remainders were either double or triple infected [62]. In 2017, another study screened *Plasmodium* DNA from 53 macaques, such as *M. fascicularis*, *M. nemenstrina*, and *Presbytis* sp. and found 38 positives, 57.9% of which were single infection, with either *P. knowlesi*, *P. cynomolgi*, *P. inui* and *P. coatneyi*, 28.9% were double infection, and 13.2% were triple infection, *P. fieldi* was not found in any macaque in this study [65]. In 2020, study from 2 captivities in Bogor, West Java using molecular detection reported 13.87% (38/274) of *P. inui* [66].

4. Zoonotic malaria among human in Indonesia

Zoonotic malaria cases had been reported in various localities in Sumatra and Kalimantan, Indonesia. Unlike in Malaysia, where zoonotic malaria is caused by *P. knowlesi*, *P.cynomolgi*, and *P. inui* [18,41,42,44,45,67,68], *Plasmodium knowlesi,* so far, was the only primate malaria species that has been reported from South Kalimantan (Borneo Island) [19], Aceh Besar [68], Batubara Langkat in Sumatra Island and South Nias [21].

In 2010, the first case was detected from an Australian that resided in South Kalimantan for 18 months and confirmed by molecular detection as 100% similar with *P. knowlesi* [19]. The second report was also in the same year, from 22 gold miners with uncomplicated malaria and were detected by nested PCR using *P. knowlesi*–specific primers that yielded a 153-bp product, in which 4 subjects were positive *P. knowlesi* [69]. The third case of *P. knowlesi* was detected by PCR from a worker at a charcoal mining company in Central Kalimantan [25]. The fourth case of *P. knowlesi* was formally reported from Aceh in 2016. The samples were diagnosed by microscopy, loop mediated isothermal amplification (LAMP), and the PCR. The result showed that *P. knowlesi* was found in 20 samples out of 43 [70]. In 2018, *P. knowlesi* cases were discovered in Sabang Municipality Aceh, an area where *P. falciparum* and *P. vivax* had been eliminated [71].

5. Perspective of zoonotic malaria in the era of malaria elimination

Indonesia's Ministry of Health has implemented malaria control, with the goal of eliminating the disease by 2030. The increased incidence and proximity of natural reservoir hosts to humans and mosquitoes makes non-human primate malaria a necessary concern with knowlesi-malaria as one of the challenges for malaria elimination efforts in Indonesia.

The potential of exposure to *P. knowlesi* outdoor transmission has increased as humans have encroached on previously forested areas. Outdoor workers (e.g., plantation and agricultural workers) are particularly vulnerable [19,27,69,72,73,75]. The transmission dynamics of *P. knowlesi* appear to be primarily macaque-vector-human. However, adaptation to human-vector-human transmission is possible whenever a large number of human infected cases and mosquito vector are present [76]. Therefore, one health approach to mitigate zoonotic malaria transmission is mandatory. The concept of One Health (OH) refer to collaborative approach to health challenges that acknowledges the intersection of human medicine, veterinary medicine and environmental science [77].

5.1. Improved zoonotic malaria surveillance in human

To develop a comprehensive plan to control zoonotic malaria, it is necessary to first accurately determine the disease's prevalence in non-human primate. Further research on the malaria prevalence among various non human primate, bionomics and blood meal preference of the incriminated mosquito vectors and the intensity of human-primate interaction are needed to assess the distribution and relative risk of zoonotic-malaria infection in human populations, in order to design an appropriate control interventions. Furthermore, tracking the genetic subpopulations of primate malaria species should help researchers better understand the transmission dynamics in areas where the human-non human primate interaction and determine whether there is a link between unique knowlesi-malaria genetic subpopulations and clinical outcomes [72,75].

5.2. Non-human primate conservation strategies related to forest restoration and deforestation regulations

Conservation efforts have been made and are still being made in Indonesia (sustainable). Since 1940 Indonesia has Java-Madura Hunting Regulation, then in 1954 worked with International Unit Conservation Nature (IUCN) for wildlife sanctuary rehabilitation, and based on the Decree of the Minister of Agriculture No. 428 / Kpts / Org / 7/1978

Table 2
Genus and species of non-human primate in Indonesia.

Genus[a,b]	Species[a,b]	Island[a,b]	Conservation Status[b]
Nycticebus	*Nycticebus coucang* Boddaert, 1785	Sumatra	VU
	Nycticebus javanicus E. Geoffroy, 1812	Java	CR
	Nycticebus bancanus Lyon, 1906	Sumatra and Kalimantan	NE
	Nycticebus borneanus Lyon, 1906	Kalimantan	NE
	Nycticebus kayan Munds et al. 2013	Kalimantan	NE
	Nycticebus managensis Trouessart, 1893	Kalimantan	VU
Tarsius	*Tarsius tarsier* Erxleben, 1777	Sulawesi	VU
	Tarsius fuscus Ischer, 1804	Sulawesi	NE
	Tarsiun dentatus Miller & Hollister, 1921	Sulawesi	VU
	Tarsius pelengensis Sody, 1949	Sulawesi	EN
	Tarsius sangirensis Meyer, 1987	Sulawesi	EN
	Tarsius tumpara Shekelle et al. 2008	Sulawesi	CR
	Tarsius pumilus Miller & Hollister 1921	Sulawesi	DD
	Tarsius lariang Merker & Groves, 2006	Sulawesi	DD
	Tarsius wallacei Merker et al. 2010	Sulawesi	DD
	Tarsius supriatnai Shekelle et al. 2017	Sulawesi	–
	Tarsius spectrumgurskyae Shekelle et al. 2017	Sulawesi	–
Cephalopachus	*Cephalopagus bancanus* Horsfield, 1821	Sumatra and Kalimantan	VU
Macaca	*Macaca nemestrina* Linnaeus, 1766	Sumatra and Kalimantan	VU
	Macaca siberu Fuentes & Olson, 1995	Sumatra	VU
	Macaca pagensis Miller, 1993	Sumatra	CR
	Macaca nigra Desmarest, 1822	Sulawesi	CR
	Macaca nigrescens Temminck, 1849	Sulawesi	VU
	Macaca tonkeana Meyer, 1899	Sulawesi	VU
	Macaca ochreata Ogilby, 1841	Sulawesi	VU
	Macaca hecki Matschie, 1901	Sulawesi	VU
	Macaca maura Schinz, 1825	Sulawesi	EN
	Macaca fascicularis Raffles, 1821	Sumatra	LC
	^Macaca brunnescens	Sulawesi	–
Hylobates	*Hylobates lar* Linnaeus, 1771	Sumatra	EN
	Hylobates agilis F. cuvier, 1821	Sumatra	EN
	Hylobates albibarbis Lyon, 1911	Kalimantan	EN
	Hylobates muelleri Martin, 1841	Kalimantan	EN
	Hylobates abbotti Kloss, 1929	Kalimantan	EN
	Hylobates funereus I. Geoffroy, 1850	Kalimantan	EN
	Hylobates klossii Miller, 1903	Sumatra	EN
	Hylobates moloch Audebert, 1798	Java	EN
Presbytis	*Presbytis thomasi* Collett, 1892	Sumatra	VU
	Presbytis melalophos Raffless, 1821	Sumatra	EN
	Presbytis sumatrana Muller & Schlegel, 1841	Sumatra	EN
	Presbytis bicolor, Aimi & Bakar 1992	Sumatra	DD
	Presbytis mitrata Eschscholtz, 1821	Sumatra	VU
	Presbytis comata Desmarest, 1822	Java	EN
	Presbytis potenziani Bonaparte, 1886	Sumatra	EN
	Presbytis siberu Chasen & Kloss, 1928	Sumatra	EN
	Presbytis femoralis Martin, 1838	Sumatra	NT
	Presbytis siamensis Muller & Schiegel, 1841	Sumatra	NT
	Presbytis natunae Thomas & Hartert, 1894	Kalimantan	VU
	Presbytis chrisomelas Muller, 1838	Kalimantan	CR
	Presbytis rubiicunda Muller, 1838	Kalimantan	LC
	Presbytis hosei Thomas, 1889	Kalimantan	VU
	Presbytis cranicus Miller, 1834	Kalimantan	EN
Trachypithecus	*Trachypithecus auratus* E. Geoffroy, 1812	Java	VU
	Trachypithecus mauritius Griffith, 1821	Java	VU
	Trachypithecus cristatus Raffless, 1821	Sumatra and Kalimantan	NT
Nasalis	*Nasalis larvatus* Wurmb, 1787	Kalimantan	EN
Symphalangus	*Simphalangus syndactilus* Raffless, 1821	Sumatra	EN
Simias	*Simias concolor* G.S. Miller 1930	Sumatra	CR
Pongo	*Pongo abelii* Lesson, 1827	Sumatra	CR
	Pongo pygmeus Linnaeus, 1760	Kalimantan	CR
	**Pongo tapanuliensis* Nurcahyo et al. 2017	Sumatra	CR

Sources: a. [54]; b. [78].
Not evaluated (NE); Data deficient (DD); Least concern (LC); Near threated (NT); Vulnerable (VU); Endangered (EN); Critically endangered (CR).
* *P. tapanuliensis* is new species.
^ [58].

dated June 10, 1978, eight Natural Resources Conservation Centers (BKSDA) were established as Technical Implementation Units (UPT) in the field of protection and preservation of nature and responsible to the Director General of Forestry. Even Indonesia has a forest police to protect forest areas, flora and fauna in conservation areas until now. But the new challenges to Indonesia's biodiversity are threatened by habitat degradation, invasive foreign species, and genetic resources theft [78].

The nature of biodiversity and zoonotic pathogen spill over risk to human is depending on the disease system, local ecology, and human social behavior. Thus, local governments should take any necessary steps to counter the concerns posed by agricultural enterprises by regulating forest conversion into either plantation or mining location, and supporting alternate uses of wooded land that are beneficial to biodiversity

5.3. Vector control strategies for the mitigation of zoonotic malaria transmission

Mosquitoes are the most common arthropod vectors of human disease, carrying malaria, lymphatic filariasis, and arboviruses like dengue and Zika virus globally. Unfortunately, most of these vector-borne diseases control still rely solely on vector control as chemotherapeutic treatment and prevention are currently nor available. Therefore, evidence-based vector control is the only option to mitigate the diseases transmission, particularly that occur in outdoor setting and in this regard necessitate a sustainable vector surveillance and control measures [79]. Traditional mosquito control methods have heavily relied on many chemicals to kill mosquitoes. Currently, many innovative vectors control intervention have been developed to control specific vector borne diseases like malaria. For outdoor/forest malaria transmission the use of personal repellent when travelling through the forest and spatial repellent could be considered in addition to the use of insecticide-treated bed nets (ITNs).

In the context of zoonotic malaria which transmission mainly occur outdoor/ or in the forest, the main mosquito vector involved in the transmission are so far members of *Anopheles leucosphyrus* group such as *An leucosphyrus* subgroup and *A. hackeri* that are distributed in Indonesia from Sumatra, Java, Kalimantan, Sulawesi and lesser Sunda islands [80,81], and co-exist with various species of non-human primates. To mitigate the transmission, therefore, emphasis should be put on human to prevent the contact with mosquito vector.

6. Conclusion

The emergence of zoonotic malaria in Indonesia, particularly in areas where non-human primates and human are living in close proximity alerts to the need of appropriate mitigation efforts to reduce the risk to people as well as to protect the non-human primates who face extinction in some species. The natural habitat of the non-human primates should be carefully considered before converting the forest into the agricultural use and human re-settlement.

Declaration of Competing Interest

The authors declare no conflict of interest.

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