Malaria due to Plasmodium knowlesi in South-Eastern Asia and America. May imported cases represent a health care alert?

Plasmodium knowlesi as the fifth malaria parasite

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Conflicts of interest, funding, sponsorship, acknowledgements: none
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Recibido: 05/10/2009 Aceptado: 05/10/2009

Key words: Malaria parasites, Plasmodium knowlesi, emerging plasmodia, human health, public health concerns

Four main malaria plasmodia involve human beings. *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* had an older evolution paralelling the human species evolution (co-evolution)[1-3], while *Plasmodium falciparum* has been encountered by humans later during their evolution, since it was acquired by monkeys probably between the end of Mesolithic and the beginning of Neolithic eras[4]. Over twenty species of malaria plasmodia are capable of infecting monkeys (**Table 1**), but the anecdotal transmission of these organisms to humans has been considered until recently a rare event, with minor public health concerns. The transmission of these plasmodia protozoa predominantly occurred in South-Eastern Asia, China, and Central-Southern America[5]. The expansion of human activities in geographic areas which remained poorly anthropized in the past (i.e. forest zones where productive activities have been recently started), and wild regions, which are increasingly visited by travellers practicing trekking activities, represent objective elements which lead to an expected increase of risk to acquire malaria plasmodia of simian origin. Moreover, the present demographic expansion of local populations in different regions of the Southern Asia and Southern America, which also involved wild areas close to rain forests, especially when villages living of agricultural or breeding activities are interested, bear further epidemiological risk factors. In these environmental contexts, an overlapping of human and simian habitats becomes evident, in presence of a common infestation by *Anopheles* mosquitoes, which are the needed vehicle for malaria transmission to humans. Among the twenty plasmodia species which may infect monkeys, five of them have been documented as potential infectious agents for humans: they are *Plasmodium simium, Plasmodium brasilianum* (South America), *Plasmodium cynomolgi, Plasmodium inui*, and *Plasmodium knowlesi* (South-Eastern Asia)[5]. The majority of malaria infection of monkeys tend to cause a mild-to-moderate disease in humans, which is frequently self-limiting, and rarely requires antimalaric chemotherapy, since they are often missed or neglected. The identification of *P. knowlesi* disease foci confirmed by biomolecular techniques in Sarawak (Malaysian Boneo), Sabah (a state belonging to the Malaysia Confederation), and Pahang (peninsular Malaysia) between the end of the past century and early XXI century[6,7], catched the attention of researchers and clinicians operating in South-Eastern Asia, and more recently of the international health care authorities[5], initially focusing the attention on episodes which presented a typical malaria course, but received a microbiological (microscopic) diagnosis of *P. malariae* infection. A distinctive feature of these patients was the elevated parasitemia and the severity of clinical course, should a rapid and appropriate treatment was not administered[6,7]; in the records of these authors also four cases with a lethal evolution were present. Later, the availability of specific *P. knowlesi* primers allowed to pose a definitive diagnosis also in subjects whose erythrocytes proved morphologically similar to those infected by *P. malariae*, but tested negative when assessed with *P. malariae* primers. The more severe impact of *P. knowlesi* malaria is related to the evidence that this Plasmodium has a daily replication cycle and may therefore reach an elevated, life-threatening parasitemia in absence of an effective treatment, whereas *P. malariae* has a replication cycle every three days (responsible of the so-called quartan fever), and never reaches so elevated blood parasite concentrations[6-8]. Recent entomology studies[9] demontrated that in the Malaysian geographic context the more efficient vector transmitting *P. knowlesi* infection to humans is *Anopheles latens*, and the most elevated bite rate is registered at the limits of forest (6.74%), while a reduce frequency regards the rain forest (1.85%) and the examined longhouses (the typical

Malaysia houses) (0.28%), which never were the site of micro-epidemic disease clusters. Based on these data, it has been hypothesized that humans acquire infection in the forest, when hunting, or after working hours, when coming home at darkness[10]. The potential simian reservoirs are *Macaca mulatta*, *M. nemestina*, *M. inus*, and *Saimiri sciurea*. After the report of Malaysia foci, where native population was involved, and the identification of single imported cases in Europe and North America by tourists who travelled for short periods close to forest areas of South-Eastern Asia[11-15], the attention of researchers for *P. knowlesi* rapidly increased. In the year 2008, the Journal "Nature" published the analysis of the nuclear genomic sequencing of *P. knowlesi*[16]. It was the first complete gene sequencing of a simian *Plasmodium*, therefore offering the opportunity for a comparation with the complete genome of *P. vivax* and other already known Plasmodia genomes. In contrast with other plasmodial genomes, putative familiar antigenic variants are scattered throughout the genome and associated with intrachromosomal telomere repeats. One of these families, called KIRs, includes genomic sequences which on the whole match around one-half of the extracellular domain CD99 of the host: this situation suggested that this form could represent an inusual molecular mimicry[16,17]. A relevant information came from recent observations and epidemiological data coming from Malaysia. The habitat of humans is more and more overlapping that of primates, and it is primarily due to two aspects: the first is related to the expansion of human activities (agriculture, deforesting, clearing of valued wood, and animal breeding), in areas also inhabitated by monkeys. The second emerging issue is related to the relevant increase of touristic activities (i.e. trekking) by intrenational visitors, who spend a proportionally limited time in this environment, and subsequently come back to their countries of origin[8]. In this last situation, the limited knowledge of simian plasmodia and thir diagnostic-identification problems, may confuse Western health care providers, especially when a basic microscopic, parasitologic examination is carried out for the research and identification of malaria plasmodia, which does not allow to distinguish *P. malariae* from *P. knowlesi*, therefore posing at risk patient's life[8]. The biomolecular techniques are extremely useful to trace the general epidemiology of malaria, and to clarify the role and importance of mixed infections, which still remain underestimated[8]. Unfortunately these sophisticated assays are costly and not easily available throughout the world, especially in developing countries. On the basis of epidemiological features of regions where epidemic foci of *P. knowlesi* malaria have been reported, and the anecdotal episodes of clinical reports occurred in Western travellers coming back in their countries of origin with a *P. knowlesi* disease, it is not possible to establish whether infections have been acquired by the most common animal reservoirs (i.e. macaques), or whether human-to-human contagion may occur. However, it is presently clear that this zoonosis is no more responsible of single, episodic cases, but it represents a true health care emrgency in South-Eastern Asian countries. The Figure 1 allows to appreciate the overal co-evolutive pathway of malaria plasmodia in parallel with that of the genus Homo, from hominids (group A), toward modern men (group C), with the appearance of *P. falciparum* which entered the epidemiological scenario infecting humans (group B) of mesolithic and early neolithic eras, who spent their lives in cabins located at the edge of rain forest and in the proximity of the first cultured fields. Just the introduction of the first organized human activities which significantly contributed to the expansion of *P. falciparum*, which up to date represents the most relevant malaria pathogen from the pathocenosis of pre-historical populations, unavoidably conditioning both economic and anthropological development. With regard to the appearance of a novel malaria parasite epidemiologi-

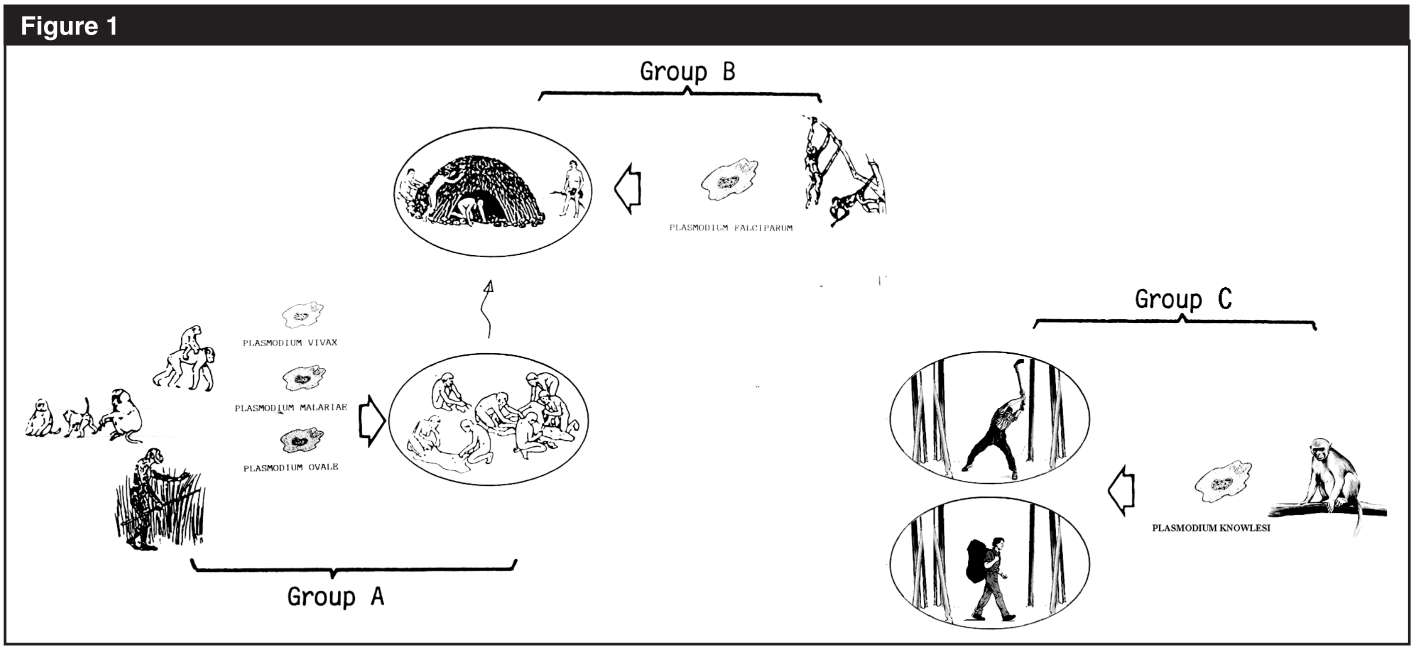
Table 1

Simian Plasmodium **species**	**Human species resembling to them**	**Regional distribution**
Asia		
P. coatney	*P. falciparum*	Malaysia, Philippines
P. cynomolgi	*P. vivax*	India, Indonesia, Malaysia, Sri Lanka, Taiwan
P. eylesi	*P. vivax*	Malaysia
P. fieldi	*P. ovale*	Malaysia
P. fragile	*P. falciparum*	India, Sri Lanka
P. hylobati	*P. vivax*	Indonesia
P. inui	*P. malariae*	India, Indonesia, Malaysia, Philippines, Sri Lanka, Taiwan
P. jeffrey	*P. vivax*	Indonesia, Malaysia
P. knowlesi	*P. malariae, P. falciparum*	China, Indonesia, Malaysia, Philippines, Singapore, Thailand, Taiwan
P. pitheci	*P. vivax*	Malaysia
P. simiovale	*P. ovale*	Sri Lanka
P. silvaticum	*P. vivax*	Malaysia
P. youngi	*P. vivax*	Malaysia
South America		
P. brasilianum	*P. malariae*	Brazil, Colombia, Mexico, Panama, Peru, Venezuela
P. simium	*P. vivax*	Brazil

Malaria species of simian origin isolated in Asia and in Southern America (modified from the reference quotation[4]). Their associated geographical distrubution, and the morphologic similarities to one of the four "classical" human plasmodia species (i.e. *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*), are pointed out.

cally relevant for humans, the hope is that this novel patocenosis remain circumscribed in some countries of South-Eastern Asia, without extension to other areas, which are susceptible due to similar climatic and environmental features. In this evenience, the impact of autochtonous populations, not naturally immunized, after the contacts which normally occur during early infancy, may be responsible for particularly severe consequences, not only for local populations lacking of a specific immune memery, but also for the growing number of tourists and excursionists, who may be exposed to the risk to come back to their countries of origin with a *P. knowlesi* malaria infection, whose diagnosis cannot rely on the routine laboratory examinations.

Figure 1



The enclosed graph depicts the biological and filogenetical evolutions of *P. vivax*, *P. malariae*, and *P. ovale* (Group A), compared with the extremely more recent evolution pathway of *P. falciparum* (group B). *P. knowlesi* (belonging to group C), is the last *Plasmodium* species which steadily entered the human pathology, and is related to productive and touristic human activities carried out in the forest regions of Malaysia and Borneo. The image has been taken and modified from some studies published by L. Capasso (quoted at reference [1]), in particular with the adjunct of group C malaria parasites.

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