Travel Medicine and Infectious Disease (2009) 7, 269–277

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

Malaria zoonoses

J. Kevin Baird*

Eijkman-Oxford Clinical Research Unit, Jalan Diponegoro No. 69, Jakarta 10430, Indonesia and The Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom

Received 3 June 2009; accepted 13 June 2009
Available online 14 July 2009

KEYWORDS
Malaria;
Zoonosis;
Primates;
Macaques;
Southeast Asia

Summary The genus *Plasmodium* includes many species that naturally cause malaria among apes and monkeys. The 2004 discovery of people infected by *Plasmodium knowlesi* in Malaysian Borneo alerted to the potential for non-human species of plasmodia to cause human morbidity and mortality. Subsequent work revealed what appears to be a surprisingly high risk of infection and relatively severe disease, including among travelers to Southeast Asia. The biology and medicine of this zoonosis is reviewed here, along with an examination of the spectrum of *Plasmodium* species that may cause infection of humans.

Introduction

Endemic zoonoses represent an important segment of the range of health risks faced by travelers. This area of risk has not included parasites of the genus *Plasmodium* that cause malaria. No animal reservoir for these species was known and human infection by non-human species of plasmodia was limited to exceedingly rare case reports or experimental settings. Indeed, in the 1960s a comprehensive search for these zoonoses in the most likely setting (Southeast Asian jungle) produced entirely negative results.[1] Malariologists since then considered important malaria zoonoses improbable, despite an extraordinary confirmed case in 1965.[2] The seminal 2004 report by Singh et al.[3] documented routine infection of humans in Malaysian Borneo by *Plasmodium knowlesi*, a parasite naturally occurring among several species of macaques in Southeast Asia. This review will describe the subsequent corroborating reports affirming the problem, along with biological, geographic, clinical, and diagnostic aspects of the infection of importance to travel medicine.

The review looks beyond the specific case of *P. knowlesi* and describes a broader scope that includes other species of plasmodia that may also be likely to occur in humans. The incrimination of *P. knowlesi* as an important zoonosis ultimately rests upon a chain of unlikely events in the early 1960s characterized by Bruce-Chwatt[4] as, ''one of the most extraordinary concatenation of circumstances that reads like a detective story''. That case reported by Chin et al.[2] and fully recounted by Coatney et al. in their 1971 monograph[5] documented the first known case of naturally acquired simian malaria in humans. Forty years later, knowledge of that singular case brought focus to *P. knowlesi* in the renewed investigation applying the tools of molecular biology.[3] The absence of confirmed naturally acquired infections among other simian species of plasmodia should not discourage consideration and investigation of them as zoonoses. This review examines underlying host–parasite biology among

* Eijkman-Oxford Clinical Research Unit, Jalan Diponegoro No. 69, Jakarta 10430, Indonesia. Tel.: +62 21 391 0414; fax: +62 21 3190 5016.
E-mail address: kbaird@eocru.org

1477-8939/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tmaid.2009.06.004

the primate malarias in order to identify other *Plasmodium* species that would appear most likely capable of causing zoonoses. That analysis points to three species: *P. knowlesi*, *Plasmodium cynomolgi* and *Plasmodium inui*, all parasites of Southeast Asian macaques.

Illness linked to travel often prompts thorough diagnostic work up, and the opportunity for definitive diagnosis hinges upon inclusion of the real agent in the differential. This review explains the rationale for considering all four of the human malarias, along with *P. knowlesi*, *P. cynomolgi*, and *P. inui* in patients with a history of travel to Southeast Asia and a microscopic diagnosis of malaria.

Microscopic diagnosis of the malarias

Most physicians, laboratorians, and even scientists specializing in the study of malaria, have little appreciation of the morphological subtleties that distinguish species of plasmodia. Parasite morphology is only useful within defined limits of application, as in distinguishing the species of parasites that normally infect a particular host species. In other words, the morphological characteristics that reliably segregate *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* in humans do not constitute a basis for specific diagnosis across the genus *Plasmodium*.[6]

Groups of species within the genus *Plasmodium* that infect primates exhibit affinities of lineage, behavior and, to a lesser extent, morphology. These groups, by virtue of our human bias, center on the species that infect us: falciparum type, vivax type, ovale type, and malariae type (Table 1). These types are grouped according to the periodicity of asexual maturation in blood, i.e., quotidian, tertian, and quartan. *P. knowlesi* stands in a class alone because it is the only primate malaria species with a quotidian (24 h) asexual blood stage development (merogonic) cycle. A group of poorly understood species, all infecting lemurs, are known only by stained blood films.[7]

The grouping by types should not be confused with a guide to affinities strictly in the sense of appearances under the microscope. The immature trophozoites of *P. knowlesi*, for example, can look a great deal like those of *P. falciparum*, whereas older trophozoites and schizonts most closely resemble those of *P. malariae*. Any given species from any group infecting a human would appear essentially similar to one or more of the species normally found in humans. No pathognomonic forms affirm alien identity of an unmistakable plasmodia. Even an expert would have great difficulty making a specific microscopic diagnosis of a species occurring in an unnatural or incidental host regardless of species involved.

A practicing clinical microscopist will usually be called upon to make a specific diagnosis of malaria from a Giemsa-stained blood film. These practitioners would have been trained to distinguish the four species of plasmodia normally occurring in humans. Until recently, that was the universe of possibilities. In this calculus, a parasite that looks like neither *P. falciparum* nor *P. vivax* (e.g., mature trophozoites in normal-sized red blood cells) will very likely be *P. malariae*, and the distinction between *P. vivax* and *P. ovale* is quite subtle. In the absence of a compelling suspicion of a zoonosis, any plasmodia infecting humans would very likely be diagnosed as one of the ordinary human species.

This perspective largely explains a very significant and important aspect of human malaria being overlooked for

Table 1 Affinities among the primate malarias.

TERTIAN MALARIAS		
Vivax type	Ovale type	Falciparum type
Plasmodium vivax	*Plasmodium ovale*	*Plasmodium falciparum*
Plasmodium cynomolgi	*Plasmodium fieldi*	*Plasmodium coatneyi*
Plasmodium eylesi	*Plasmodium simiovale*	*Plasmodium fragile*
Plasmodium gonderi		*Plasmodium reichenowi*
Plasmodium hylobati		
Plasmodium jefferyi		
Plasmodium pitheci		
Plasmodium silvaticum		
Plasmodium schwetzi		
Plasmodium simium		
Plasmodium youngi		
QUARTAN MALARIAS	QUOTIDIAN MALARIA	UNKNOWN MALARIAS
Malariae type	**Knowlesi type**	**Inadequate information (all in lemurs)**
Plasmodium malariae	*Plasmodium knowlesi*	*Plasmodium girardi*
Plasmodium inui		*Plasmodium lemuris*
Plasmodium rodhaini		*Plasmodium foleyi*
Plasmodium brasilianum		*Plasmodium coulangesi*
		Plasmodium percygharnhami
		Plasmodium uilenbergi
		Plasmodium bucki