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REVIEW

Plasmodium cynomolgi in humans: current knowledge and future directions of an emerging zoonotic malaria parasite

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Abstract

Plasmodium cynomolgi (*Pcy*), a simian malaria parasite, is a recent perfect example of emerging zoonotic transfer in human. This review summarizes the current knowledge on the epidemiology of natural *Pcy* infections in humans, mosquitoes and monkeys, along with its biological, clinical and drug sensitivity patterns. Knowledge gaps and further studies on *Pcy* in humans are also discussed. This parasite currently seems to be geographically limited in South-East Asia (SEA) with a global prevalence in human ranging from 0 to 1.4%. The *Pcy* infections were reported in local SEA populations and European travelers, and range from asymptomatic carriage to mild/moderate attacks with no evidence of pathognomonic clinical and laboratory patterns but with *Pcy* strain-shaped clinical differences. Geographical distribution and competence of suitable mosquito vectors and non-primate hosts, globalization, climate change, and increased intrusion of humans into the habitat of monkeys are key determinants to emergence of *Pcy* parasites in humans, along with its expansion outside SEA. Sensitization/information campaigns coupled with training and assessment sessions of microscopists and clinicians on *Pcy* are greatly needed to improve data on the epidemiology and management of human *Pcy* infection. There is a need for development of sensitive and specific molecular tools for individual diagnosis and epidemiological studies. The development of safe and efficient anti-hypnozoite drugs is the main therapeutic challenge for controlling human relapsing malaria parasites. Experience gained from *P. knowlesi* malaria, development of integrated measures and strategies—ideally with components related to human, monkeys, mosquito vectors, and environment—could be very helpful to prevent emergence of *Pcy* malaria in humans through disruption of transmission chain from monkeys to humans and ultimately contain its expansion in SEA and potential outbreaks in a context of malaria elimination.

Keywords Malaria · *Plasmodium cynomolgi* · Emerging zoonosis · Biology · Epidemiology · Clinical patterns · Drug sensitivity · Future directions

Abbreviations

18S rRNA	Small subunit ribosomal RNA gene
ACT	Artemisinin-based combination therapy
AMA-1	Antigen membrane antigen 1
CQ	Chloroquine
CSP	Circumsporozoite protein
CVC	Caveola—vesicles complexes
Cyt-b	Cytochrome b
COX-I	Partial cytochrome c oxidase sub-unit 1 gene
DBP	Duffy binding protein
EBL/EBP	Erythrocyte binding ligand/protein
G6PD-d	Glucose-6-phosphate dehydrogenase deficiency
msp	Merozoite surface protein
NBP/RBP	Normocyte/Reticulocyte binding protein
mtDNA	*Complete mitochondrial genome*
Pbra	*Plasmodium brasilianum*
Pct	*Plasmodium coatneyi*
Pcy	*Plasmodium cynomolgi*
Pf	*Plasmodium falciparum*
Pfld	*Plasmodium fieldi*
Pin	*Plasmodium inui*
Pk	*Plasmodium knowlesi*
Pm	*Plasmodium malariae*
Po	*Plasmodium ovale*
Pv	*Plasmodium vivax*
PfRh	*P. falciparum* Reticulocyte-binding homologue

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PCR	Polymerase chain reaction
PQ	Primaquine
RBC	Red blood cell
rRNA	Ribosomal ribonucleic acid
SEA	South East Asia
sSA	Sub-Saharan Africa
TQ	Tafenoquine
TRAg	Tryptophan-rich antigen
WHO	World Health Organization

Introduction

Plasmodium falciparum (*Pf*) and *Plasmodium vivax* (*Pv*) are the main species involved in human malaria burden worldwide [1]. Though *Pv* is the most geographically distributed species in the world, *Pf* is the main malaria species responsible for a large fraction of global morbidity and mortality cases [1, 2]. African populations especially children and pregnant women are most vulnerable to malaria contributing to over 90% of the total global burden [1]. *Pf* is the predominant species in sub-Saharan Africa (sSA) and *Pv* is found to be highly prevalent in Latin America and South East Asia (SEA) where it can outcompete *Pf* as seen in some regions of India [3].

The *Pf* and *Pv* burden has been greatly decreased over the last decades due to the implementation and/or scaling-up of control measures such as long-lasting insecticide-treated nets, preventive treatment with sulfadoxine-pyrimethamine (SP), and artemisinin-based combination therapy (ACT) used as first-line treatment for uncomplicated malaria [1]. However, the World Health Organization (WHO) has noted a slowdown of malaria control since 2015 by mitigated reduction in malaria burden for these recent years. The emergence and spread of ACT-resistant *Pf* isolates is now well established in The Greater Mekong subregion in SEA, the likely reason for this slowdown. ACT resistance has also been recently reported in two African countries (Uganda and Rwanda) [4–6]. Other factors related to mosquito vectors (e.g., insecticide resistance), populations (e.g., self-medication, misuse of malaria preventive tools), and parasites particularly non-*Pf*/*Pv* malaria have also greatly impacted the effectiveness of malaria control measures [1].

The epidemiology of non-*Pf*/*Pv* species is largely understudied especially in sSA [7, 8], with few reports highlighting the presence of *P. ovale spp* (*Po*) and *P. malariae* (*Pm*) in a Tanzanian area where concomitant decline in *Pf* transmission was observed, thereby suggesting a possible shift from *Pf* to non-*Pf* malaria in this area [9]. Also, other non-*Pf*/*Pv* species such as *P. cynomolgi* (*Pcy*) could be a future public health problem as the case with *P. knowlesi* (*Pk*) parasites. Indeed, *Pk* is currently well established in humans especially in SEA countries such as Malaysia where it can elicit severe clinical attacks and deaths [10]. Thus, such emerging malaria species such as *Pcy* could jeopardize malaria elimination objectives if not addressed timely.

Data on the epidemiology and clinical outcomes of *Pcy* in humans are currently available from different studies and case reports, but very few reviews are currently available [11, 12]. In the present review, we summarized the current knowledge on the epidemiology of natural infections of humans with *Pcy* parasites and its biological, clinical and drug sensitivity patterns. Current knowledge gaps and further studies on this emerging zoonotic parasite and related simian malaria parasites are also discussed.

Addendum search strategy

We used PubMed, Google scholar, Google, Scopus, Wiley Online library, the World Malaria Report, The WHO regional websites, and ClinicalTrials.gov to search for publications on *Plasmodium cynomolgi*, that were published between January 1900 and August 2022, and written either in English or French. The archives of local scientific associations/journals and websites of national malaria programmes were also consulted. We used the search terms "malaria", "*Plasmodium cynomolgi*" and "simian malaria". Additionally, we reviewed relevant articles cited in references of identified literature and included them as primary sources. Publications were considered of interest if they addressed any aspect of *Pcy* parasites including its biology, prevalence, clinical presentation and course, and treatment aspects. Principal investigators were contacted to request a full length paper and/or more details on studies. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Origin and diversity

The first description of *Pcy* was done in 1907 by M. Mayer who isolated it from a *Macaca fascicularis* long-tailed macaque, originally designated *M. irus*, in Java [13]. The strain was then extensively re-described and laboratory-established by H.W Mulligan ~ 30 years later [14]. In the late 1950s, a second *Pcy* strain was established by Prof. P.C.C. Garnham who named it *Pcy bastianiellii* and is currently called "B" strain [15]. The *Pcy* strain described by Mulligan was analyzed by research laboratories across the world and variably termed between 1959 and 1963. This strain was finally called M or Mulligan strain in honor of H.W Mulligan [16, 17]. Between 1965 and 1971, other new *Pcy* strains (e.g., Berok, Cambodian, RO, PT-I, Gombak, Ceylonensis, Smithsonian) was isolated from monkeys and mosquitoes and their developmental phases (i.e., sporogony, erythrocytic

and exoerythrocytic steps) in both mosquito vectors and macaques (Fig. 1) [18–25]. Later, investigations have been conducted to address several aspects of *Pcy* parasites such as evaluation of candidate anti-relapse drugs, vaccine development, epidemiology in monkeys/mosquitoes/humans, and genetic diversity studies (Fig. 2).

Studies have assessed the genetic diversity of *Pcy* parasites by analyzing the polymorphism within genes and comparing sequences to different *Pcy* strains and other *Plasmodium* species. The main objective of such studies was to determine the role of evolutionary drivers within *Pcy* species. On analyzing 18S sequences, Wong and coworkers found a clear pattern of geographical structuration of *Pcy* populations from two Malaysian regions (Sabah and Peninsular Malaysia) [26]. In Thailand, one study reported high nucleotide diversity in Duffy binding protein genes (DBP) of *Pcy* (*PcyDBP1*), *Pv* (*PvDBP*), and *Pk* (*PkDBPα*, *PkDBPβ*, *PkDBPγ*) populations, with occurrence of positive selection in domain V of *PcyDBP1*, and domains I, II and III of *PvDBP* [27]. Similarly, high nucleotide and haplotype diversity but occurrence of purifying selection were found on analysis of *PcyDBP2* domain II from *Pcy* isolates collected from wild macaques in Peninsular Malaysia [28]. Pacheco and colleagues have reported higher genetic diversity in merozoite surface protein 8 and 10 genes of *Pcy* and *Plasmodium inui* (*Pin)* compared to that of *Pf*, *Pk* and *Pv* isolates. Also, some studies found the role of purifying selection on both *msp8* and *msp10* from *Pcy* parasites from different geographical origins (Cambodian, Gombak, Ceylonensis, B, Mulligan, PT-I, and RO) [29].

Epidemiology of natural *P. cynomolgi* infections in monkeys, mosquito vectors and humans

Monkeys

Monkeys of the genera *Macaca* and *Presbytis* are natural hosts of *Pcy* parasites. In addition to *Macaca* monkeys, other genera (i.e., *Aotus* and *Saimiri*) are largely used for experimental studies aiming at addressing different aspects of *Pcy* infections like parasite biology, drug sensitivity and pathophysiological aspects [30, 31]. Given the difficulties in continuous culture for *Pv*, simian models using *Pcy* are considered to be a good proxy for *Pv* biology and pathophysiology for genetic similarities between these two malaria species [32–34]. In natural conditions, *Pcy* has been reported as mono-infections and/or mixed infections with other simian malaria parasites such as *P. inui* (*Pin*), *P. coatneyi* (*Pct*) and *P. fieldi* (*Pfld*) (Table 1 and Supplementary material 1). A recent systematic review reported an average *Pcy* prevalence of 33.05% in macaques from Malaysia [35]. In Philippines, the prevalence of *Pcy* was 23.2% in captive and wild *M. fascicularis* long-tailed monkeys [36]. Fungfuang and colleagues reported a similar *Pcy* prevalence rate (20%) in Thailand among three macaque species (*M. fascicularis*, *M. leonina*, *M. arctoides*) [37]. Great Apes such as orangutans are not natural hosts of *Pcy* parasites [38, 39].

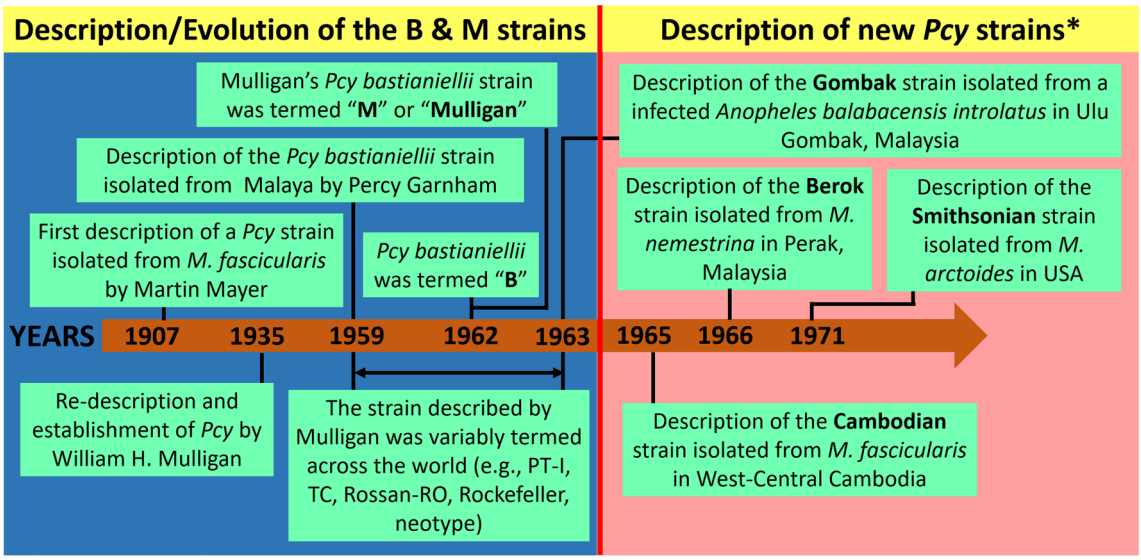

Fig. 1 Brief timeline on discovery and description of *P. cynomolgi* strains. *Only mainly studied *P. cynomolgi* strains are depicted

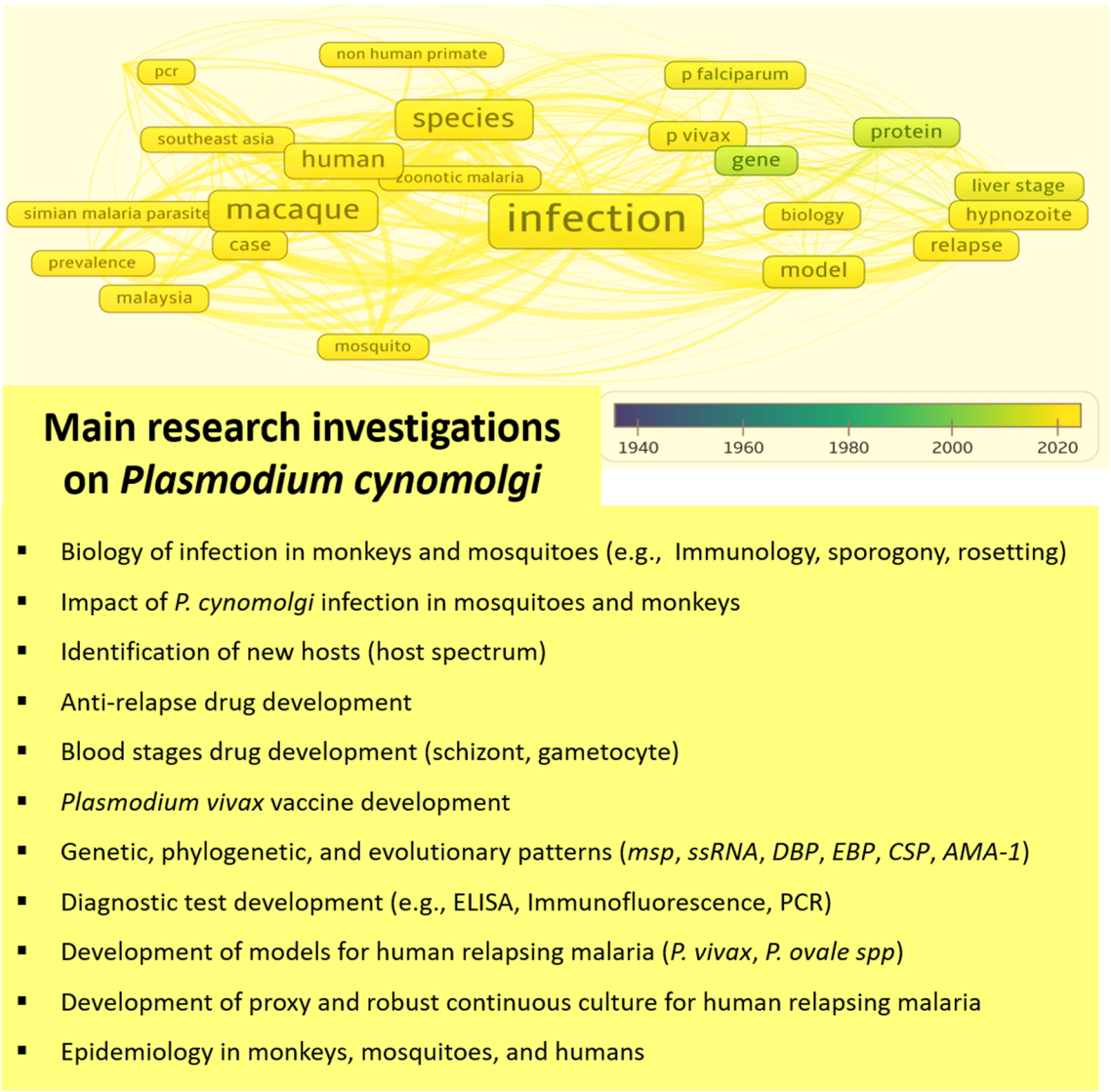

Fig. 2 Main research investigations on *Plasmodium cynomolgi* parasites-identified through brief bibliometric analysis of studies on *Pcy* parasites. Studies were sourced from PubMed database, 1946–2022. Bibliometric analysis was performed using the search term "*Plasmodium cynomolgi*", and overlay visualization maps were generated using VOSViewer software v1.6.18 (Leiden University, The Netherlands). Keywords used to generate overlay visualization maps were retrieved from paper titles and abstracts, and counted using full counting method. A minimum of 10 occurrences was chosen as threshold for selecting keywords. Some redundant/synonymous keywords were removed during extraction process of and keyword co-occurrence analysis. AMA-1: Apical membrane antigen 1, CSP: Circumsporozoite protein, DBP: Duffy binding protein, EBP: Erythrocyte binding protein, *msp*: Merozoite surface protein, PCR: Polymerase chain reaction, ssRNA: Small subunit ribosomal RNA gene

Mosquitoes

In mosquito vectors, data on infection with *Pcy* are consistent with those seen in monkeys, with several mosquito species (e.g., *A. dirus*, *A. barbirostris*) collected from Malaysia and Vietnam where *Pcy* was found in mono-infections and more frequently in mixed infections with *Pv*, *Pin*, *Pk*, *Pfld* and *Pct* (Table 2 and Supplementary material 1). A brief presentation of distribution and biting behavior of *Anopheles* species associated with *Pcy* transmission to humans both in laboratory and natural conditions is presented in Table 3 [40–45].

Humans

Several reports on accidental and experimental human *Pcy* infections are a proof of possible detection of natural human infections with this simian malaria parasite, an emerging zoonotic malaria infection [46–50]. The first case of natural human infections was reported in 2014 from a 39-year

Table 1 Studies on natural infections of monkeys with *Pcy* parasites using molecular tools

Monkey species	Country	Total number of samples	Target parasite gene	*Pcy* prevalence rate (*n*)	Other *Plasmodium* species (*n*) and association with *Pcy*
M. fascicularis, *M. nemestrina*	Malaysia	Blood ($n=82$ and $n=26$)	*18S rRNA*	63.4% ($n=52$) and 34.6% ($n=9$)	In *M. fascicularis*: Dual infections [*Pcy*+*Pin*, $n=2$; *Pcy*+*Pk*, $n=2$], Triple infections [*Pcy*+*Pin*+*Pk*, $n=4$; *Pcy*+*Pct*+*Pk*, $n=3$; *Pcy*+*Pct*+*Pin*, $n=1$], quadruple infections [*Pcy*+*Pct*+*Pin*+*Pk*, $n=38$], Quintuple infections [*Pcy*+*Pct*+*Pin*+*Pfld*+*Pk*, $n=1$] In *M. nemestrina*: Dual infections [*Pcy*+*Pin*, $n=2$], Triple infections [*Pcy*+*Pin*+*Pk*, $n=3$; *Pcy*+*Pct*+*Pin*, $n=1$], quadruple infections [*Pcy*+*Pct*+*Pin*+*Pk*, $n=3$]
M. fascicularis, *M. nemestrina, Pongo pygmaeus*[c]	Malaysia	Blood ($n=15$, $n=26$ and $n=38$)	*Cyt-b*	6.7% ($n=1$) and 11.5% ($n=3$) and 0% ($n=0$)	–
M. fascicularis	Malaysia	Blood ($n=70$)	*18S rRNA*	25.7% ($n=18$)	Dual infections [*Pcy*+*Pin*, $n=3$; *Pcy*+*Pct*, $n=1$; *Pcy*+*Pk*, $n=1$], Triple infections [*Pcy*+*Pin*+*Pk*, $n=4$; *Pcy*+*Pct*+*Pin*, $n=3$; *Pcy*+*Pct*+*Pk*, $n=1$], quadruple infections [*Pcy*+*Pct*+*Pin*+*Pk*, $n=3$]
M. fascicularis	Laos, Singapore, Cambodia, Philippines, Indonesia	Blood ($n=44$, $n=40$, $n=54$, $n=68$ and $n=70$)	*18S rRNA*	63.6% ($n=28$), 65% ($n=26$), 50% ($n=27$), 5.9% ($n=4$) and 87.1% ($n=61$)	Laos: - Singapore: Dual infections [*Pcy*+*Pin*, $n=1$; *Pcy*+*Pct*, $n=1$], Triple infections [*Pcy*+*Pin*+*Pfld*, $n=1$] Cambodia: Dual infections [*Pcy*+*Pin*, $n=2$; *Pcy*+*Pfld*, $n=1$] Philippines: Dual infections [*Pcy*+*Pct*, $n=1$] Indonesia: Dual infections [*Pcy*+*Pin*, $n=2$; *Pcy*+*Pfld*, $n=1$], Triple infections [*Pcy*+*Pin*+*Pfld*, $n=1$]
M. radiata[a,b,c]	India	Blood, spleen and liver	*Cyt-b, msp1*$_{42}$*, 18S rRNA*	–	One *Pcy* case was identified in blood samples using the three molecular markers

Table 1 (continued)

Monkey species	Country	Total number of samples	Target parasite gene	*Pcy* prevalence rate (*n*)	Other *Plasmodium* species (*n*) and association with *Pcy*
M. fascicularis[c,d]	Malaysia	Blood ($n=43$)	*mtDNA, ClpM*	11.5% ($n=13$) using *mtDNA*, 4.5% ($n=4$) using *ClpM*	–
M. fascicularis[b,e]	Philippines	Blood ($n=95$)	*18S rRNA*	24.2% ($n=23$)	Triple infections [*Pcy*+*Pin*+*Pfld*, $n=7$], Quadruple infections [*Pcy*+*Pct*+*Pin*+*Pfld*, $n=5$; *Pcy*+*Pin*+*Pfld*+*Pk*, $n=3$], Quintuple infections [*Pcy*+*Pct*+*Pin*+*Pfld*+*Pk*, $n=8$]
M. fascicularis, *M. nemestrina*[e]	Malaysia	Blood ($n=98$ and $n=5$)	*18S rRNA*	41.8% ($n=41$) and 20% ($n=1$)	In *M. fascicularis*: Dual infections [*Pcy*+*Pin*, $n=13$; *Pcy*+*Pct*, $n=2$], Triple infections [*Pcy*+*Pin*+*Pk*, $n=6$; *Pcy*+*Pfld*+*Pin*, $n=1$] and quadruple infections [*Pcy*+*Pin*+*Pfld*+*Pk*, $n=1$] In *M. nemestrina*: Triple infections [*Pcy*+*Pct*+*Pin*, $n=1$]
M. fascicularis, *M. nemestrina, M. arctoides*[b,e]	Thailand	Blood ($n=93$)	*18S rRNA*	8.6% ($n=8$)	Dual infections [*Pcy*+*Pin*, $n=1$; *Pcy*+*Pct*, $n=1$], Triple infections [*Pcy*+*Pfld*+*Pin*, $n=2$]
M. fascicularis	Malaysia	Blood ($n=176$)	*18S rRNA*	65.9% ($n=116$)	Dual infections [*Pcy*+*Pct*, $n=14$; *Pcy*+*Pfld*, $n=1$; *Pcy*+*Pk*, $n=14$], Triple infections [*Pcy*+*Pct*+*Pk*, $n=22$], quadruple infections [*Pcy*+*Pfld*+*Pin*+*Pk*, $n=2$; *Pcy*+*Pct*+*Pfld*+*Pin*, $n=2$], Quintuple infections [*Pcy*+*Pct*+*Pin*+*Pfld*+*Pk*, $n=2$]
M. fascicularis, *M. nemestrina*	Thailand	Blood ($n=1015$)	*COX-I*	16.95% ($n=172$)	Not specified
M. fascicularis, *M. nemestrina*	Malaysia	Blood ($n=48$ and $n=25$)	*18S rRNA*	18.75% ($n=9$) and 12% ($n=3$)	In *M. fascicularis*: Dual infections [*Pcy*+*Pin*, $n=1$; *Pcy*+*Pct*, $n=1$], Triple infections [*Pcy*+*Pct*+*Pk*, $n=1$; *Pcy*+*Pct*+*Pin*, $n=3$], quadruple infections [*Pcy*+*Pct*+*Pin*+*Pk*, $n=4$] In *M. nemestrina*: Dual infections [*Pcy*+*Pin*, $n=1$], Triple infections [*Pcy*+*Pct*+*Pin*, $n=1$]

Table 1 (continued)

The references used for this table as listed as supplementary file 2

Pcy: Plasmodium cynomolgi, *Pin: Plasmodium inui*, *Pct: Plasmodium coatneyi*, *Pfld: Plasmodium fieldi*, *Pk: Plasmodium knowlesi*

18S rRNA: Small subunit ribosomal RNA gene, *ClpM: Apicoplast caseinolytic protease M*, *Cyt-b: Cytochrome b*, *COX-1: Partial cytochrome c oxidase sub-unit 1 gene*, *msp: Merozoite surface protein*, *mtDNA: Complete mitochondrial genome*

[a]Prevalence was not computable as total number of different tissue samples was not clearly given in the study

[b]Some captive monkeys were sampled in the studies (*M. nemestrina* in Malaysia, *M. radiata* in India)

[c]Data on mixed infections were not available in the study although other simian/human *Plasmodium* species (*Pin*, *Pct*, *Pk*, *Pfld*, *Pf*, *P. fragile*, *P. simiovale*) were found

[d]Malaria speciation was inferred using Bayesian phylogenetic analysis, and proportion of *Pcy* was computed using the total number of sequences generated for each of gene

[e]We reported only mixed infections cases where *Pcy* parasites were found by the authors

old woman in the Hulu Terengganu area, East coast of Peninsular Malaysia [51]. Malaria parasites were microscopically misidentified as *Pm/Pk* mixed infections at a hospital and then as *Pv* at a reference medical institute in Malaysia. Molecular data coupled with sequencing and phylogenetic analysis confirmed this infection case with *Pcy* even though initially *Pv* was identified using nested polymerase chain reaction (PCR) protocol only [51]. Several other reports of natural human infections with *Pcy* parasites in Malaysia and other countries (Thailand, Cambodia) have also been published [52–58]. Hartmeyer and colleagues reported natural *Pcy* infections in European traveler (37 years old Danish woman) returning from Thailand and Malaysia [53]. Geographical distribution of naturally acquired *Pcy* infections in humans are presented in Fig. 3 and supplementary material 2. The *Pcy* infections have been reported in adults as mono-infections and/or mixed infections with *Pf*, *Pv* and *Pk* from macaques inhabited forest areas restricted currently to Malaysia, Thailand and Cambodia (Supplementary material 2).

Role of other zoonotic species in human malaria: *Plasmodium brasilianum, P. simium, P. inui* and others

There is a growing body of evidence on less restricted host tropism of simian malaria parasites as exemplified by the ability of *Pcy* to naturally infect other hosts such as humans, even though the human infections seem to be limited in few SEA countries. In this context, it is likely to see human infections with simian malaria species other than *Pcy*. Analyzing the *18S rRNA* and circumsporozoite genes of *Plasmodium* species, one study reported natural human infections with *P. brasilianum* (*Pbra*), an *Alouatta* monkeys' parasite, in individuals from the Venezuelan Amazon, South America [59]. Likewise, *Pbra* was also reported to cause human infection in some coastal areas in Brazil [60]. In Malaysia, *Pin*, *Pin*-like, *Pct*, and *P. simiovale* parasites were found to infect humans based on analysis of the *18S rRNA* and *COXI* genes [58, 61]. In Brazil, one study reported an outbreak of human malaria infections caused by *P. simium* [62].

Biological, clinical, and drug sensitivity patterns of *P. cynomolgi* infections

Biological and clinical patterns

Biological, morphological and clinical characteristics of *Pcy* are quite similar to non-*Pf* species with incubation and pre-patent periods roughly shorter than that of *Pf* (Table 4). The erythrocytic cycle of *Pcy* parasites lasts for about 48 h,

Table 2 Publications on molecular detection of *Pcy* parasites in wild *Anopheles* mosquitoes

Country	Anopheles species	Target parasite gene	N	Total number of *Pcy* reported	Type of mixed infections
Vietnam	*A. dirus*	*18S rRNA*	79	11 (6 mono-infections, 5 mixed infections)	Dual: *Pcy* + *Pv* (*n* = 3) Triple: *Pcy* + *Pv* + *Pk* (*n* = 1) Quadruple: *Pcy* + *Pv* + *Pin* + *Pct* (*n* = 1)
Malaysia	*A. balabacensis*	*18S rRNA*	23	8 (4 mono-infections, 4 mixed infections)	Dual: *Pcy* + *Pin* (*n* = 2), *Pcy* + *Pk* (*n* = 1), *Pcy* + *Pfld* (*n* = 1)
Vietnama	*A. dirus, A. maculatus, A. minimus, A. aconitus*	*18S rRNA*	49	9 (6 mono-infections, 3 mixed infections)	Triple: *Pcy* + *Pv* + *Pin* (*n* = 3)
Malaysia	*A. balabacensis*	*18S rRNA*	38	24 (5 mono-infections, 19 mixed infections)	Dual: *Pcy* + *Pin* (*n* = 9), *Pcy* + *Pk* (*n* = 2) Triple: *Pcy* + *Pct* + *Pin* (*n* = 2), *Pcy* + *Pin* + *Pk* (*n* = 4) Quadruple: *Pcy* + *Pct* + *Pin* + *Pk* (*n* = 2)
Malaysia	*A. barbirostris (s.l.)*	*18S rRNA*, *COXI*, *ITS2*	16	2 (2 mixed infections)	Dual: *Pcy* + *Pk* (*n* = 1) Triple: *Pcy* + *Pfld* + *Pin* (*n* = 1)
Malaysia	*A. laten, A. roperi*	*18S rRNA*	11	3 (3 mixed infections)	Triple: *Pcy* + *Pfld* + *Pin* (*n* = 1), *Pcy* + *Pct* + *Pk* (*n* = 1) Quadruple: *Pcy* + *Pfld* + *Pin* + *Pk* (*n* = 1)

The references used for this table as listed as supplementary file 2

Pcy: *Plasmodium cynomolgi*, *Pin*: *Plasmodium inui*, *Pct*: *Plasmodium coatneyi*, *Pfld*: *Plasmodium fieldi, Pk: Plasmodium knowlesi*

18S rRNA: Small subunit ribosomal RNA gene, COXI: Mitochondrial cytochrome c oxidase subunit 1, ITS2: Internal transcribed spacer 2

N: Total number of *Plasmodium*-infected mosquitoes

[a]Mosquito species infected with *Pcy* was not clearly specified

and at the end of this cycle each mature schizont produces 14–20 merozoites in the infected RBC. Once released in bloodstream, the newly produced merozoite can infect fresh RBCs to either multiply asexually or sexually. There is no evidence of rosetting and sequestration of *Pcy* parasites in the bloodstream as seen in *Pf* infections. In contrast, the simian species *Pcy* is quite closer to its *Pv* sister species on several attributes like preferential invasion of reticulocytes (young erythrocytes), early formation of infectious gametocytes, production of particular structures inside erythrocytes called caveola—vesicles complexes (CVCs), tertian periodicity and relapses of infections due to dormant stages (hypnozoites) (Table 4 and Supplementary material 3). Even within *Pcy* parasites, these biological characteristics are strain-dependent (e.g., the extent of avidity for reticulocytes was demonstrated to be higher for Cambodian and Berok compared to B and Gombak strains) [63].

Clinical and laboratory findings—Pcy strains/species

Data on the clinical spectrum of *Pcy* infections are limited to findings from experimental studies in non-immune individuals and fewer from field studies in both non-immune and immune indigenous individuals (Fig. 4). In 1961, an accidental infection case of a 31-year old student with *Pcy* was reported from New York University, School of Medicine, USA. The student presented chills, tertian-pattern high fever, severe headache and slight alterations in some biochemical (serum bilirubin, lactate dehydrogenase) and hematological parameters (hemoglobin, hematocrit and red blood cell count) [50]. Few years later, accidental infections with the B strain were reported from France in two individuals with high fever, headache, nausea and various aches [49].

The clinical signs/symptoms of *Pcy* infections are similar to those of other malaria species with slight differences between the *Pcy* strains. One experimental study outlined similar major symptoms (high fever, cephalgia, anorexia, myalgia and nausea) for the *Pcy* M and B strains, but differences in duration, frequency of fever and spleen enlargement [16]. Longer duration and higher frequency of the tertian fever, higher frequency of splenomegaly were seen in *Pcy M*–infected volunteers as compared to their *Pcy B*–infected counterparts. Also, chills and vomiting were specifically seen in individuals experimentally infected with the strain M [16]. The sister species *Pcy* and *Pv* exhibit similar clinical course which is mild to moderate for *Pcy* (B strain), and moderately severe for *Pv* [47]. Several other *Pcy*-related signs/symptoms like diffuse abdominal pain, thrombocytopenia, generalized malaise, reduction in adrenal response, anemia-accompanying reticulocytosis, leucopenia, increase in erythrocyte sedimentation, low back pain, hypoalbuminemia, and hypergammaglobulinemia have also been reported [47, 48]. Some of the above mentioned signs/symptoms (i.e.,

Table 3 Distribution and bionomics of *Anopheles* species infected with *Pcy* parasites in natural conditions

Anopheles species	Geographical distribution (countries)**	Biting behavior	Laboratory susceptibility to *Pcy* infections
A. dirus#	Asia–Pacific (Myanmar, Thailand, Malaysia)	Zoophilic and anthropophilic, Both endophagic and exophagic	–
A. maculatus‡#a	Asia–Pacific (Myanmar, Singapore)	Zoophilic and anthropophilic, Both endophagic and exophagic	High
A. minimus#	Asia–Pacific (India, Myanmar, Thailand, Malaysia, Vietnam)	Zoophilic and anthropophilic, Both endophagic and exophagic	–
A. aconitus#	Asia–Pacific (Australia, Bangladesh, Bhutan, Cambodia, India, Indonesia, Laos, Myanmar, Sri Lanka)	Zoophilic and anthropophilic, Both endophagic and exophagic	Low
A. balabacensis#	Asia–Pacific (Indonesia, Malaysia, Philippines)	Zoophilic and anthropophilic, Strongly exophagic	High
A. barbirostris (s.l.) #	Asia–Pacific (Myanmar, India, Indonesia, Philippines, Thailand)	Zoophilic and anthropophilic	Low to high
A. latens#	Asia–Pacific (Indonesia, Malaysia, Thailand)	Zoophilic and anthropophilic, Both endophagic and exophagic	–
A. roperi#	Asia–Pacific (Cambodia, India, Indonesia, Malaysia, Thailand)	Zoophilic and anthropophilic, Both endophagic and exophagic	Low
A. freeborni‡a	North America (Canada, Mexico, USA)	Zoophilic and anthropophilic, Both endophagic and exophagic	High
A. atroparvus‡	Europe and Middle East (France, Germany, Iran, Italy, Portugal, Spain)	Zoophilic and anthropophilic, Both endophagic and exophagic	High
A. stephensi‡a	Asia–Pacific (Bangladesh, Myanmar, India, Iraq, Iran), Horn of Africa (Ethiopia, Djibouti)	Zoophilic and anthropophilic, Both endophagic and exophagic	Moderate to high
A. elegans‡c	Asia–Pacific (India, Solomon Islands, Sri Lanka, Thailand)	Zoophilic and anthropophilic, Both endophagic and exophagic	High
A. kochi‡abc	Asia–Pacific (Bangladesh, Cambodia, China, India, Indonesia, Laos, Malaysia, Myanmar, Nepal, Philippines, Singapore, Thailand, Vietnam)	Zoophilic and anthropophilic, Both endophagic and exophagic	Moderate to high
A. letifer‡	Asia–Pacific (Cambodia, Indonesia, Malaysia, Singapore, Thailand, Vietnam)	Zoophilic and anthropophilic, Strongly exophagic	Moderate
A. lesteri‡	Asia–Pacific (China, Japan, Korea, Philippines)	Zoophilic and anthropophilic, Both endophagic and exophagic	Moderate
A. sundaicus‡	Asia–Pacific (India, Indonesia, Malaysia, Thailand, Vietnam)	Zoophilic and anthropophilic, Both endophagic and exophagic	High
A. vagus‡	Asia–Pacific (Afghanistan, Bangladesh, Bhutan, Cambodia, Guam, India, Indonesia, Laos, Malaysia, Myanmar, Nepal, People's Republic of China, Philippines, Singapore, Sri Lanka, Thailand, Vietnam)	Zoophilic and anthropophilic, Both endophagic and exophagic	Low to moderate
A. quadrimaculatus‡	North America (Belize, Canada, Costa Rica, Cuba, Dominican Republic, Mexico, Panama, Puerto Rico, USA)	Zoophilic and anthropophilic, Both endophagic and exophagic	Moderate to high
A. philippinensis‡	Asia–Pacific (Bangladesh, Bhutan, Cambodia, India, Indonesia, Laos, Malaysia, Myanmar, Nepal, People's Republic of China, Philippines, Thailand, Vietnam)	Zoophilic and anthropophilic, Both endophagic and exophagic	Moderate

Underlined term outlines the main biting behaviour of the mosquito species

#Field studies found *Pcy* parasites in salivary glands of these mosquito species

‡These mosquito species have shown moderate-to-high susceptibility to *Pcy* infections and successful transmission and infection to monkey with viable sporozoites[13, 19–22]

Several *Pcy* strains were used for experimental infections of *Anopheles* mosquitoes: Berok[a], Cambodian[b], Gombak[c],

**Some examples of countries where this mosquito species/complex are given in brackets

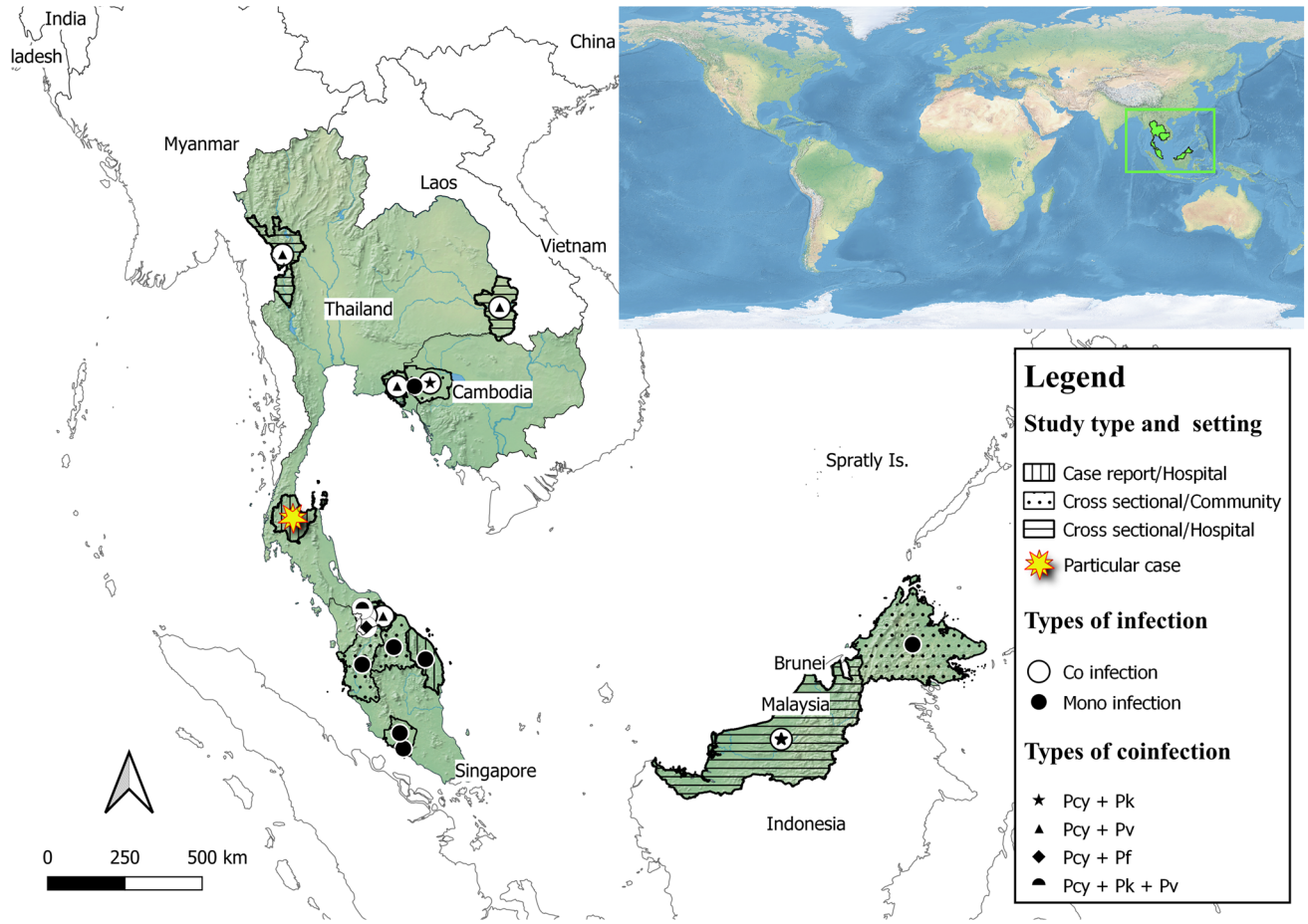

Fig. 3 Geographical distribution of natural *P. cynomolgi* infections in humans. *Pf*: *Plasmodium falciparum*, *Pcy*: *Plasmodium cynomolgi*, *Pk*: *Plasmodium knowlesi*, *Pv*: *Plasmodium vivax*. Maps were created using the QGIS software v3.10 (https://qgis.org/en/site/). References used to generate the map are presented in Supplementary file 1. The yellow star refers to a particular case for which an European patient (Danish) travelled to Malaysia and Thailand, but the exact origin of *Pcy* infection was unclear [53]. Based on the patient's reports on staying in treehouses for three days, mosquito bites and sightings of macaques in Jungle, Khao Sok, Thailand is assumed as probable origin of the *Pcy* infection

anemia, thrombocytopenia, and anemia-accompanying reticulocytosis) have also been reported in macaques experimentally infected with *Pcy* B strain sporozoites [30, 32].

Regarding field investigations mild-to-moderate fever, chills and rigors, cough and cold were reported in a Danish woman visiting the Terengganu state, Malaysia [51]. Another study reported fever, chills, rigors, headache and myalgia in a man living in the Kelantan state, Malaysia (Fig. 4) [55].

Drug sensitivity patterns and hypnozoites

The shared biological peculiarity for *Pv*, *Po* and *Pcy* parasites to provoke malaria relapses is due to reactivation of dormant development stages ("hypnozoites") in several weeks to years after the first malaria attack [64]. Current antimalarial drugs (e.g., chloroquine, sulfadoxine-pyrimethamine, atovaquone-proguanil, and ACTs) are effective against blood stages of all human malarias, but unable to kill hypnozoites to prevent relapses. Two 8-aminoquinolones, primaquine (PQ) and tafenoquine (TQ), have high hypnozoiticidal activity, but their therapeutic response against *Pv* blood stages is slower than that of ACTs and chloroquine (CQ), and this jeopardizes their usage as monotherapy [65, 66].

In practice, the concomitant elimination of blood stages and exoerythrocytic stages, including hypnozoites, known as radical cure, is obtained by utilization of a blood stage-killing drug (e.g., CQ or Atovaquone-proguanil) and an anti-relapse drug [67]. Radical cure with PQ is WHO-endorsed and is adopted in national guidelines of several *Pv*-endemic countries [68]. However, the routine administration of PQ and TQ is challenging in these areas due to compliance, economic, ethical and safety issues [69, 70]. These hypnozoiticidal drugs can elicit severe hemolytic anemia in patients

Table 4 Comparison of *P. cynomolgi* with five human *Plasmodium* species

Characteristics	*P. falciparum*	*P. vivax*	*P. malariae*	*P. ovale*	*P. knowlesi*	*P. cynomolgi*
Sporogonic cycle duration (days)[§]	~8–21	~8–15	~14–17	~12–14	~9–15	~7.5–28
Pre-erythrocytic cycle (days)[†]	~5–10	~6–12	~14 –16	~9	~5–9	~8–10
Incubation period from the infecting mosquito bite (days)[‡]	~9–14[a]	~12–17[b]	~18–40	~9–14[b]	~9–12	~15–37
Pre-patent period (days)[*]	~6—25[c]	~11–13[b]	~15–59	~10–20	~5–12	~7–16[d]
Erythrocytic cycle (hours)	48 (Tertian)	48 (Tertian)	72 (Quartan)	50 (Tertian)	24 (Quotidian)	48 (Tertian)
Number of merozoites released by erythrocyte infected	~8–20[e]	~14–20[e]	~6–14	~8–20	~16	~14–20[e]
Early development of mature gametocytes[**]	No	Yes	Yes	Yes	Yes	Yes
Dormant stages (Hypnozoites)	No	Yes	No	Yes	No	Yes
Relapse latency[#]	-	Short to Long	–	Short to Long	–	Short
Rosetting	Yes	Yes	No	No	Yes[f]	No
Sequestration in human blood-stream	Yes[g]	Yes[f]	No	No	Yes[g]	No
Preferred erythrocytes for invasion	All	Reticulocytes	Older normocytes	Reticulocytes	All	Reticulocytes
Some examples of ligands for human erythrocyte invasion[##]	EBL (EBA-175, EBA-140, EBA-1, & EBA-181); PfMSP1; PfRh (PfRh1, PfRh2, PfRh3, PfRh4, PfRh5)	DBP (PvDBP1, PvDBP2)[h]; RBP (PvRBP 1a, 1b, 2a, 2b, 2c); PvMSP1; PvTRAg (PvTRAg38, PvTRAg35.2)	RBP (PmRBP1a, 1b, 2a, 2b and 3)	RBP	DBP (PkDBP-α); NBP (NBPXa, NBPXb)	DBP (PcyDBP-1 and Pcy-DBP-2); RBP (PcyRBP1, 1a, 1b, 2a, 2b, 2c, 2d, 2e, 2f, 3)
Stained structures in the infected erythrocytes on microscopic examination	None	Schüffner's dots	Maurer's clefts	Schüffner's dots	Sinton-Mulligan's clefts	Schüffner's dots
Ring stage chromatin	Single to Double	Single	Single	Single	Single to Double	Single
Severe malaria in humans	Yes	Yes	Yes[i]	Yes[i]	Yes	No

Table 4 continued

The references used for this table as listed as supplementary file 1

DBP Duffy binding protein, EBL/A: Erythrocyte binding ligand/Antigen, MSP1: Merozoite surface protein 1, NBP/RBP: Normocyte/Reticulocyte binding protein, PfRh: *P. falciparum* reticulocyte-binding homologue, *Pcy*: *P. cynomolgi*, *Pf*: *P. falciparum*, *Pv*: *P. vivax*, TRAg: Tryptophan-rich antigen

[§]Parasite development in the mosquito till production and migration of sporozoites to salivary glands. These values are strongly dependent on several factors such as parasite strains and environment temperature

[†]Period spacing the liver development of sporozoites and releasing merozoites into the bloodstream

[‡]Time period between the sporozoite inoculation and the appearance of symptoms

[*]Time between the sporozoite inoculation and first detection of parasites in the bloodstream

[**]This time is > 10 days for *Pf*, and ≤ 3 days for others species

[a]Some studies occasionally reported shorter incubation period

[b]Very long incubation and pre-patent periods were reported for this malarial species

[c]Based on studies with several *Pf* strains (e.g., Panama, McLendon, New Guinea, Rhodesian, Thailand; Santee-Cooper)

[d]Based on studies with several *Pcy* strains (B, M, Cambodia, Ceylonensis, Berok, Gombak, RO)

[e]The usual number of merozoites released is 16 for these species

[f]Only demonstrated experimentally

[g]Demonstrated both using experimental and field studies

[h]Some reports outlined the ability of *Pv* to infect Duffy-negative reticulocytes

[i]These species can occasionally elicit severe malaria

[#]Duration of the latency is strain-specific. Short relapse latency (3–4 weeks) and long relapse latency (8 to 9 months)

[##]These are the main parasite ligands involved in erythrocyte invasion

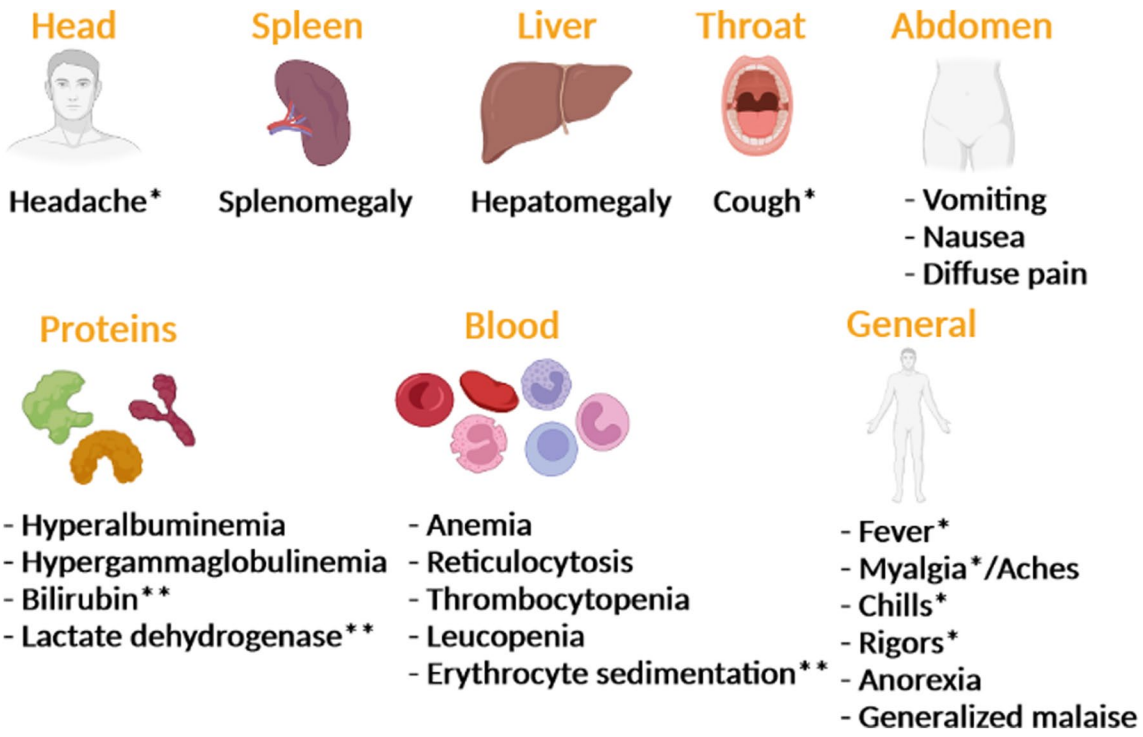

Fig. 4 Clinical signs/symptoms seen in natural, accidental and experimental human infections with *P. cynomolgi* malaria parasites. *These signs/symptoms were reported in natural infections. **Rise in erythrocyte sedimentation, bilirubin and lactate dehydrogenase. Created with BioRender.com

suffering from glucose-6-phosphate dehydrogenase deficiency (G6PD-d) and testing for G6PD-d should be routinely done before PQ/TQ administration [3].There is a need for new drugs with high hypnozoiticidal activity and little or no risk of hemolysis in *Pv*-infected patients. The discovery of such drugs is hampered by the absence of robust in vitro continuous culture systems of *Pv* parasites [71]. Its sister species *Pcy*, which is now reported to cause natural infections in humans, is cultivable in vitro for longer periods [34], and this offers an opportunity to develop safer hypnozoiticidal drugs for control *Pcy, Po spp* and *Pv* relapses.

Several authors addressed these aspects by evaluating PQ derivatives and repurposing drugs of inflammatory, bacterial, parasitic and viral ailments (rheumatic problems, lymphatic filariasis, human immunodeficiency virus infection, urinary tract infections). Very few molecules such as elubaquine (CRDI 80/53), a PQ analogue, have exhibited interesting anti-relapse potential and little adverse effects on oxidative functions in *Pv*-infected individuals from India and Thailand [72–74], while in vitro studies reported potent *Pcy*- and *Pv*-related anti-hypnozoite activity of antiparasitic compounds including KAI407 (non-8-aminoquinoline) and KDU691 (imidazopyrazine) [75, 76]. These molecules are still under investigation and not currently recommended by WHO for managing relapses. In contrast, repurposed drugs like antibiotics (trimethoprim, sulfamethoxazole, demeclocycline, cyclophosphamide, mirincamycin), antiparasitic (ivermectin), antiviral (lopinavir), anti-inflammatory (dexamethasone) and other drugs (guanylhydrazone, tetrahydrofuran derivative) have failed to prevent *Pcy* relapses in experimentally infected macaques [77–83].

Knowledge gaps and future directions

Human infections with *Pcy* parasites are a growing public health problem which raises many challenges. The first challenge and gap is mainly the diagnosis as this parasite is mostly misdiagnosed given its morphological similarities with *Pv* using light microscopy at health facilities and reference microscopy centers in SEA countries, and the lack of awareness of microscopists vis-à-vis to *Pcy*. *Pcy*. The microscopic detection of *Pcy* can still pose another problem as *Pcy* infections can be submicroscopic [52, 57]. In this regard, sensitization/information campaigns coupled with training and assessment sessions of microscopists on *Pcy* are greatly needed.

Molecular methods are also needed to overcome challenges related to microscopic detection of *Pcy* parasites. The *18S rRNA* gene is commonly targeted in nested and quantitative PCR protocols for *Plasmodium* species, but high similarity of the *18S rRNA* gene of *Pcy*, *Pv*, *Pk*, *Pm* can produce

false-positive as seen in Malaysia, Cambodia, and French Guiana [51, 54, 55] [84, 85]. One solution to the problem would be to target at least two nucleic and mitochondrial genes such as *cyt-b*, *COXI* and $msp1_{42}$, and further analyses including sequencing, phylogenetic analyses and external cross-checking. These challenges on microscopic and molecular diagnostic explain greatly the underlying difficulties about estimation of real burden of *Pcy* in humans. Furthermore, clinicians from SEA settings should be sensitized on *Pcy* malaria and its treatment for better management. As emerging parasites in human, it is possible that clinicians are not knowledgeable about *Pcy* parasite relapses, and clinicians are to be made aware that prescription of PQ to be associated with a main antimalarial drug treatment [55, 86].

The absence of evidence on natural circulation of *Pcy* and other simian parasites in humans in Latin America, Western Asia and sSA is likely due to the lack of studies addressing zoonotic transmission of simian *Plasmodia* in these areas. In todays era of world globalization due to human migration, surveillance of zoonotic malaria is no doubt crucial for achieving malaria control and elimination objectives. This will also serve better for imported malaria cases in countries where successful malaria elimination has been achieved [8, 87].

The SEA area, especially Thailand, Malaysia, and Cambodia, seems to be the only foci of *Pcy* infections in humans based on the current data. It is clear that zoonotic infections with *Pcy* parasites are shaped by a conjunction of factors: driving closer contacts between monkeys (natural vertebrate hosts), mosquitoes (invertebrate host) and human (accidental vertebrate hosts). This relationship between monkeys, mosquitoes, and human is crucial for emergence of and spread of *Pcy* parasites in humans. The expansion of humans and anthropogenic activities such as deforestation, forestry activities, and climate change are probably the leading drivers, thereby increasing chances for simian parasites to enlarge their host spectrum through emergence to local human populations from these countries, as seen for *P. knowlesi* and other emerging pathogens [88–91]. Such possibility for invading humans is also driven by the presence of competent and anthropophilic mosquito vectors. Several factors related to bionomics, vector capacity and competence of *Anopheles* species as well as *Pcy* parasites and monkey hosts are also crucial [18–20]. Evidently, its prevalence and distribution could be likely underestimated as discussed here. It would be worthwhile to address these questions in future research topics i) If the zoonotic transmission of *Pcy* is advantageous? ii) how *Pcy* infection dynamics and natural history are influenced in mixed infections with *Pf* and *Pv*? and iii) what is the scope of expansion in *Pcy* human infections in SEA?

Both sSA and Latin America not only have the highest forest area diversity and non-human primates of the world [92, 93], but also have highly diverse *Anopheles* species fauna [42, 45]. In Western Asia, the primate diversity is also high with numerous forested areas [93]. Few of *Anopheles* species such as *A. freeborni* and *A. stephensi* are among the major malaria vectors in North America and Western Asia, respectively, which are also able to produce viable *Pcy* sporozoites and transmit them to humans in laboratory studies [42, 45, 46, 50]. Also, the risk of *Pcy* spreading to other countries is also probably due to given reports of *A. stephensi* in the horn of Africa (e.g., Djibouti, Ethiopia) [94, 95]. Mosquitoes such as *A. freeborni* and *A. stephensi* are both anthropophilic and zoophilic, moderately to highly sensitive to *Pcy* infections, and are able to successfully transmit parasites to monkeys in laboratory conditions [13] (Table 3). Thus, these mosquito species could be vectors of zoonotic malaria parasites such as *Pcy* in areas where these mosquito species are present. In addition, the nature, distribution and susceptibility of monkey and non-primate hosts (e.g., New World monkeys, apes, macaques) to *Pcy* infections is also a key determinant modulating the risk and establishment of zoonotic transmission of *Pcy* to humans. Evidence pointed out directional transmission between humans and African apes as well as humans and New World monkeys for species such as *Pv* and *Pm* [96]. Africa and Americas have high diversity of monkeys, but data on efficiency of transmission of *Pcy* from these monkeys to mosquito vectors and humans in these areas are still lacking. Despite this set of zoonotic transmission-favoring factors in these areas, no report of natural human infections with *Pcy* has been reported outside SEA till now.

As seen for *Pk*, control of *Pcy* malaria could pose a problem in the absence of strategies for controlling the mainly forest-dwelling mosquito vectors and primate reservoir of *Pcy* parasites [86]. Repellents, odor-based mosquito traps, and insecticide-treated clothes have been proposed, but evidences for their effectiveness are still lacking [97]. Thus, there is need for more studies on *Pcy* especially on development, evaluation, and implementation of integrated intervention measures (vector control, personal level protection and community engagement, environment control) to curb the chain of transmission of simian parasites from animals to humans [97, 98].

Finally, treatment of *Pcy* malaria is a significant knowledge gap. No strong evidence for efficacy of current antimalarial drugs is available, even though some studies reported resolution of clinical and laboratory symptoms in *Pcy*-infected patients treated with Atovaquone + proguanil followed by PQ in European traveler, artemether + lumefantrine followed by PQ in Malaysian patients, and CQ + PQ or artesunate + mefloquine in Thailand patients [53, 55, 57, 99]. With an increasing number of reports on *Pcy* infections and its therapeutic management, evidence could be generated

as seen for therapeutic management of uncomplicated and severe *Pk* malaria [100, 101].

Concluding remarks

We reviewed the current knowledge on the epidemiology of natural *Pcy* infections in humans, mosquitoes and monkeys, along with its biological, clinical and drug sensitivity patterns. A brief snapshot of emergence of other simian malaria parasites was also presented. Also, important knowledge gaps and further studies on *Pcy* malaria in human were presented and discussed. There are evidences on the ability of *Pcy* parasites to naturally infect humans, with all natural infection cases reported from either local populations or European travelers returning from SEA countries (Malaysia, Thailand, Cambodia). Clinical presentation of *Pcy* malaria encompasses mild-to-moderate signs which are mainly represented by fever, chills, and rigors associated with microscopic or submicroscopic parasitemia. Complex interaction involving factors related to human, monkeys (natural vertebrate hosts), mosquitoes, and environment is crucial for emergence of *Pcy* and other Simian parasites (e.g., *P. brasilianum*, *P. simium*, *P. inui*) in humans from SEA region and outside. Unfortunately, the knowledge of microscopists and clinicians on *Pcy* malaria is still low, thereby jeopardizing its diagnosis, epidemiological study-related findings, and therapeutic management. Also, in the absence of RDTs for simian malaria, molecular methods have been developed to specifically detect *Pcy* parasites. However, the high level of similarities of target *Pcy* genes with those of other species is still a big challenge to molecular diagnostics due to chances of false-positive results. From experience gained from *Pk* malaria control, development of integrated measures and strategies—ideally with components related to human, monkeys, mosquito vectors, and environment—could be very helpful to prevent emergence of *Pcy* malaria in humans through disruption of transmission chain from monkeys to humans and, ultimately contain its expansion in SEA and potential outbreaks.

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Authors contributions LPKF and VS conceived the paper. LPKF, AK and JH did the literature search. JH and LPKF generated maps. LPKF conceived figures and drafted the first version of the manuscript with the help of AK and JH. AK, JH and VS revised the manuscript for important intellectual content. VS supervised the work at all stages. All authors read and approved the final version of the paper before submission.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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