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Zoonotic malaria in sub-Saharan Africa: A Mini-Review

Aklilu Alemayehu[1, 2]

[1]School of Medical Laboratory Sciences, Institute of Health, Jimma University, Jimma, Ethiopia.
[2]Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Arba Minch University, Arba Minch, Ethiopia

***Corresponding Author**: Aklilu Alemayehu. School of Medical Laboratory Sciences, Institute of Health, Jimma University, Jimma, Ethiopia. Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Arba Minch University, Arba Minch, Ethiopia.

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Abstract

Malaria is a serious public health problem worldwide despite concerted efforts to control and eliminate it. Zoonotic malaria is emerging as a big threat to malaria elimination efforts. There is a big knowledge gap in our understanding of zoonotic malaria. It is difficult to adequately detect and identify Plasmodium species responsible for zoonotic malaria with conventional diagnostic tools. Although molecular tools have good sensitivity and specificity to diagnose zoonotic malaria, they are not readily available in resource-limited settings. There is limited data on the epidemiology of zoonotic malaria in sub-Saharan Africa. However, various reports signal for the presence of its risk lurking in the area. Therefore, organized and comprehensive studies are needed to characterize its epidemiology in sub-Saharan Africa to guide strategies of mitigating zoonotic malaria in particular and malaria in general.

Keywords: *Zoonotic Malaria; Plasmodium knowlesi; sub-Saharan Africa.*

Acronyms and Abbreviations: *DBP: Duffy binding protein, NHP: Non-human primates, PCR: Polymerase Chain Reaction, RDT: Rapid Diagnostic Test*

Introduction

Zoonotic pathogen is a microorganism that colonizes or infects animals and can be transmitted to humans through vector or via direct contact with the animal or its products. Zoonotic disease causation in humans, usually, is accidental and not primarily for evolutionary survival [1]. An interest in potentially zoonotic malaria started after accidental infection of laboratory workers with *Plasmodium cynomolgi* (*P. cynomolgi*) via an Anopheles mosquito in 1960 [2]. Recent scientific developments show the possibility of zoonotic malaria. Various studies have reported human infection by macaque and simian malaria parasites, mainly by *Plasmodium knowlesi* (P. knowlesi, *P. simium*) and *Plasmodium brasilianum* (P. brasilianum) [3-6]. *P. knowlesi* is common in Southeast Asia [3], whereas Plasmodium simium (*P. simium*) and *P. brasilianum* are common in Latin America [5, 6]. However, we lack concrete evidence on whether all human cases originate from animals or human-to-human transmission is occurring [4]. This mini review focuses on the biology, clinical pictures, diagnosis, treatment and epidemiology of zoonotic malaria in sub-Saharan Africa, and its implication for malaria elimination.

Biology and Clinical Picture

According to various experimental studies, parasites of monkeys, such as *P. cynomolgi*, *P. brasilianum*, *P. eylesi*, *P. inui*, and *P. simium* have been shown to infect human via mosquitoes [7, 8]. Besides, isolation of the DNAs of the Plasmodium species commonly infecting human from African anthropoid ape's alarm for possibility of zoonosis [9]. However, *P. knowlesi* is the widely accepted Plasmodium parasite of zoonotic malaria, particularly in Southeast Asian countries, and recently became the fifth human malaria parasite [10]. Monkeys are reservoir host of knowlesi malaria [9]. Furthermore, a recent molecular study in Africa revealed zoonotic origin of the human malaria parasite *P. malariae*, which is known to infect chimpanzees [9, 11].

Due to close similarity between *P. vivax*, and *P.*

cynomolgi, various experimental studies including culturing *P. cynomolgi* helped to understand the life-cycle of *P. vivax* [12, 13]. Similar to *P. vivax*, *P. cynomolgi* produces dormant liver stage hypnozoite. It also favors infecting reticulocytes and have the Schuffner's dot visible on infected erythrocyte membrane [14, 15]. Zoonotic malaria exhibits similar symptoms of the known human malaria including myalgia, anorexia, fever, nausea and others. Human malaria caused by simian Plasmodium is often mild [9, 14]. The clinical picture of malaria due to *P. knowlesi* infections is often uncomplicated. However, it can cause severe malaria in about 10% of patients in Malaysia [4, 16, 17]. The incubation period of knowlesi malaria lasts for 9- 15 days [9]. The developmental cycle of *P. knowlesi* occurs every 24 h, and hence cause quotidian malaria in which patient fevers peak every day [7, 9]. Similar to P. vivax, P. cynomolgi commonly causes asymptomatic malaria and produces dormant liver stage hypnozoite [14].

Transmission

Leucosphyrus group of Anopheline mosquitoes transmit *P. knowlesi* and the transmission is mainly zoonotic. This type of malaria is dominant malaria in Malaysia, where its transmission is restricted to jungle thereby putting humans entering jungle in transmission area at risk. It is quite common to see human cases of *P. knowlesi* in travelers returning from Southeast Asia [4].

A recent sequencing study has shown that *P. simium*, a malaria parasite of non-human primates (NHP), can cause zoonotic infection of human in Brazil. In fact, the study revealed that ability of the parasite to undergo genetic adaptations underscore its advantage to switch between host species [18]. An. vinckei, An. moucheti and An. marshallii serve as competent vectors of ape Laverania and non-Laverania parasites thereby mediating transmission of zoonotic malaria [19].

Management of Zoonotic Malaria

Diagnosis

Microscopic examination of Giemsa stained thick and thin blood film is the routine diagnosis for malaria of humans and monkeys. However, it is difficult to differentiate between simian Plasmodium and the known human Plasmodium species solely by morphological criteria. Besides, the capacity of an extensively used malaria RDTs to sufficiently characterize simian Plasmodium species is limited [9, 20].

The development of molecular methods such as polymerase chain reaction (PCR) was instrumental in the knowledge gained on zoonotic malaria [10, 14]. For long time, *P. knowlesi* has been misdiagnosed as *P. malariae*. Nevertheless, PCR is now the definitive method for differentiating *P. knowlesi* from *P. malariae* and other human malaria parasites [21]. Likewise, PCR helped to differentiate between *P. cynomolgi* and *P. vivax* (14). Nevertheless, due to low prevalence (in terms of detected cases); high cost and inadequate availability of PCR, it is conceivable that zoonotic malaria is under diagnosed [20]. Generally, highly sensitive and specific tools such as PCR are critical for accurate detection of both zoonotic and human-only *Plasmodium* species [22].

Treatment

Chloroquine is the drug of choice for zoonotic malaria treatment regardless of resistance to the drug by other species of Plasmodium. In the case of *P. knowlesi* infection, a chloroquine-primaquine combination therapy is recommended [9].

Epidemiology in Sub-Saharan Africa

Various reports indicate the circulation of primate-infecting Plasmodium species in the equatorial forest region of Africa [23, 24]. Despite the lack of an organized and comprehensive study, there are many reports from human and monkeys in different countries signaling for the presence of zoonotic malaria risk revolving in the continent [24-27]. A molecular study targeting cytochrome b gene conducted by Duval et al. in Cameroon showed similarity of the Plasmodium species between human and chimpanzee in which a chimpanzee Plasmodium strain was found to be genetically identical to variant Plasmodium ovale (*P. ovale*) type [27]. A variant *P. ovale* species is detected from a patient in Ghana. This parasite is highly similar to a variant *P. ovale* detected from Chimpanzee in Cameroon [25].

There are no reports of confirmed *P. knowlesi* infection in sub-Saharan Africa. The possible explanation for this absence of zoonotic malaria in the region can be absence of the common reservoir hosts (the pig-tailed and the long-tailed monkeys) and the potential misdiagnosis [26].

Factors determining Zoonotic malaria

According to reports of recent studies, risk factors for infection with zoonotic malaria parasites include the male sex, contact with macaque monkeys, agricultural expansion, presence of mosquito vector, human behavior, travel to forest areas and forest fragmentation [28-31]. Generally, host factors, species of the Plasmodium, social factors such as migration, environmental factors such as dense

jungle and vector factors are pivotal to the risk of zoonotic malaria [32, 33].

Gaps

Data on zoonotic malaria epidemiology is limited, particularly in sub-Saharan Africa. This might be partly due to low prevalence or misdiagnosis. In co-endemic settings, misdiagnosis is expected since microscopic morphological appearance of *P. cynomolgi* and *P. knowlesi* is similar to *P. vivax* and *P. malariae*, respectively [20, 22, 34]. A recent analysis of the *P. simium* genome showed a close phylogenetic relationship between *P. simium* and P. vivax [18]. We have limited knowledge on zoonotic malaria that can guide designing effective intervention to combat and eliminate it [33].

The five Plasmodium species that infect humans have been found in non-human primates (NHPs). This means these NHPs can potentially serve as reservoirs for transmission of malaria to humans. Besides, given evolutionary process, Plasmodium species those infecting NHPs may eventually become causes for human malaria [35, 36]. Based on molecular epidemiology studies, Laverania infected apes do not currently serve as a reservoir of human infection [37, 38]. Nevertheless, in depth researches are critical to resolve these discrepancies and devise interventions.

Impact of Zoonotic Malaria on Elimination Efforts

Considering the recent malaria outbreaks of *P. knowlesi* in Southeast Asia and *P. simium* in Brazil, it is conceivable that intensified human intervention on the natural forest might increase the risk of zoonotic malaria [37]. The deletion of Duffy binding protein (DBP1) gene in *P. simium* may facilitate invasion of human red blood cells thereby facilitating zoonotic infection, which in turn sustains malaria transmission [18].

If we do not have clear knowledge on zoonotic malaria with its epidemiology in time and space, we might not be in better position to mitigate it. Moreover, it could eventually complicate efforts to eliminate malaria [1]. In the presence of continued human contact with the monkey reservoir and the presence of competent mosquito vectors, zoonotic malaria will not be eliminated by current intervention that mainly focused at human-only *Plasmodium* species [17]. Following decline in the prevalence of human-only malaria due to intensified elimination efforts, zoonotic malaria could become prominent public health problem in co-endemic settings. Besides, if areas approaching elimination use molecular surveillance, the previously misdiagnosed zoonotic malaria by conventional tools might persist and delay the achievement of elimination [34, 39].

Conclusion and Recommendation

Zoonotic malaria is becoming public health problem by threatening malaria elimination efforts. There is a big knowledge gap in our understanding of zoonotic malaria. There is paucity of data on the epidemiology of zoonotic malaria in sub-Saharan Africa. Admirable advancements of molecular techniques with their promising application in epidemiology can fine-tune our understanding on zoonotic malaria. That knowledge will prompt discovery of mitigation tools and intervention strategies to mitigate zoonotic malaria in particular and keep us on the track to eradicate malaria in general.

A concerted effort is needed on basic science to understand the biology of simian Plasmodium species with zoonotic potential. An integrated control program including ecological approach is required to mitigate the eminent public health threat from zoonotic malaria. Considering zoonotic malaria into mitigation efforts is key to consolidate gains and advance towards malaria elimination.

Author Contributions

Aklilu Alemayehu has conceived, made online search of relevant articles, and wrote the first draft. Then, he critically reviewed, wrote the final draft, read and approved it for this submission.

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