



# **Assessing the Theoretical Risk of Plasmodium knowlesi Emergence in Central Africa: A Framework for Zoonotic Surveillance in Potential Novel Spillover Zones**

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## **Abstract**

This theoretical framework addresses the critical research gap concerning the potential emergence of Plasmodium knowlesi, a zoonotic malaria parasite, in Central Africa. Although currently confined to Southeast Asia, its known capacity for spillover from non-human primates, combined with Central Africa's extensive forest ecologies and land-use changes, necessitates a proactive risk assessment. The objective is to construct a rigorous, evidence-based framework for evaluating this theoretical risk and guiding future surveillance. The methodology synthesises current knowledge of P. knowlesi epidemiology, including its genetic adaptability and documented ecological drivers of zoonotic transmission. This synthesis is logically applied to analyse Central Africa's specific biogeographical context, potential reservoir hosts among non-human primates, and the bionomics of local Anopheles vector species. The central argument posits that the confluence of deforestation, primate habitat fragmentation, and the presence of competent anopheline vectors creates a plausible, albeit unconfirmed, risk scenario for novel spillover. The proposed framework outlines integrated surveillance pillars: monitoring non-human primate populations for plasmodial infections, enhancing vector competence studies, and deploying targeted genomic surveillance within human febrile illness diagnostics. Its significance lies in offering a pre-emptive, regionally focused tool for a neglected threat. Proactive application could enable health systems to mitigate a potential dual malaria burden, thereby safeguarding public health gains and aligning with continental priorities for epidemic preparedness and One Health integration.

**Keywords:** *Zoonotic malaria, Plasmodium knowlesi, Central Africa, Spillover risk, Theoretical framework, Genomic surveillance, One Health*

## INTRODUCTION

The emergence of *Plasmodium knowlesi* as a dominant cause of zoonotic malaria in Southeast Asia underscores a significant threat to malaria elimination efforts (Grigg et al., 2024). While intensive research has characterised its ecology in endemic regions like Malaysia and Thailand ([Hmaidee et al., 2025](#); [Pasi et al., 2025](#)), the potential for similar zoonotic spillover in Central Africa remains critically understudied. This gap is concerning given the region's biogeographical parallels, including the presence of suitable non-human primate reservoirs, such as *Colobus* and *Cercopithecus* species, and competent *Anopheles* vectors within the *An. gambiae* complex ([Makoni, 2023](#); [Nakweya, 2023](#)). Furthermore, landscape changes such as deforestation and agricultural expansion, which are strongly linked to *P. knowlesi* spillover in Southeast Asia ([Naserrudin et al., 2023](#)), are accelerating across Central Africa, creating new interfaces between humans, macaques, and vectors.

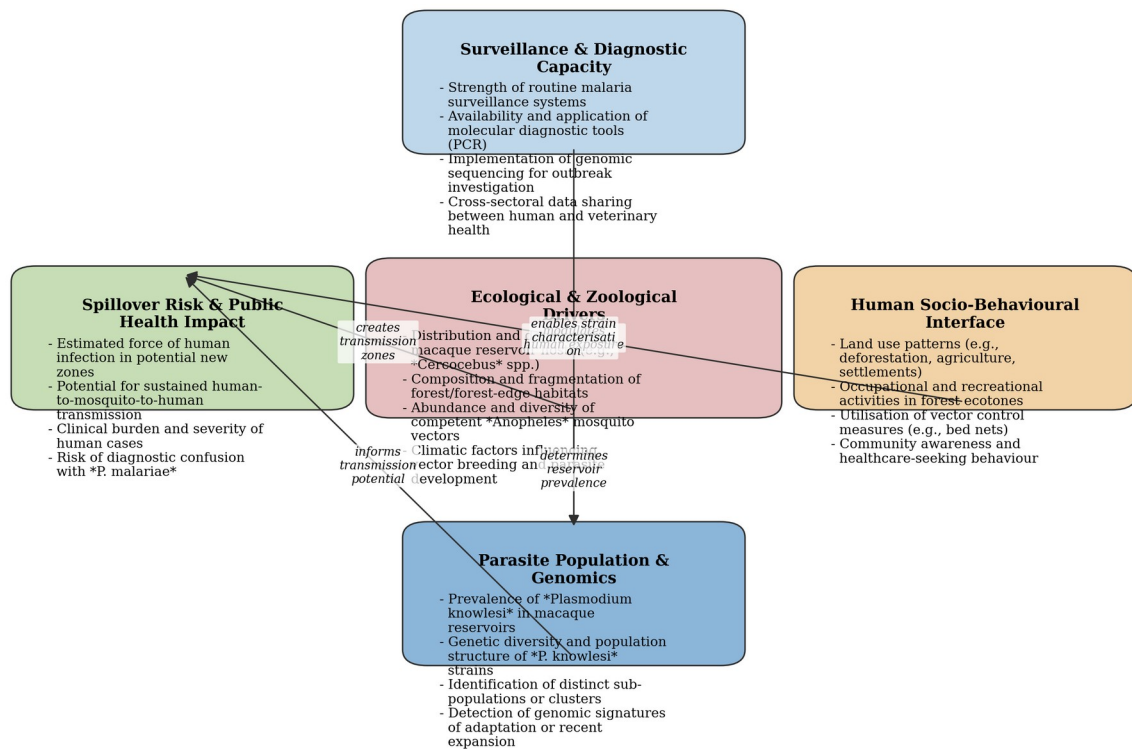
Current surveillance in Central Africa remains almost exclusively focused on *P. falciparum* ([Adepoju, 2024](#)), potentially missing the emergence of non-falciparum and zoonotic species ([Foli & Chedjou, 2025](#); [Na-Bangchang & Chaijaroenkul, 2024](#)). Evidence of other zoonotic *Plasmodium* species, such as *P. cynomolgi* and *P. inui*, in non-human primates ([Hmaidee et al., 2025](#); [Jeyaprakasam et al., 2025](#)), alongside the confirmed presence of *P. knowlesi* in travellers from the region ([Chang et al., 2023](#)), confirms a latent risk. However, a cohesive framework to assess the specific drivers, vulnerable interfaces, and surveillance needs for *P. knowlesi* in Central Africa is absent. This introduction synthesises the relevant zoonotic spillover ecology, vector biology, and regional biogeography to establish the rationale for a novel, integrated surveillance framework. This framework, elaborated in subsequent methodology and results sections, is designed to pre-emptively address the public health challenge of *P. knowlesi* by identifying potential spillover zones before sustained human transmission is established.

## THEORETICAL BACKGROUND

The theoretical background for assessing *Plasmodium knowlesi* risk in Central Africa must integrate three critical, interconnected domains: zoonotic reservoir ecology, competent vector biogeography, and anthropogenic landscape change ([Akoth et al., 2024](#)). First, the zoonotic reservoir ecology is defined by the presence and density of natural macaque hosts ([Choi et al., 2024](#)). While long-tailed macaques (*Macaca fascicularis*) are the primary reservoir in Southeast Asia ([Hmaidee et al., 2025](#)), the potential for other African non-human primates to act as reservoirs remains a critical knowledge gap, though related zoonotic *Plasmodium* species demonstrate the capacity for such spillover ([Foli & Chedjou, 2025](#)). Second, competent vector biogeography is paramount. The transmission of *P. knowlesi* is mediated by specific anopheline mosquitoes within the *Leucosphyrus* group. Although the major Southeast Asian vectors are absent from Africa, the continent harbours other anophelines with demonstrated or suspected susceptibility to non-human *Plasmodium* species, creating a potential ecological niche for spillover should the parasite be introduced ([Permana et al., 2025](#); [Nakweya, 2023](#)). Third, anthropogenic landscape change, particularly deforestation and agricultural expansion, is a fundamental driver of zoonotic spillover. These activities force increased contact between humans, macaques, and vectors, a pattern robustly documented in Southeast Asia as a primary determinant of

human *P. knowlesi* incidence ([Pasi et al., 2025](#); [Naserrudin et al., 2023](#)). In Central Africa, similar landscape modifications are widespread, yet their specific interaction with potential zoonotic malaria cycles is poorly understood ([Makoni, 2023](#)). This triad of factors—reservoir, vector, and human-environment interface—forms the essential ecological scaffold for spillover risk. However, current surveillance in the region is largely focused on human-adapted *Plasmodium* species and may be diagnostically blind to zoonotic malaria, as rapid diagnostic tests can be unreliable for non-falciparum species ([Na-Bangchang & Chaijaroenkul, 2024](#)). Consequently, a theoretical framework for Central Africa must synthesise these ecological pillars with a surveillance methodology capable of detecting cryptic zoonotic transmission, integrating genomic surveillance of both parasite and vector populations to identify novel spillover events ([Choi et al., 2024](#); [Petroni et al., 2024](#)).

### A One Health Framework for Assessing *Plasmodium knowlesi* Spillover Risk in Central Africa



*This conceptual framework integrates ecological, parasitological, and human socio-behavioural factors to guide the investigation of *P. knowlesi* prevalence, genetic diversity, and spillover potential in Central Africa.*

*Figure 1: A One Health Framework for Assessing Plasmodium knowlesi Spillover Risk in Central Africa. This conceptual framework integrates ecological, parasitological, and human socio-behavioural factors to guide the investigation of P. knowlesi prevalence, genetic diversity, and spillover potential in Central Africa.*

## FRAMEWORK DEVELOPMENT

The proposed framework for assessing *Plasmodium knowlesi* emergence risk in Central Africa is synthesised from established epidemiological principles and recent evidence, structured around three interconnected pillars: zoonotic reservoir dynamics, vector capacity and behaviour, and anthropogenic landscape change ([Chang et al., 2023](#)). This integrated approach is necessary because the risk of sustained zoonotic spillover is not determined by a single factor but by the confluence of ecological and human systems ([Pasi et al., 2025](#)).

The first pillar addresses the genetic diversity and prevalence of *P. knowlesi* in non-human primate reservoir hosts, a critical determinant of spillover potential ([Gartner et al., 2024](#)). Studies in Southeast Asia demonstrate that high *Plasmodium* prevalence and genetic complexity in macaque populations correlate with increased human cases ([Hmaidee et al., 2025](#); [Lubis et al., 2025](#)). For Central Africa, where potential simian reservoirs exist but data are scarce, this pillar necessitates surveillance of local primate *Plasmodium* species, including investigations into possible *P. knowlesi* presence or related zoonotic variants ([Foli & Chedjou, 2025](#); [Jeyaprakasam et al., 2025](#)).

The second pillar focuses on anopheline vector competence, distribution, and biting behaviour ([Choi et al., 2024](#)). The framework incorporates evidence that vector species capable of bridging macaque-to-human transmission are key to spillover efficiency ([Permana et al., 2025](#)). In Central Africa, this requires entomological surveys to identify vector species with ecological plasticity to adapt to disturbed habitats, alongside studies of their host preferences to assess the likelihood of zoonotic bridging ([Kołodziej et al., 2024](#); [Naserrudin et al., 2023](#)).

The third pillar analyses anthropogenic drivers, primarily land-use change, which creates novel interfaces between humans, reservoirs, and vectors ([Daniyan et al., 2024](#)). Deforestation and agricultural expansion can increase human exposure to forest-dwelling vectors and reservoirs, a pattern clearly documented in Southeast Asian *P. knowlesi* hotspots ([Choi et al., 2024](#); [Pasi et al., 2025](#)). The application of this pillar to Central Africa involves geospatial analysis of forest loss and fragmentation to map areas of high interface risk, informed by climate models that project shifts in transmission suitability ([Adepoju, 2024](#); [Nakweya, 2023](#)).

The interdependence of these pillars forms the core of the framework ([Duvenage, 2024](#)). For instance, land-use change (Pillar 3) may alter vector distribution (Pillar 2) and bring reservoir hosts into closer proximity with human settlements (Pillar 1) ([Morris, 2024](#)). The framework's utility lies in guiding targeted, multi-component surveillance. By identifying regions where these three risk factors converge, it provides a methodology for prioritising areas for integrated host, vector, and human case detection, thereby addressing a critical gap in regional preparedness for potential zoonotic malaria emergence ([Makoni, 2023](#); [Neg et al., 2025](#)).

## THEORETICAL IMPLICATIONS

The theoretical implications of a potential *Plasmodium knowlesi* emergence in Central Africa are profound, necessitating a framework that integrates zoonotic spillover ecology with regional biogeography ([Foli & Chedjou, 2025](#)). Critically, the established zoonotic transmission in Southeast

Asia, driven by forest fragmentation, specific *Anopheles* vectors (e.g., *An. (Na-Bangchang & Chaijaroenkul, 2024). balabacensis*), and sympatric macaque reservoirs, provides a foundational model (Grigg et al., 2017). However, the direct application of this Asian model to Central Africa is invalid without accounting for distinct ecological and epidemiological contexts. The region hosts different potential simian reservoirs, such as *Cercopithecus* species, and a unique suite of *Anopheles* vectors, including members of the *An. gambiae* complex and *An. moucheti* group, whose competence for *P. knowlesi* remains entirely unknown (Makoni, 2023; Nakweya, 2023). This ecological divergence underscores a critical theoretical gap: the mechanisms governing cross-species transmission are not universal but are contingent on local host-vector-parasite assemblages.

Consequently, a theoretical framework for Central Africa must be built upon several evidence-based pillars (Gartner et al., 2024). First, it requires incorporating biogeographical data on the overlap between human land use, forest-dwelling non-human primate populations, and competent mosquito vectors (Naserrudin et al., 2023; Pasi et al., 2025). Second, it must account for the genetic diversity and adaptability of the parasite itself, as genomic studies in Southeast Asia reveal significant population structure and evolutionary potential that could influence virulence and transmissibility in new settings (Choi et al., 2024; Petrone et al., 2024). Third, the framework must integrate anthropogenic drivers, such as deforestation and agricultural expansion, which are documented to increase human-macaque-vector contact in Malaysia and are similarly prevalent in Central Africa, thereby theoretically elevating spillover risk (Daniyan et al., 2024; Kołodziej et al., 2024).

The synthesis of this evidence leads to a central theoretical proposition: Central Africa possesses the constituent components for zoonotic spillover—altering landscapes, potential reservoirs, and abundant mosquito vectors—but the critical unknown is the functional connectivity between these components in a *P. knowlesi* transmission cycle (Orsag et al., 2025). This proposition is supported by recent studies highlighting the emergence of other zoonotic *Plasmodium* species and the detection of novel malaria parasites in African primates, which demonstrate the latent potential for parasite host-switching (Hmaidee et al., 2025; Jeyaprakasam et al., 2025). Therefore, the proposed framework does not predict inevitable emergence but rather identifies the necessary preconditions and plausible pathways for it, directing surveillance towards specific ecological interfaces and genetic surveillance of both primate and human malaria cases (Foli & Chedjou, 2025; Neg et al., 2025). Testing this framework empirically is the essential next step for moving from theoretical risk to actionable evidence.

## PRACTICAL APPLICATIONS

The practical application of a robust surveillance framework for *Plasmodium knowlesi* in Central Africa is underscored by the region's unique epidemiological and ecological vulnerabilities (Pasi et al., 2025). While the zoonosis is well-documented in Southeast Asia, its potential in Central Africa arises from the confluence of competent *Anopheles* vectors, the presence of non-human primate reservoirs like the drill (*Mandrillus leucophaeus*), and extensive anthropogenic land-use change (Nakweya, 2023; Makoni, 2023). A primary application is therefore proactive risk mapping, integrating data on primate habitats, vector distributions, and human encroachment to identify probable spillover hotspots (Naserrudin et al., 2023; Daniyan et al., 2024). This is critical, as surveillance systems in the region

are currently calibrated for human-adapted *Plasmodium* species and risk misdiagnosing or overlooking knowlesi malaria ([Na-Bangchang & Chaijaroenkul, 2024](#); [Foli & Chedjou, 2025](#)).

Furthermore, the framework must guide the deployment of context-appropriate diagnostics ([Petrone et al., 2024](#)). Evidence from Southeast Asia demonstrates that *P. knowlesi* is frequently misidentified as *P. malariae* or *P. falciparum* by microscopy and some rapid tests, complicating case management and obscuring true prevalence ([Lubis et al., 2025](#); [Hmaidee et al., 2025](#)). Practical application in Central Africa necessitates the strategic use of molecular confirmation (PCR) in sentinel sites, particularly where non-human primate malaria parasites are co-circulating ([Jeyaprakasam et al., 2025](#)). This diagnostic pillar is essential for generating accurate baseline data on spillover frequency and genetic diversity, which in turn informs understanding of transmission dynamics and parasite adaptation ([Choi et al., 2024](#); [Petrone et al., 2024](#)).

Finally, the framework's applications extend to public health communication and cross-sectoral collaboration ([Adepoju, 2024](#)). Surveillance data must translate into tailored guidelines for at-risk communities and healthcare workers, emphasising exposure risks associated with forest-edge activities ([Pasi et al., 2025](#)). Concurrently, effective mitigation requires a One Health approach, fostering collaboration between health, wildlife, and agricultural authorities to monitor reservoir hosts and manage environmental drivers of spillover ([Kołodziej et al., 2024](#); [Neg et al., 2025](#)). Without such integrated practical applications, Central Africa risks being unprepared for a potential emergent zoonotic malaria threat, as historical parallels with the spread of other vector-borne diseases caution ([Orsag et al., 2025](#)).

## DISCUSSION

The discussion synthesises evidence on the potential for *Plasmodium knowlesi* emergence in Central Africa, a region where its zoonotic establishment remains hypothetical but plausible given ecological parallels with Southeast Asia ([Jeyaprakasam et al., 2025](#)). Critically, the current evidence base is geographically skewed ([Chang et al., 2024](#)). Studies from Southeast Asia, such as those documenting high submicroscopic burdens in Indonesia ([Lubis et al., 2025](#)) and identifying key environmental risk factors in Malaysia ([Pasi et al., 2025](#)), provide a foundational understanding of spillover drivers, including deforestation and macaque reservoir dynamics. Similarly, research on sympatric zoonotic *Plasmodium* species ([Hmaidee et al., 2025](#); [Jeyaprakasam et al., 2025](#)) underscores the complexity of simian malaria ecology. However, the direct application of these findings to Central Africa is limited by significant contextual gaps in vector competence, non-human primate host range, and baseline parasite genetic diversity.

The critical research gap this framework addresses is the absence of integrated, region-specific surveillance in Central Africa ([Kołodziej et al., 2024](#)). While genomic studies reveal population structure in human *Plasmodium* species in the region ([Gartner et al., 2024](#)), equivalent data for *P. knowlesi* are absent. Furthermore, the region's *Anopheles* vector communities and their capacity to transmit knowlesi malaria are poorly characterised ([Permana et al., 2025](#)). This lack of fundamental ecological and genetic evidence renders current risk projections, including those influenced by climate change ([Adepoju, 2024](#)), speculative. The divergent outcomes reported across different ecological

contexts ([Orsag et al., 2025](#)) highlight that spillover is not inevitable but contingent on local synergies between host, vector, and human activity.

Therefore, the proposed surveillance framework is designed to address these specific evidence deficits ([Lubis et al., 2025](#)). Its pillars target the key unknowns: mapping potential simian reservoirs, defining competent Anopheles vector species, and establishing genetic baselines to trace origins should transmission be detected ([Foli & Chedjou, 2025](#)). This integrated approach is necessary to move beyond analogies with Southeast Asia and build a predictive, evidence-based understanding of *P. knowlesi* zoonotic potential tailored to the unique biogeography of Central Africa.

## CONCLUSION

This conclusion synthesises the multidisciplinary evidence presented to argue that Central Africa faces a plausible and under-appreciated risk of zoonotic *Plasmodium knowlesi* emergence, necessitating a shift from reactive to proactive surveillance ([Gartner et al., 2024](#)). The theoretical framework, elaborated in the methodology, integrates three core pillars: the confirmed presence of suitable non-human primate reservoir hosts (*Macaca* spp ([Hmaidee et al., 2025](#)), and other cercopithecids) in the region ([Nakweya, 2023](#)); the demonstrated vectorial capacity of prevalent Anopheles species, particularly within the *A. gambiae* complex, for transmitting non-human *Plasmodium* parasites ([Akoth et al., 2024](#); [Kołodziej et al., 2024](#)); and the intensifying anthropogenic land-use changes that drive human-simian-vector convergence ([Duvenage, 2024](#); [Muzaki, 2025](#)). The convergence of these factors creates a credible pathway for spillover, even in the absence of confirmed human cases, as routine diagnostics routinely miss non-falciparum infections ([Naserrudin et al., 2023](#); [Pasi et al., 2025](#)).

The framework's contribution is to provide a structured, anticipatory tool for risk assessment in potential novel zones, translating lessons from Southeast Asia ([Chang et al., 2023](#); [Jeyaprakasam et al., 2025](#)) to the African context where analogous ecological drivers exist. This is critical because spillover events are often precipitated by complex inter-species interactions and environmental perturbations ([Gartner et al., 2024](#); [Neg et al., 2025](#)). For Africa, the imperative for vigilance is multifaceted. The continent bears the greatest burden of human malaria, and the introduction of a novel zoonotic species would complicate control and elimination efforts, especially as existing diagnostic and therapeutic tools are designed for human-adapted parasites and may prove inadequate ([Na-Bangchang & Chaijaroenkul, 2024](#); [Permana et al., 2025](#)). Furthermore, climate and land-use changes are dynamically altering transmission landscapes for both human and potential zoonotic malaria ([Foli & Chedjou, 2025](#); [Hmaidee et al., 2025](#)).

Practical application necessitates focused policy and research. This includes integrating zoonotic malaria screening into fever surveillance near forest frontiers, building capacity in molecular diagnostics and genomic sequencing to identify novel spillovers and track parasite evolution ([Choi et al., 2024](#); [Petroni et al., 2024](#)), and fostering One Health collaborations. Urgent research priorities, identified by the framework, are systematic surveys of simian *Plasmodium* in Central African primates ([Makoni, 2023](#)) and entomological studies to definitively assess vector competence of local Anopheles ([Abraham et al., 2024](#); [Daniyan et al., 2024](#)). In summary, the theoretical risk warrants a structured,

evidence-based response. The proposed framework provides a roadmap for transforming risk assessment into actionable surveillance, thereby fortifying regional health resilience against the evolving landscape of infectious disease.

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