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REVIEW ARTICLE

# MOLECULAR LANDSCAPE OF ARTEMISININ RESISTANCE: INSIGHTS FROM PLASMODIUM FALCIPARUM GENOMICS

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**ABSTRACT**

Artemisinin-based combination therapies (ACTs) are the primary treatment for Plasmodium falciparum malaria. However, the emergence of parasites with reduced susceptibility to artemisinin, a phenomenon often observed as delayed parasite clearance, presents a challenge to malaria control. Mutations in the kelch13 (PfK13) gene are considered a key molecular marker for this resistance. Certain PfK13 mutations, including C580Y and R539T, have been correlated with reduced susceptibility in vitro and in vivo. The resistance mechanism appears to involve contributions from other genetic factors related to processes such as endocytosis and phosphatidylinositol metabolism. Genomic surveillance has documented the spread of these mutations, showing established prevalence in Southeast Asia and independent emergences in Africa. Monitoring these variants through molecular surveillance is a critical component of efforts to track resistance patterns. Integrating genomic data with clinical efficacy studies can help inform public health strategies aimed at preserving ACT utility. Future research should focus on functionally validating new mutations and enhancing surveillance capabilities in endemic regions.

**KEYWORDS**

Artemisinin resistance, Plasmodium falciparum, PfK13, genetic mutations, genomic surveillance

## 1. INTRODUCTION

Artemisinin-based combination therapies (ACTs) remain the cornerstone of *Plasmodium falciparum* malaria treatment worldwide and underpin the significant progress toward malaria control and elimination (Dhorda et al., 2024). However, the emergence of parasites with reduced susceptibility to artemisinin, clinically manifest as delayed parasite clearance, threatens ACT efficacy and global malaria control (World Health Organization WHO, 2018 ; Ogieuhi, et al., 2018). This problem is especially concerning in regions with high malaria transmission, such as Southeast Asia, where artemisinin resistance was first detected, and in parts of sub-Saharan Africa, where resistance is emerging (Conrad et al., 2023).

Genomic investigations over the last decade have provided critical insights into the molecular underpinnings of artemisinin partial resistance. These studies have identified major molecular markers, described their functional consequences, and revealed complex evolutionary dynamics across geographic regions (Ariey *et al.,* 2014 ; Straimer *et al.,* 2015 ; Balikagala *et al.,* 2021). This narrative review synthesizes genomic and molecular evidence concerning artemisinin resistance in P. falciparum, emphasizing recent advances (2019–2025), the central role of PfK13, accessory genetic factors, omics-level insights, genomic surveillance approaches, and the implications for treatment policy.

## 2. GENOMIC ARCHITECTURE AND THE RATIONALE FOR GENOMIC SURVEILLANCE

The genome of *P. falciparum* is compact and AT-rich, featuring frequent structural variants and copy-number polymorphisms that facilitate rapid adaptation to environmental pressures, including drug treatment (Ndwiga et al., 2021). Whole-genome sequencing (WGS), targeted amplicon deep sequencing, and population genomic analyses have revealed selective sweeps, haplotype structures, and soft versus hard sweep dynamics that characterize resistance emergence and spread (Stokes et al., 2021). Genomic surveillance provides a sensitive tool to detect emergent resistance alleles, trace their origins, and inform public health responses (Menegon et al., 2016 ; WHO, 2018)

## 3. MECHANISM OF ARTEMISININ ACTION AND PARASITE STRESS RESPONSES

Artemisinins are fast-acting endoperoxides that cause broad proteotoxic and oxidative damage in parasites, acting preferentially on early ring-stage forms. The proposed activation mechanisms involve heme- or iron-catalyzed cleavage of the endoperoxide bridge, generating reactive intermediates that alkylate parasite proteins and lipids (Conrad et al., 2023).

The parasite's survival strategies under artemisinin exposure include induction of proteostasis pathways, modulation of the ubiquitin–proteasome system, and entry into a slow-growing/quiescent ring-stage phenotype that reduces susceptibility to the drug (Straimer et al., 2015 ; Kucharski et al., 2024). These stress-adaptive responses provide a mechanistic framework for understanding how genetic changes translate into phenotypic tolerance to artemisinin.

## 4. THE CENTRAL ROLE OF PFK13

### 4.1 Discovery and Validation

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In 2014, Ariey and colleagues identified nonsynonymous mutations in the P. falciparum kelch13 (PfK13) propeller domain as molecular markers correlated with artemisinin resistance in the Greater Mekong Subregion (Ariey et al., 2014). Subsequent functional validation by gene editing and ring-stage survival assays (RSA) confirmed that many of these mutations causally increase survival after artemisinin exposure (Straimer et al., 2015).

### 4.2 Structure–Function and Biological Role

PfK13 encodes a Kelch-domain protein hypothesized to act as an adaptor in ubiquitin ligase complexes. Mutations in the propeller domain likely perturb PfK13 function, altering protein degradation pathways and remodeling parasite responses to proteotoxic stress (Straimer et al., 2015 ; Stokes et al., 2021). Molecular and cellular studies suggest that PfK13 mutations reduce hemoglobin endocytosis and digestion, thereby lowering the intracellular activation of artemisinin through decreased availability of heme/iron-derived activators — a proposed mechanistic link between genotype and drug activation (Straimer et al., 2015 ; Kucharski et al., 2024).

### 4.3 Key PfK13 Alleles and Geographic Distribution

Several PfK13 mutations have been validated as markers of partial artemisinin resistance in Southeast Asia (e.g., C580Y, R539T, Y493H), which are associated with high RSA levels and delayed parasite clearance in clinical settings (Ariey et al., 2014 ; Straimer et al., 2015). In the last five years, independent emergences of PfK13 mutations have been documented in Africa, such as R561H in Rwanda (de novo emergence and clonal expansion), and A675V/C469Y in Uganda and other areas (Uwimana et al., 2020 ; Balikagala et al., 2021). These findings indicate that PfK13-mediated resistance can arise independently in regions outside Southeast Asia (Uwimana et al., 2020; Balikagala et al., 2021).

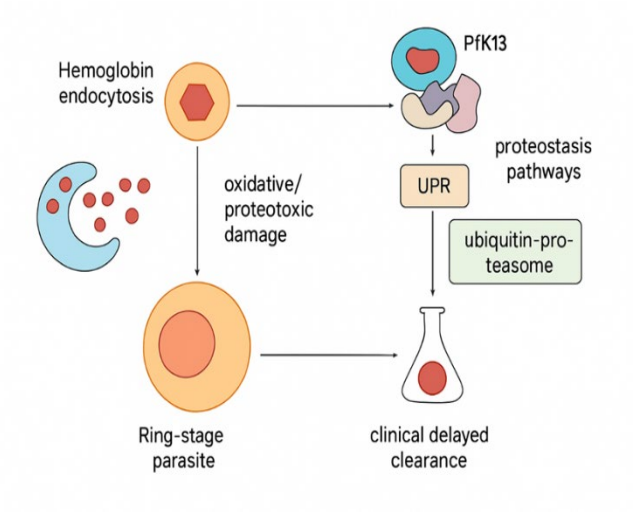


**Figure 1:** Schematic Mechanism of artemisinin activation, PfK13 role, and parasite stress response pathways. Adapted from (Ariey et al., 2014 ; Straimer et al., 2015).

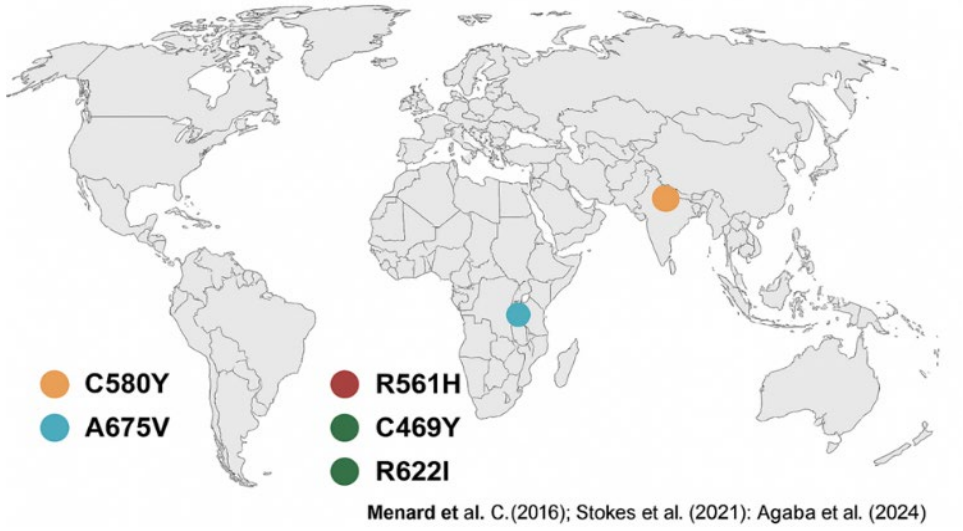


**Figure 2**: Global map of notable PfK13 mutations and regional prevalence trends. Data synthesized from {Ariey et al., 2014; Uwimana et al., 2020; Balikagala et al., 2021; Stokes et al., 2021.)

## 5. Accessory Genetic Determinants And Epistasis

Artemisinin partial resistance is polygenic and context-dependent. PfK13 mutations often require permissive or compensatory genetic backgrounds to manifest robust phenotypes (Stokes et al., 2021 ; Conrad et al., 2023). Notable accessory loci implicated in the modulation of resistance include:

- PfPI3K and PI3P pathway: Elevated phosphatidylinositol-3-phosphate (PI3P) levels have been associated with PfK13-mediated resistance; alterations in PI3K activity can modulate stress signaling and survival (Mbengue et al., 2015).
- Coronin and endocytosis genes: Mutations in pfcoronin and other cytoskeletal/endocytic components may modulate hemoglobin
- uptake, linking to proposed mechanisms of reduced artemisinin activation (Stokes et al., 2021 ; Kucharski et al., 2024).
- Ubiquitin–proteasome system genes (e.g., UBP1): Variants affecting proteostasis are thought to interact with PfK13 alterations to confer survival advantages (Straimer et al., 2015).
- Transporter genes (Pfcrt, Pfmdr1): While historically implicated in partner drug resistance, these loci may influence the genetic background permissive for artemisinin-resistant parasites (Ndwiga et al., 2021).

**Table 1:** Summary of Accessory Genes Associated with Artemisinin Partial Resistance and Their Functions

| Accessory Gene | Putative Function | Evidence Summary | References |
|---|---|---|---|
| PfPI3K(phosphatidylinositol-3-kinase) | Regulator of PI3P levels; interacts with *PfK13*-mediated stress signalling and survival | Elevated PI3P observed in *K13*-mutant parasites; influences ring-stage survival | Mbengue et al. (2015) |
| Coronin (pfcoronin) | Cytoskeletal/endocytic function; modulates hemoglobin uptake or endocytic trafficking | Suggested as modifier of *K13* phenotype (Stokes et al., 2021) | Stokes. et al. (2021) |
| UBP1 (Ubiquitin-specific protease) | Proteostasis regulation; interacts with proteotoxic stress from artemisinin | Associated with survival phenotypes in *PfK13*-backgrounds | Straimer et al. (2015) |

| **Table 1 (Cont):** Summary of Accessory Genes Associated with Artemisinin Partial Resistance and Their Functions | | | |
|---|---|---|---|
| Pfmdr1 / Pfcrt | Transporter genes affecting partner drug susceptibility; influence genetic background permissive for artemisinin resistance | Genomic surveillance studies show potential links | Various studies (e.g., Shafik et al., 2022) |

## 6. Omics-Level Insights: Transcriptomics, Proteomics, And Metabolomics

Beyond single-gene perspectives, transcriptomic studies have revealed how resistant strains respond to drug exposure. Comparative analysis of resistant versus sensitive strains indicates upregulation of stress-response, chaperone, and protein-degradation pathways and downregulation of growth-associated transcripts (Zhang et al., 2023). Proteomic and metabolomic studies corroborate shifts in proteostasis and metabolic states consistent with a quiescent/survival phenotype (Zhang et al., 2023 ; Kucharski et al., 2024). Integrative network analyses highlight recurrent modules, such as UPR and autophagy-related processes, indicating conserved adaptive responses to artemisinin exposure across different datasets.

## 7. Genomic Epidemiology And Patterns Of Spread

Population genomics of artemisinin resistance shows contrasting dynamics between the Greater Mekong Subregion (GMS) and Africa. In GMS, hard selective sweeps have accompanied the rapid regional spread of validated PfK13 variants (Ariey et al., 2014). In Africa, however, available data suggest multiple independent emergences with variable local expansions, including the R561H lineage in Rwanda, which showed phylogenetic evidence of local expansion (Uwimana et al., 2020 ; Kirby et al., 2023). Similarly, rising prevalence of A675V and C469Y mutations in Uganda has been linked to delayed clearance signals (Balikagala et al., 2021).

## 8. Molecular Surveillance: Methods And Platforms

Molecular surveillance has become a cornerstone of detecting and monitoring resistance. Various techniques, such as PCR-Sanger sequencing, amplicon deep sequencing, and WGS, provide essential tools for resistance monitoring. Table 2 summarizes these methods, highlighting their description, advantages and limitations.

| **Table 2:** Molecular Surveillance Methods, Strengths, Limitations, and Recommended Use Cases | | | | |
|---|---|---|---|---|
| Method | Description | Advantages | Limitations/Considerations | Key References |
| PCR + Sanger sequencing | Targeted amplification and sequencing of *PfK13* propeller domain | Low cost; established method in many malaria labs | Limited sensitivity for minority variants; no linkage data | Menegon et al., 2016) |
| Amplicon deep sequencing | Next-gen sequencing for *PfK13* (and possibly flanking regions) | Higher sensitivity; detects low-frequency variants | Requires more advanced infrastructure and bioinformatics | Menegon et al., 2016) |
| Whole-Genome Sequencing (WGS) | Sequencing full parasite genome from field isolates | Enables discovery of novel resistance loci and haplotype analysis | Costlier; requires high-quality DNA and bioinformatics capacity | Stokes et al., 2021) |
| Consortium/Shared Platforms (e.g., MalariaGEN) | Aggregated data across sites with standardized pipelines | Enables cross-region comparability, detection of emerging alleles | Data-sharing agreements required, delayed real-time updating | Ménard et al., 2016) |

## 9. Clinical Correlation And Implications For ACT Efficacy

While PfK13 mutations are robust predictors of delayed parasite clearance, clinical treatment failure depends on multiple factors, including partner drug efficacy, transmission intensity, host immunity, and parasite genetic background (Balikagala et al., 2021 ; Conrad et al., 2023). In Southeast Asia, the expansion of PfK13 C580Y and partner drug resistance (e.g., piperaquine resistance) has driven significant ACT failures (Ariey et al., 2014 ; Conrad et al., 2023). In Africa, while ACTs remain effective, the increase in PfK13 mutations and RSA phenotypes raises concerns about future risks if partner drug protection erodes (Uwimana et al., 2020 ; Balikagala et al., 2021).

## 10. Knowledge Gaps And Future Directions

Key gaps remain in understanding the functional roles of many emerging PfK13 variants, such as G533S and R622I, which are currently being characterized (Mihreteab et al., 2023 ; Siddiqui et al., 2025). Additionally, the network of accessory loci and the fitness landscapes that allow PfK13 mutations to spread need deeper elucidation through experimental evolution and population genomics (Stokes et al., 2021 ; Kucharski et al., 2024).

Advances in real-time genomic surveillance capacity, integrating sequencing pipelines with clinical monitoring and ensuring open-data sharing, are essential to effectively track resistance (WHO, 2018). Emerging technologies such as single-cell genomics, long-read sequencing, and machine learning for genotype–phenotype prediction promise higher-resolution insights into resistance evolution and transmission (Zhang et al., 2023 ; Conrad et al., 2023).

## 11. Conclusion

Genomic studies have significantly advanced our understanding of artemisinin partial resistance in P. falciparum, identifying PfK13 as a central determinant of resistance. However, the spread of resistance is not confined to Southeast Asia, as recent findings from Africa underscore the need for vigilance and genomic surveillance across regions. To preserve the efficacy of ACTs, sustained investment in genomic surveillance, integrated with clinical monitoring, and public health responses, is essential. Real-time genomic surveillance, combined with robust data-sharing frameworks and local sequencing capacity, will be crucial in combating this growing threat to malaria control.

## Consent For Publication

All authors consent to publication of this article.

## Availability Of Data And Material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing Interests

The authors declare that they have no competing interests

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## Authors' Contributions

- Conception and design of the study: Saheed A. Odediji and Monsuru A. Adeleke
- Research framework: Saheed A. Odediji, Surakat A. Olabanji, Abdullahi O. Olawuyi
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## Statements And Declarations

This study has not been published before or is not under consideration for publication elsewhere (except as as part of an academic thesis); its publication is permitted by all authors and after acceptance for publication, it will not be submitted for publication anywhere else, in English or in any other language, without written approval. No use of artificial intelligence tools in manuscript preparation.

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## References

Agaba, B. B., Travis, J., Smith, D., Rugera, S. P., Zalwango, M. G., Opigo, J., and Cheng, Q. 2024. Emerging threat of artemisinin partial resistance markers (pfk13 mutations) in Plasmodium falciparum parasite populations in multiple geographical locations in high transmission regions of Uganda. Malaria Journal, 23(1), 330.

Ariey, F., Witkowski, B., Amaratunga, C., Beghain, J., Langlois, A. C., Khim, N., and Menard, D. 2014. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature, 505(7481), Pp. 50–55.

Balikagala, B., Fukuda, N., Ikeda, M., Katuro, O. T., Tachibana, S. I., Yamauchi, M., and Mita, T. 2021. Evidence of artemisinin-resistant malaria in Africa. New England Journal of Medicine, 385(13), Pp. 1163-1171.

Conrad, M. D., Asua, V., Garg, S., Giesbrecht, D., Niaré, K., Smith, S., and Rosenthal, P. J. 2023. Evolution of partial resistance to artemisinins in malaria parasites in Uganda. New England Journal of Medicine, 389(8), Pp. 722-732.

Dhorda, M., Kaneko, A., Komatsu, R., Kc, A., Mshamu, S., Gesase, S., and von Seidlein, L. 2024. Artemisinin-resistant malaria in Africa demands urgent action. Science, 385(6706), Pp. 252-254.

Ishengoma, D. S., Mandara, C. I., Bakari, C., Fola, A. A., Madebe, R. A., Seth, M. D., and Warsame, M. 2024. Evidence of artemisinin partial resistance in northwestern Tanzania: clinical and molecular markers of resistance. The Lancet Infectious Diseases, 24(11), Pp. 1225-1233.

Kirby, R., Giesbrecht, D., Karema, C., Watson, O., Lewis, S., Munyaneza, T., and Mazarati, J. B. 2023, April. Examining the early distribution of the artemisinin-resistant Plasmodium falciparum kelch13 R561H mutation in areas of higher transmission in Rwanda. In Open Forum Infectious Diseases (Vol. 10, No. 4, p. ofad149). US: Oxford University Press.

Kojom Foko, L. P., Jakhan, J., Narang, G., Hawadak, J., Eboumbou Moukoko, C. E., and Singh, V. 2025. Novel Plasmodium falciparum Kelch13 polymorphisms in Cameroon with structural and physicochemical impact. Antimicrobial Agents and Chemotherapy, 69(5), e00884-24.

Kucharski, M., Nayak, S., Gendrot, M., Dondorp, A. M., and Bozdech, Z. 2024. Peeling the onion: how complex is the artemisinin resistance genetic trait of malaria parasites?. Trends in Parasitology, 40(11), Pp. 970-986.

Mbengue, A., Bhattacharjee, S., Pandharkar, T., Liu, H., Estiu, G., Stahelin, R. V., and Haldar, K. 2015. A molecular mechanism of artemisinin resistance in Plasmodium falciparum malaria. Nature, 520(7549), Pp. 683-687.

Menegon, M., Nurahmed, A. M., Talha, A. A., Nour, B. Y., and Severini, C. 2016. Molecular surveillance of antimalarial drug resistance related genes in Plasmodium falciparum isolates from Eritrea. Acta tropica, 157, Pp. 158–161. https://doi.org/10.1016/j.actatropica.2016.02.007

Mihreteab, S., Platon, L., Berhane, A., Stokes, B. H., Warsame, M., Campagne, P., Criscuolo, A., Ma, L., Petiot, N., Doderer-Lang, C., Legrand, E., Ward, K. E., Zehaie Kassahun, A., Ringwald, P., Fidock, D. A., and Ménard, D. 2023. Increasing Prevalence of Artemisinin-Resistant HRP2-Negative Malaria in Eritrea. The New England journal of medicine, 389(13), Pp. 1191–1202. https://doi.org/10.1056/NEJMoa2210956

Ndwiga, L., Kimenyi, K. M., Wamae, K., Osoti, V., Akinyi, M., Omedo, I., Ishengoma, D. S., Duah-Quashie, N., Andagalu, B., Ghansah, A., Amambua-Ngwa, A., Tukwasibwe, S., Tessema, S. K., Karema, C., Djimde, A. A., Dondorp, A. M., Raman, J., Snow, R. W., Bejon, P., and Ochola-Oyier, L. I. 2021. A review of the frequencies of Plasmodium falciparum Kelch 13 artemisinin resistance mutations in Africa. International journal for parasitology. Drugs and drug resistance, 16, Pp. 155–161. https://doi.org/10.1016/j.ijpddr.2021.06.001

Ogieuhi, I. J., Ajekiigbe, V. O., Kolo Manma, K., Akingbola, A., Odeniyi, T. A., Soyemi, T. S., and Awolola, B. D. 2024. Discover Public Health.

Shafik, S. H., Richards, S. N., Corry, B., and Martin, R. E. 2022. Mechanistic basis for multidrug resistance and collateral drug sensitivity conferred to the malaria parasite by polymorphisms in PfMDR1 and PfCRT. PLoS biology, 20(5), e3001616.

Siddiqui, F. A., Chim-Ong, A., Wang, C., Miao, J., and Cui, L. 2025. The PfK13 G533S mutation confers artemisinin partial resistance in multiple genetic backgrounds of Plasmodium falciparum. Antimicrobial Agents and Chemotherapy, e00162-25.

Stokes, B. H., Dhingra, S. K., Rubiano, K., Mok, S., Straimer, J., Gnädig, N. F., Deni, I., Schindler, K. A., Bath, J. R., Ward, K. E., Striepen, J., Yeo, T., Ross, L. S., Legrand, E., Ariey, F., Cunningham, C. H., Souleymane, I. M., Gansané, A., Nzoumbou-Boko, R., Ndayikunda, C., and Fidock, D. A. 2021. Plasmodium falciparum K13 mutations in Africa and Asia impact artemisinin resistance and parasite fitness. eLife, 10, e66277. https://doi.org/10.7554/eLife.66277

Straimer, J., Gnädig, N. F., Witkowski, B., Amaratunga, C., Duru, V., Ramadani, A. P., and Fidock, D. A. 2015. K13-propeller mutations confer artemisinin resistance in Plasmodium falciparum clinical isolates. Science, 347(6220), Pp. 428-431.

Uwimana, A., Legrand, E., Stokes, B. H., Ndikumana, J. L. M., Warsame, M., Umulisa, N., and Menard, D. 2020. Emergence and clonal expansion of in vitro artemisinin-resistant Plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. Nature medicine, 26(10), Pp. 1602-1608.

Uwimana, A., Umulisa, N., Venkatesan, M., Svigel, S. S., Zhou, Z., Munyaneza, T., and Lucchi, N. W. 2021. Association of Plasmodium falciparum kelch13 R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study. The Lancet Infectious Diseases, 21(8), Pp. 1120-1128.

World Health Organization. 2018. Status report on artemisinin resistance and ACT efficacy (August 2018). Geneva: World Health Organization.

Zhang, J., Fu, Y., Bian, X., Han, H., Dong, H., Zhao, G., and Zhang, L. 2023. Molecular identification and genotyping of Blastocystis sp. in sheep and goats from some areas in Inner Mongolia, Northern China. Parasitology International, 94, 102739.