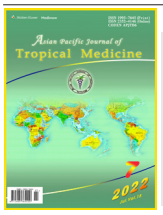

Perspective

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.351762 Impact Factor: 3.041

# Unravelling the situation of malaria misdiagnosis in India: Its adverse impact and management strategies

Gaurav Kumar[1], Hari Shankar[2]✉

[1]*ICMR-National Institute of Malaria Research, Sector-8, Dwarka, Delhi, India*

[2]*Indian Council of Medical Research, New Delhi, India*

Malaria is a public health problem in several parts of India. A continuous decrease in malaria has been reported in India, from about 2.0 million cases in 2000 to about 0.2 million in 2020[1]. In February 2016, the Government of India formally launched the National Framework for Malaria Elimination, which outlines the strategies for eliminating malaria from India by 2030[2]. It aims to interrupt indigenous malaria transmission (zero indigenous case reporting) throughout the country, prevent the re-establishment of transmission in areas where it has been eliminated, and maintain national malaria-free status by 2030 and beyond, using the existing intervention tools and strategies. In 2017, India launched its five-year National Strategic Plan for Malaria Elimination, which is mainly district focused rather than the National Framework for Malaria Elimination, which was state focused[3]. India has shown a 71% reduction of malaria cases in 2019 compared to 2015, which was achieved by strengthening surveillance, improving diagnosis and treatment, and intensive vector control measures using existing tools. In India, Odisha state contributed 37.4% of total malaria cases in 2015, which was reduced to 12% in 2019 using the Durgama Anchalare Malaria Nirakaran initiative and comprehensive case management of malaria[4]. The key to success in keeping the momentum of this reduction and catching malaria elimination goal is the accurate diagnosis of malaria cases. Among the five *Plasmodium* species, *Plasmodium (P.) falciparum (Pf)* and *P. vivax (Pv)* cause more cases than other species. And their diagnosis is complicated by the varied distribution of mono and mixed infections. Microscopy remains the gold standard method but requires highly skilled microscopists with genuine knowledge of different stages of *Plasmodium* species and the capability to read low-density parasitemia. Fulfilling such a requirement in rural India is a daunting task; consequently, more than a quarter of malaria cases are missed by microscopy. Rapid diagnostic kits are used where microscopy is not feasible due to its ease of use in remote settings.

In the current scenario when health agencies are emphasizing on test and treatment strategies for *Plasmodium* infections, here we summarized the scanty evidence of misdiagnosis in detecting *Plasmodium* infections in India. An Indian study reported that out of 1 521 microscopy-confirmed *Pf* infections, 265 samples (mixed *Pf*-*Pv* infections) were misdiagnosed as *Pf* infections[5]. A similar prevalence of unreported mixed infections (18%) amongst microscopically declared *Pf* cases were reported in another study that examined the blood samples collected from almost all malaria endemic regions of India[6]. A recent case report about the misdiagnosis of *Plasmodium* species in the high endemic district Gadchiroli of Maharashtra state, India, revealed the consequences of misdiagnosis resulted in the loss of life of a patient[7].

Although the proportion of misdiagnosis in India is consistent (about 17%-18%) since 2015, still it is significant enough to collapse the system of disease tracking and management. The proportion of *Pv* is majorly misdiagnosed as *Pf* infections which requires immediate attention. A fundamental limitation is that mixed infections (*Pf*-*Pv*) are recorded as *Pf* malaria in aggregated reports, and mixed infections are often likely to be missed in microscopy. In addition, *Pv* malaria deaths in India are investigated and recorded; however, these are not included in the annual report[8].

While observing malaria trend for the last five years (2016-2021) in India, it is observed that *Pf* cases declined from 65.5% in 2016

✉To whom correspondence may be addressed. E-mail: harishankarnioh@gmail.com



**How to cite this article:** Kumar G, Shankar H. Unravelling the situation of malaria misdiagnosis in India: Its adverse impact and management strategies. Asian Pac J Trop Med 2022; 15(7): 290-292.

**Article history:** Received 15 July 2022 Revision 17 July 2022
Accepted 25 July 2022 Available online 28 July 2022

to 46.4% in 2019. However, during 2020 and 2021, the scenario was reversed with an increase in the proportion of *Pf* to about 63%. Elimination of *Pv* foci is achievable but not in less than three years, compared with the one year for *Pf*[9]. In fact, due to relapse in *Pv* malaria, it is difficult to control and eliminate *Pv* malaria. It is expected that there will be an increase in the cases of *Pv* malaria during this lean phase of malaria transmission in the country. However, a decrease in the percentage of *Pv* cases raises concerns about the proper diagnosis of malaria cases. There is a possibility that the majority of *Pv* and mixed infections are being misdiagnosed as *Pf* cases. The authors have conducted a mass blood survey in two districts of North-East India ($n$=3 322) in 2017, which revealed that more than 55.4% (169/305) of PCR confirmed *Pf* infections were misdiagnosed with rapid diagnostic kits, of which 97.6% (165/169) were false negative. A total of 37.5% (15/40) of the PCR confirmed *Pv* samples were declared *Pf*. A similar proportion was declared negative by rapid diagnostic kits, and 2.5% (1/40) was *Pf*–*Pv* mixed infections. PCR confirmed *Pf*–*Pv* mixed infections ($n$=18) were majorly misdiagnosed as *Pf* (72.2%, 13/18), *Pv* (5.6%, 1/18) and negative (11.1%, 2/18) using rapid diagnostic kits[10].

Bivalent *Pf/Pv* antigen detecting rapid diagnostic kits was introduced to ensure access to malaria diagnosis in 2013. Since then, malaria diagnosis dependency has shifted from microscopy to rapid diagnostic kits in inaccessible and malaria-endemic areas. However, deletions in the histidine rich protein-2 gene resulted in misdiagnosis of *Plasmodium* species.

Misdiagnoses can have severe consequences on a person's health and disease trajectory. It can delay recovery and sometimes call for harmful treatment, as per the drug treatment guidelines of National Vector Borne Disease Control Programme (NVBDCP). There is different treatment regime for *Pf* and *Pv* infections. In uncomplicated *Pf* infections, three days of artemisinin combination therapy is recommended. But for *Pv* cases, a three-day regimen of chloroquine with 14 days regimen of primaquine is recommended in India (NVBDCP). Therefore, misdiagnosis can lead to the treatment of *Pv* cases with the drug recommended for *Pf* infection, which may result in wrong treatment and chances of relapse.

Moreover, the lack of access to radical cure due to misdiagnosis will continue to fuel the number of *Pv* malaria cases because one infective bite has the potential for several relapses, and such relapses maintain *Pv* transmission[8]. The consequences of misdiagnosis also include underestimating the transmission and burden of *Plasmodium* parasites with sub-critical levels and hindering effective, prospective monitoring of changes in transmission. It may impair effective monitoring of malaria, and accordingly, the sensitivity of diagnostics should also be considered in evaluating the surveillance systems.

To reduce misdiagnosis of malaria, the first and foremost option is to improve the quality of microscopy by refresher training of the microscopist involved. Regular training is a key to succeed in solving the problem of misdiagnosis. It is evident from the published literature that the refresher training improved the participants' knowledge, competencies, and skill set in malaria microscopy.

Human factor is another leading cause of the misdiagnosis of malaria in microscopy. Therefore, using artificial intelligence (AI) based microscopy might be a better option as it increases diagnostic precision which is playing a vital role in battling infectious diseases. Automated modern deep learning techniques are foreseeing for the microscopic examination of malaria parasites. The emerging technologies of machine learning with complex image patterns have accelerated research in medical image analysis. An automated, accurate, and efficient model can significantly reduce the need for trained personnel. Nevertheless, AI-based microscopy is in the nascent development phase, and a few prototypes have shown good sensitivity and specificity.

Another option to overcome the issue of misdiagnosis is the use of molecular surveillance techniques. There is an added advantage of detecting sub-microscopic infections with the help of molecular tools. The specificity and sensitivity are also comparable with that of microscopy, the gold standard. Moreover, point-of-care molecular tools like Trunat are a much better option being portable, battery operated, and technologically accessible to the application[11].

Though the countdown to the malaria elimination goal has begun, still the misdiagnosis of *Plasmodium* species, especially *Pv* and *Pf*–*Pv* mixed infections remain a significant issue. This article aims to draw the immediate attention of the policymakers and stakeholders to deal with the misdiagnosis of *Plasmodium* species in India.

## Conflict of interest statement

The authors declare there are no conflicts of interest.

## Acknowledgements

Authors are thankful to the Director, ICMR-National Institute of Malaria Research, Delhi for providing necessary facilties.

## Funding

The authors did not receive funding to write this perspective. However, grant no. NER/55/2015-ECD-I was received from Indian Council of Medical Research, India to carry-out the investigations in the North-East India region, and a part of observations are reported in this paper.

## Authors' contributions

GK and HS conceptualized, drafted, and reviewed the manuscript.

## References

[1] National Vector Borne Disease Control Programme. *Malaria: Magnitude of problem*. 2022. [Online]. Available from: https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=420&lid=3699. [Accessed on 17 July 2022].

[2] National Vector Borne Disease Control Programme. *National framework for malaria elimination in India (2016–2030)*. 2016. [Online]. Available from: https://nvbdcp.gov.in/WriteReadData/l892s/National-framework-for-malaria-elimination-in-India-2016%E2%80%932030.pdf. [Accessed on 15 September 2021].

[3] National Vector Borne Disease Control Programme. *National strategic plan for malaria elimination in India 2017–2022*. 2017. [Online]. Available from: http://www.indiaenvironmentportal.org.in/files/file/nsp_2017-2022-updated.pdf. [Accessed on 15 September 2021].

[4] Nema S, Ghanghoria P, Bharti PK. Malaria elimination in India: Bridging the gap between control and elimination. *Indian Pediatr* 2020; **57**(7): 613-617. doi:10.1007/s13312-020-1888-5.

[5] Krishna S, Bharti PK, Chandel HS, Ahmad A, Kumar R, Singh PP, et al. Detection of mixed infections with *Plasmodium* spp. by PCR, India, 2014. *Emerg Infect Dis* 2015; **21**(10): 1853-1857.

[6] Nema S, Singh A, Krishna S, Poriya R, Dubey S, Ali NA, et al. Unreported mixed *Plasmodium* species infection may increase vivax malaria in India: A challenge for malaria elimination. *Trans R Soc Trop Med Hyg* 2022; **116**(7): 600-603.

[7] Singh RK, Kumar G, Karlekar R, Manjhi J, Singh OP. Case study of misdiagnosis of malaria in primary care set-up leading to rapid complications and death in a high malaria endemic district of India. *J Vector Borne Dis* 2020; **57**: 114-116.

[8] Anvikar AR, Shah N, Dhariwal AC, Sonal GS, Pradhan MM, Ghosh SK, et al. Epidemiology of *Plasmodium vivax* malaria in India. *Am J Trop Med Hyg* 2016; **95**(6 Suppl): 108-120.

[9] Ahmad SS, Rahi M, Sharma A. Relapses of *Plasmodium vivax* malaria threaten disease elimination: Time to deploy tafenoquine in India? *BMJ Glob Health* 2021; **6**(2): e004558.

[10] Shankar H, Singh MP, Phookan S, Singh K, Mishra N. Diagnostic performance of rapid diagnostic test, light microscopy and polymerase chain reaction during mass survey conducted in low and high malaria-endemic areas from two North-Eastern states of India. *Parasitol Res* 2021; **120**(6): 2251-2261.

[11] Shankar H, Kumar G. Truenat: An affordable and user-friendly option for screening of sub-microscopic *Plasmodium* infections in low resource countries. *Lancet Reg Health–Southeast Asia* 2022. doi: 10.1016/j.lansea.2022.100032. In press.