Probing newer possibilities for detecting drug resistance in malaria

Sir,

Malaria is a major public health disease attributed to 214 million of new cases and more than 4 lakh deaths in 2015 [1]. African countries have the highest incidence followed by Southeast Asian (SEA) countries, among which India has the maximum disease burden. However, smear microscopy and use of rapid diagnostic test have strengthened early diagnosis and timely initiation of treatment. Emerging drug resistance such as chloroquine resistance in *Plasmodium vivax* and the evolving tolerance in *Plasmodium falciparum* to artemisinin combination therapy (ACT) has further superadded to the existing problems. According to the World Health Organization (WHO), Thai-Cambodian border region has been the focus for the emerging artemisinin resistance due to several factors [1]. *P. falciparum* has become resistant to almost all available antimalarial medicines in this region. Charles Woodrow et al. have reviewed in detail the expanding artemisinin resistance in SEA which is leading to failure of all the artemisinin-based combinations [2]. Rapid dissemination of resistant parasite to the other parts of this subregion as well the other parts of the world is the major threat at present [3]. India is at the highest risk for the acquisition of this entity due to the close approximation of its territorial border with that Myanmar, Bangladesh and the existence of freely moving livelihood across these boundaries [4].

WHO has defined "artemisinin resistance" as delayed parasite clearance following treatment with either artesunate monotherapy or ACT [5]. Such resistance is regarded as partial resistance which may be due to artemisinin resistance or resistance to partner drug in ACT. Routine monitoring of the ACT treatment failure rates based on the presence of parasitemia on day 3 and treatment failure rate at 28 or 42 days follow-up is essential to make a timely decision for changing the drug policy [5]. Delayed parasite clearance has been shown to be associated with mutations in the Kelch13 (K13) propeller region by both *in vitro* and *in vivo* studies. Delayed parasite clearance along with K13 mutations in a single patient will be suggestive of confirmed artemisinin resistance. A total of 186 K13 alleles, including 108 non-synonymous mutations, have been reported from different parts of the world. The presence of mutants does not lead to resistance in all, as most of the mutants represent "passer-by" with no alteration in parasite clearance. However, recent studies have documented four mutants (493H, 539T, 543T, and 580Y) as confirmed K13 propeller mutations from both *in vivo* and *in-vitro* experiments [5]. Recently, the MalariaGEN *P. falciparum* Community Project has shown that the K13 mutations responsible for resistance were present in low frequency in the African region when compared to SEA region. Most of the African K13 mutations originated locally when compared to the SEA region which showed a strong evolutionary spread and selection [6]. Therefore, detection of K13 mutation in the SEA region is important to detect resistance and thereby enforce newer interventions to prevent the further spread of resistance.

A disease similar to malaria is tuberculosis (TB) with a worldwide burden of 9.6 million cases attributing to around 1.5 million death annually [7]. Worldwide TB also bears a similar threat of emerging multidrug resistance TB (MDR) and even extensive drug resistance. Techniques like line probe assay (LPA) are capable of detecting the mutations responsible for resistance. Genotype® MTBDRsl assay which is capable of detecting resistance even in the second line antitubercular drugs has been approved by WHO before initiating therapy for MDR cases [7]. LPA has been utilized in many fields like detection of drug resistance in TB, genotyping of hepatitis C virus, and others [8]. LPA is suitable for use at reference laboratories, or at laboratories where molecular testing facilities are available.

K13 mutation detection for artemisinin resistance requires PCR and sequencing which are costly, time consuming and not feasible at all health-care facilities. Therefore, the need of the hour is to develop an innovative platform like the LPAs for the detecting the mutations responsible for drug resistance in *P. falciparum* and other *Plasmodium* spp. LPA will be a rapid and cost-effective technique with limited equipment need. Based on the resistance patterns obtained by LPA, an effective alternative therapy can be decided. The use of this technique will also enhance the implementation of stewardship policy for the right use of antimalarial similar to that of antibiotics.

Kamran Zaman, Kapil Goyal

From Department of Medical Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to: Dr. Kamran Zaman, Department of Medical Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
Phone: 0172-275169. Fax: 0172-2744401.
E-mail: kamran3zaman@gmail.com

Received – 27 March 2017
Initial Review – 07 April 2017
Published Online – 08 May 2017

REFERENCES

1. WHO. World Malaria Report. Geneva: World Health Organization; 2015. Available from: http://www.who.int/malaria/publications/world_malaria_report/en/. [Last accessed on 2016 Aug 20].
2. Woodrow CJ, White NJ. The clinical impact of artemisinin resistance in

Southeast Asia and the potential for future spread. FEMS Microbiol Rev. 2016;pii:fuw037.
3. Wangdi K, Gatton ML, Kelly GC, Banwell C, Dev V, Clements AC. Malaria elimination in India and regional implications. Lancet Infect Dis. 2016;16(10):e214-24.
4. Tun KM, Imwong M, Lwin KM, Win AA, Hlaing TM, Hlaing T, et al. Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: A cross-sectional survey of the K13 molecular marker. Lancet Infect Dis. 2015;15(4):415-21.
5. WHO. Artemisinin and artemisinin-based combination therapy resistance. April 2016. Available from: http://www.apps.who.int/iris/bitstream/10665/208820/1/WHO_HTM_GMP_2016.5_eng.pdf. [Last accessed on 2016 Aug 20].
6. MalariaGEN Plasmodium Falciparum Community Project. Genomic epidemiology of artemisinin-resistant malaria. Elife. 2016;5.pii:e08714.
7. WHO. Global Tuberculosis Report. Geneva: World Health Organization; 2015b. Available from: http://www.who.int/tb/publications/global_report/en/. [Last accessed on 2016 Aug 20].
8. Verbeeck J, Maes P, Wollants E, Van der Merwe S, Song E, Nevens F, et al. Use of a commercially available line probe assay for genotyping of hepatitis C virus 5a strains. J Clin Microbiol. 2005;43(12):6117-9.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Zaman K, Goyal K. Probing newer possibilities for detecting drug resistance in malaria. East J Med Sci. 2017;2(2):39-40.