Editorial

Malaria in 2018: Looking to the Past and Moving into the Future

Po Ying Chia, [1]*MBBS, MRCP*, Li Yang Hsu,[1,2]*MBBS, MPH*, Tsin Wen Yeo, [1,3]*MBBS, PhD*

World Malaria Day is observed and commemorated annually on 25 April in recognition of the ongoing global burden and the efforts to control it. Malaria is caused by *Plasmodium* parasites, of which 5 species are known to cause disease in humans, namely *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*.[1] It is a vector borne disease and is transmitted by Anopheles mosquitoes. Although potentially life threatening, prognosis is excellent if the disease is diagnosed early, and treated promptly with effective antimalarials.[1]

In the late 1990s, the incidence of malaria was at a peak and globally it was the major contributor of morbidity and mortality from an infectious aetiology. Since then, effective control efforts have led to a major reduction in both the incidence rate and mortality by 41 and 62 percent during the period 2000-2016.[2] However, in 2016, malaria still caused an estimated 216 million cases and 445,000 deaths.[2] The greatest burden of disease is in the World Health Organization (WHO) African region which has approximately 90 percent of cases; the next major area is Southeast Asia where Singapore is geographically located, with an estimated 6-7 percent of the global incidence.[2,3] Singapore's malaria control efforts in the 1970s and 1980s were effective and it achieved and maintained its malaria-free status (defined as no local transmission of all human parasites for 3 consecutive years) since 1982.[4] In fact, Singapore is 1 of only 4 countries in Asia, which has accomplished this, the others being Brunei in 1987, Maldives in 2015, and Sri Lanka in 2016.[2,3]

Since then, Singapore has reported clusters of human malaria suggestive of autochthonous transmission. These include a 3-cluster outbreak involving 29 individuals in 2009 with all cases within each cluster being epidemiologically linked.[3] In 2007 and 2008, Singapore also reported 5 cases of locally acquired *P. knowlesi* infection, which is strictly not a human but a simian malaria which causes zoonotic human disease.[5] The reservoir for *P. knowlesi* is the long-tailed macaque commonly seen in our nature reserves, and local studies have shown that forest dwelling but not urban monkeys harbour these parasites.[5] Human *P. knowlesi* infections have been reported in almost every Southeast Asian country with large foci in Indonesian Sumatera, Peninsular Malaysia and Malaysia Borneo where it is now the most common cause of malaria. Significantly, *P. knowlesi* is difficult to differentiate from *P. malariae* on microscopy alone and may require molecular diagnostic tools such as polymerase chain reaction and loop-mediated isothermal amplification.[6]

In 2016, Singapore only reported 31 laboratory-confirmed malaria cases of which all were imported. While this suggests that the risk of re-emergence is low, Singapore's geographical location in Southeast Asia, position as a travel and tourism hub, reliance of foreign workers from malaria-endemic countries, high population density and presence of Anopheles mosquitoes are reasons why Singapore remains vulnerable. A comprehensive system of vector surveillance and control, early case detection and notification system, aggressive prevention and actions upon detection of cases are thus necessary to allow Singapore to maintain its malaria-free status.

Clinical management of malaria requires accurate diagnosis and effective antimalarial agents. Microscopy is sensitive for detection of all *Plasmodium* species infecting humans but may not be able to differentiate *P. knowlesi* from the other species as mentioned above. Rapid diagnostic tests are sensitive for *P. falciparum* infections, but this decreases significantly for the other species.[6] Resistance to antimalarial agents is a defining feature of *P. falciparum* (and to a lesser degree, *P. vivax)* which complicates the clinical management of malaria especially in resource-challenged countries.[7] Increasing resistance of *P. falciparum* to first and even second-line drugs contributed to the high global mortality rate of malaria in the late 1990s.[7] Mefloquine resistance has already resulted in changes in choice of malaria chemoprophylaxis in the Cambodia and Thailand region. The development and widespread implementation of highly effective artemisinin-based combination therapies (ACT) which consists of an artemisinin derivative and a

[1]Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital, Singapore
[2]Saw Swee Hock School of Public Health, National University of Singapore, Singapore
[3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
Address for Correspondence: Dr Yeo Tsin Wen, Institute of Infectious Disease and Epidemiology, Communicable Diseases Centre, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: Tsin_Wen_YEO@ttsh.com.sg

partner drug, has been a major contributor to the significant decrease in malaria-related deaths since the early 2000s.[7] However, development of subclinical resistance to artesunate (the major active ingredient in ACT) was first noted in Western Cambodia in 2008 with delayed parasite clearance.[7] This has been attributed to mutations in the Kelch 13 propeller domain.[8] Despite major efforts to counter this threat, reports of clinical failures to ACTs (including partner drugs) widely used in national malaria programmes in Southeast Asia emerged in Cambodia in 2016, and has since spread to Thailand, Laos, Cambodia and Vietnam.[9] This confirmed that *P. falciparum* had developed resistance to both artemisinin and the partner drug and in a repeat of the scenario with chloroquine, the possibility of spread of this drug-resistant strain to the rest of Asia and Africa with a recurrence of the high mortality associated with malaria in the 1990s.[7] Currently, major efforts led by the Global Fund's Regional Artemisinin Initiative are ongoing to try and avert this possible catastrophe. However, there is still debate and controversy about the optimal methods to achieve this.

While *P. vivax* is perceived to be less of a global threat, recent reports from Asia suggest that in contrast to traditional literature, vivax malaria can also cause severe disease.[1] In addition, resistance to chloroquine, considered the most cost-effective drug in the treatment of *P. vivax* malaria, is widespread in Indonesia and has been also reported in Malaysian Borneo as well other Southeast Asian countries.[7]

The development of ACTs in the late 20th century was pioneered by scientists from China which resulted in the award of a Nobel Prize in Medicine to Tu Youyou in 2015.[10] Recently, Singapore, (led by scientists at the Novartis Institute of Tropical Disease) has discovered 2 new agents, KAE609 and KAF156 from 2 novel antimalarial groups, the spiroindolones and imidazolopiperazines.[11,12] These drugs in phase 2 trials have shown superior or comparable parasite killing rates compared to even the ACTs.[11,12] However, the widespread use and deployment of these compounds require further studies to further evaluate safety, pharmacokinetic/pharmacodynamic parameters and barriers to the development of resistance with use of suitable partner drugs.

Malaria elimination has been on the global health agenda since 1955 and the Global Malaria Eradication Programme using a programme of effective case management and vector control successfully eradicated malaria from North America, parts of South-Central America, Europe, and parts of Asia.[13] However, the programme was suspended in 1969 due to resistance to drug and insecticide, lack of funding and inadequate community participation, as well as social unrest.[13] Consequently, malaria re-emerged in parts of Europe and central Asia. To continue the fight against malaria, the Roll Back Malaria initiative was launched in 1998, along with a set of interconnected goals consisting of action and investment to defeat malaria. This has continued with a Global Technical Strategy for Malaria, and Sustainable Development Goals in 2016, all of which are scheduled to continue until 2030.[2] The strategy aims for at least 90% reduction in malaria incidence and mortality rates globally (compared to 2015), to eliminate malaria in at least 35 countries, and to prevent resurgence in all countries that are malaria-free by 2030.[2] This has been mostly successful as mentioned above from 2000-2015, and there are 22 countries with the potential to eliminate malaria by 2020. In the Asian region, these include Bhutan, Nepal, Timor-Leste, China, Malaysia and the Republic of Korea.[2] However, in the recent 2017 World Malaria Report, it was noted that the rate of decline had stalled and even reversed, resulting in an increase of 5 million cases from 2015-2016 in all regions including Southeast Asia.[2] This has been coincident with decreased funding for malaria control since 2014 with the WHO estimating that USD$6.5 billion is required annually to achieve the 2030 targets but with only USD$2.7 billion invested in 2016.[2] These observations and the lack of an effective malaria vaccine with long-term protection suggests that the potential for a resurgence of malaria is always a possibility without continued resources invested in ongoing control and elimination programmes.

Historically, malaria has been prevalent in Singapore and the potential for resurgence is still present. Malaria knows no borders and it is imperative that we persevere in constant vigilance and commit necessary resources to eradicate it. However, much progress has been made and there is still hope, with renewed political efforts and substantial resources being allocated to fight malaria, novel drug candidates in the pipeline and vaccines being developed, that we can achieve targets set for 2030 and eventually, total eradication.

REFERENCES

1. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet 2014;383:723-35.
2. WHO. World Malaria Report 2017.
3. Ng LC, Lee KS, Tan CH, Ooi PL, Lam-Phua SG, Lin R, et al. Entomologic and molecular investigation into Plasmodium vivax transmission in Singapore, 2009. Malar J 2010;9:305.
4. Lee YC, Tang CS, Ang LW, Han HK, James L, Goh KT. Epidemiological characteristics of imported and locally-acquired malaria in Singapore. Ann Acad Med Singapore 2009;38:840-9.
5. Jeslyn WP, Huat TC, Vernon L, Irene LM, Sung LK, Jarrod LP, et al. Molecular epidemiological investigation of Plasmodium knowlesi in humans and macaques in Singapore. Vector Borne Zoonotic Dis 2011;11:131-5.

6. Mathison BA, Pritt BS. Update on Malaria Diagnostics and Test Utilization. J Clin Microbiol 2017;55:2009-17.
7. Menard D, Dondorp A. Antimalarial drug resistance: a threat to malaria elimination. Cold Spring Harb Perspect Med 2017;7:a025619.
8. Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois A-C, Khim N, et al. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature 2013;505:50-5.
9. Imwong M, Hien TT, Thuy-Nhien NT, Dondorp AM, White NJ. Spread of a single multidrug resistant malaria parasite lineage (PfPailin) to Vietnam. Lancet Infect Dis 2017;17:1022-3.
10. Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med 2011;17:1217-20.
11. White NJ, Pukrittayakamee S, Phyo AP, Rueangweerayut R, Nosten F, Jittamala P, et al. Spiroindolone KAE609 for falciparum and vivax malaria. N Engl J Med 2014;371:403-10.
12. White NJ, Duong TT, Uthaisin C, Nosten F, Phyo AP, Hanboonkunupakarn B, et al. Antimalarial activity of KAF156 in falciparum and vivax malaria. N Engl J Med 2016;375:1152-60.
13. Nájera JA, González-Silva M, Alonso PL. Some lessons for the future from the Global Malaria Eradication Programme (1955-1969). PLoS Med 2011;8:e1000412.