THE BULLETIN OF THE

SRI LANKA COLLEGE OF MICROBIOLOGISTS

29th ANNUAL SCIENTIFIC SESSIONS

VIRTUAL SCIENTIFIC PROGRAMME

13 - 14 AUGUST 2020

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VOL 18 | AUGUST 2020 | ISSN 1391-930X

CHEMOPROPHYLAXIS FOR MALARIA: A SRI LANKAN PERSPECTIVE

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Background

Malaria, continues to ravage the world, causing disease in 228 million people in 2018, and resulting in more than 400,000 deaths [1]. Ten Sub-Saharan nations and India are identified as greatly burdened by the disease by the World Health Organization (WHO) [1]. Sri Lanka eliminated the disease in 2016. Yet, with 378 imported malaria cases reported between 2013-2019 and the presence of the primary vector *Anopheles culicifacies*, the country faces a threat of reintroduction of the disease.

Unlike in the era prior to elimination when indigenous transmission was ongoing, today, both Sri Lankan travelers and foreigners form a major source of imported malaria. Migrant workers originating from malaria endemic Asian countries and working on development projects throughout the country, form a major reservoir of infection. An Indian national, the probable index case in the first introduced case of malaria reported from Sri Lanka after elimination, was a migrant worker in the Moneragala district [2]. Asylum seekers [3,4], Sri Lankan pilgrims returning from travel to India and other Asian nations [3], fishermen [4], gem miners [5] and military personnel travelling to the African continent [6] are also major sources of imported malaria. The threat of malaria resurgence increased after *Anopheles stephensi* was reported from the Northern Province [7]. Unlike *A.culicifacies*, a rural vector, *A.stephensi* is an urban vector currently causing disease transmission in South India [8]. A container breeder similar to the *Aedes* mosquito, it has now been reported from Kalmunai in the Eastern Province [7]. With an influx of daily flights from Chennai to Palali International Airport, the threat of reintroduction of malaria in to Sri Lanka remains high.

Malaria prevention in travelers is dependent on increased awareness, personal protection against mosquito bites and chemoprophylaxis [9]. Chemoprophylaxis is recommended by WHO for those travelling to the endemic nations with indigenous transmission. The Anti Malaria Campaign (AMC) of Sri Lanka recommends chemoprophylaxis to Sri Lankan travelers as per WHO guidelines and issues drugs free of charge. This review aims to highlight the importance of chemoprophylaxis in the Sri Lankan context, AMC-recommendations of chemoprophylactic drugs for Sri Lankan travelers, factors affecting adherence to chemoprophylaxis and the role of mefloquine in long-term chemoprophylaxis.

Recommendations of the Anti Malaria Campaign

The AMC of Sri Lanka currently recommends mefloquine and doxycycline for travelers to countries with risk of *Plasmodium falciparum* malaria or chloroquine-resistant *P.vivax* malaria. List of such countries includes all malarious countries except, India, Nepal and Haiti with *P.vivax* malaria transmission [9]; chloroquine is prescribed for chemoprophylaxis for travelers to these named countries. Chemoprophylaxis should commence one week prior to departure and continue for up to four weeks upon return.

Chloroquine

Chloroquine, prophylaxis is administered as a weekly dose [9], and can be safely given to pregnant and lactating women as well as to children for short term use. It is well absorbed by mouth and has an enormous volume of distribution [10]. Although generally well tolerated, it may induce gastrointestinal disturbances and pruritus affecting the palms, soles and scalp. An increased risk of retinopathy is associated with long-term usage [10].

Mefloquine

Mefloquine, recommended as a weekly dose is safe in pregnancy and lactation, but it is not recommended for children under 3 months of age or those with body weight less than 5 kg [9]. It is moderately well absorbed, extensively distributed and slowly eliminated from the liver. Gastrointestinal, sleep disturbances and severe neuropsychiatric reactions are the main adverse effects when given for prophylaxis [10]. Several contraindications

...e active psychiatric illness, epilepsy, and history ...ebral malaria [10].

...ycycline

...ycycline is given as a daily dose [9]. It is con-...dicated in liver dysfunction, pregnancy, lactation and ...ildren under 8 years [9]. It should be taken with ...ss of water, well before going to sleep to avoid gastric ...esophageal irritation [9].

...emoprophylaxis to India

...e percentage of travelers to India and other Asian ...untries who obtain chemoprophylaxis from the AMC ...or to departure is reported to be extremely low [11]. ...en though more than 200,000 Sri Lankans travel to ...dia each year [6], and approximately 2/5 of imported ...laria cases between 2013 to 2017 have originated from ...dia [6], the risk of a Sri Lankan acquiring malaria while ...ere is low [11]. If chloroquine is issued for all travellers ...India (cost per tablet 2.00 LKR), it would consume ...65% of the annual budget of the AMC. The alternative ...eatment mefloquine will cost 250 LKR per tablet, which ...a greater expense to the AMC. Although chloroquine ...sistant *Plasmodium falciparum* is found in India, the ...k of infection is low [9]. Thereby it has been suggested ...at while chemoprophylaxis is important, it should not ...e considered as a major strategy to prevent reintroduction ...f the disease through travellers to India [11].

Chemoprophylaxis to Africa

Sri Lanka Tri-forces and Police Department are continuously sending troops on United Nations Peace Keeping missions to African destinations. Supplying sufficient anti-malarial medicines for these groups (approximately 200-400 individuals each contingent) has become a challenge to the AMC. Mefloquine is issued to security forces personnel (other than pilots of the Sri Lanka Air Force who are issued doxycyline) deployed in African nations. Medicines are issued for 6 months by the AMC with instructions to purchase the balance required for the duration of stay which is usually one year. However, in some instances, troops spend over one year in the African nations.

There is currently a dilemma about the duration for which mefloquine can be taken safely without significant adverse effects. A Cochrane review revealed that the relative risk of insomnia, depressed mood, anxiety and abnormal thoughts and perceptions were higher among recipients of long term prophylaxis (6 months or longer) compared to short term [12]. It also revealed that participants who took mefloquine were more likely to discontinue chemoprophylaxis compared to those who obtained atovaquone-proguanil (AP).

A study targeting a group of Sri Lankan security forces personnel who returned to Sri Lanka in 2017 following a period of deployment in South Sudan for 12 months revealed that the compliance for mefloquine was 100% [6]. Further, a majority (121/144, 84%) reported no adverse effects. Of the adverse effects reported, two people complained of neuropsychiatric symptoms (and thus the chemoprophylactic drug was replaced with doxycycline), while the others mainly complained of abnormal sweating and gastrointestinal disturbances; none of these were serious enough to discontinue mefloquine. In contrast, only 3/5 of a group of Air Force personnel, returning to Sri Lanka in late 2015, after 14 months of deployment in the Central African Republic, had adhered to chemoprophylaxis [13]. The better adherence to chemoprophylaxis in the recent past may be attributed to awareness programmes conducted by the AMC staff, better educational levels of the travellers and institutional supervision using a directly observed treatment strategy.

Long term chemoprophylaxis prescribed differs from country to country. The French military uses doxycycline as first-line chemoprophylaxis for both short and long term deployments since 2002 [14]. The USA followed suit in 2011 by recommending atovaquone-proguanil (AP) and the US drug regulatory authorities issued a 'boxed' warning that mefloquine should be discontinued if psychiatric and neurological symptoms occur during prophylactic use [15]. In 2016, the UK parliament instructed its Ministry of Defence to prescribe mefloquine only as the last resort [16]. Mefloquine is known to be associated with an increased risk of mental disorders, suicide and violence towards others including homicide [15]. Taking the above into consideration, the AMC is also in the process of recommending AP for long term prophylaxis in military personnel.

Factors affecting adherence to chemoprophylaxis

Older travellers, travellers to African destinations or individuals travelling with an organized tour by a reputed organization are more likely to adhere to chemoprophylaxis than young travellers, business travellers, backpackers and those travelling to India [17]. As education, pre-travel advice and increased awareness have shown to increase adherence to prophylaxis [17], AMC staff at its Headquarters and Regional Malaria Officers are attempting to understand the level of the travellers' knowledge of malaria and tailor the advice based on the endemicity of the destination.

Currently, the AMC works in collaboration with other departments such as the Ports Health Authority and the military to promote chemoprophylaxis [6,18]. It is compulsory for those travelling to Africa to take the Yellow Fever vaccine from the Ports Health Authority or Medical Research Institute. From here, individuals are directed to the AMC to obtain prophylaxis for malaria. Provision of printed material and visual display of messages on malaria prophylaxis at the Bandaranaike International Airport (BIA) are other measures implemented to minimise the risk of reintroduction of malaria to the country by international travel. Further, an office of the AMC is in-situ at the BIA so as to enable travellers to obtain chemo-prophylaxis free of charge [18].

Consequences of non-adherence: case histories

Malaria has been reported amongst individuals who have returned to Sri Lanka with a history of non-adherence to the recommended chemoprophylaxis regime. In 2016, an army officer returning from military training in Malaysia, presented with fever for 10 days and was treated as viral flu, prior to malaria was suspected. He had not taken chemoprophylaxis and was subsequently diagnosed with *P.knowlesi*, a zoonotic infection, prevalent in South East Asia [18]. It has the ability to cause severe malaria in humans, and is difficult to distinguish morphologically from *P.malariae* [18]. Fortunately, the natural macaque hosts *Macaca fascicularis* and *Macaca nemestrina* are not found in Sri Lanka, thus preventing the onward transmission and resultant high morbidity and mortality.

A Sri Lankan gem miner, a frequent visitor to Madagascar since 2005, initially obtained chemoprophylaxis, but subsequently defaulted [5]. He has had several episodes of malaria, thus in 2018, he self referred himself to AMC four days after return to Sri Lanka and was tested negative. Eleven days later, he was diagnosed in a private sector laboratory, when he requested for screening upon developing fever. He was treated for severe *P.vivax* malaria from which he recovered completely.

In 2015, a Police Officer, upon return from India, developed fever. He was diagnosed with vivax malaria [19]. However, molecular testing gave a diagnosis of *P.ovale* infection. A travel history to Liberia prior to India was elicited; the officer had been on chemoprophylaxis (with mefloquine) in Liberia, but not in India. Since Liberia is endemic for *P.ovale* in contrast to India and since mefloquine prophylaxis cannot prevent relapses due to *P.ovale*, it was concluded that this patient got infected in Liberia.

In 2015, an Air Force personnel succumbed to severe malaria whilst on a Peacekeeping mission in the Central African Republic [13]. He had not adhered to chemoprophylaxis. Among the group of 120, 37 individuals reported 44 episodes of malaria; all of them admitted poor adherence to prophylaxis, the main reason being forgetfulness during long-term field deployment. The relationship between non-adherence and acquisition of malaria was statistically significant [13].

Current gaps and way forward

A formal referral mechanism does not exist for those travelling to India and other malarious nations in Asia to obtain chemoprophylaxis from the AMC. A study conducted at the AMC revealed that out of the civilians who obtained chemoprophylaxis, only 5% to Asian destinations [6]. After its elimination, malaria has now become a forgotten disease [11,18]. Increasing awareness among primary level health-care providers and first contact medical officers in both the public and private sectors regarding chemoprophylaxis will ensure referrals prior to departure to endemic countries.

Sri Lanka, which nearly eliminated malaria in the 1960s, faced a resurgence and it took nearly half a century to attain the elimination status [20]. The cost for prevention of reintroduction is around 0.6 USD per citizen per annum, 12 million USD per year. Should malaria resurface, it is estimated that over 169 million USD over five years would be needed for treatment and control [20]. Thus, it is a responsibility of all citizens of this country to maintain the status of malaria elimination in Sri Lanka.

Acknowledgements

The authors wish to thank Prof. Kamini Mendis for reading and providing useful comments to improve the quality of the manuscript.

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