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Fast elimination of malaria by infectious source eradication with artemisinin-based compound

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Malaria is one of the three most hazardous infectious diseases (HIV/AIDS, Malaria and tuberculosis) in the world. Since 1960, falciparum malaria gradually became resistant to original antimalarial drugs such as Chloroquine and Fansidar. With the global spread of drug-resistant falciparum malaria, morbidity and mortality increased greatly. In May of 2014, the World Health Organization (WHO) announced that the drug combination with artemisinin-based compound is by far the only effective drug around the world in the treatment of falciparum malaria.

In October 1974, when whether or not Qinghaosu affects falciparum malaria was known, the National Head Office of 523 Project requested Guoqiao Li's team to perform a clinical trial with Huanghaosu (*Artemisia scoparia*) tablets (renamed as Qinghaosu after 1978) produced by the Yunnan Institute of Materia Medica. Li's team tested the drug on 14 falciparum malaria cases (including 3 cases of cerebral malaria) and 4 cases of vivax malaria from October to December of 1974. This was the first study to show the effectiveness of Qinghaosu (artemisinin) against falciparum malaria (Li et al., 2015). Based on these results, a nationwide collaborative research on the antimalarial Qinghaosu was conducted in April 1975. In 1978, China succeeded in antimalarial studies on Qinghaosu. This success offered a new hope for the treatment of drug-resistant falciparum malaria. The 1984 article in *The Lancet* "A randomized comparative study of mefloquine, Qinghaosu and pyrimethamine-sulfadoxine in patients with falciparum malaria" by Guoqiao Li, Keith Arnold (Director of Roche Fareast Research Foundation based in Hong Kong), Xingbo Guo et al was the first to use an artemisinin-based combination in treating falciparum (Li et al., 1984).

The first generation of artemisinin-based compound-piperquine phosphate tablet, researched and developed by Guangzhou University of Traditional Chinese Medicine, was registered and produced in Vietnam in 1997 (Brand name "Malaria Tablet CV8" in Vietnam). As a frontline antimalarial drug, Malaria Tablet CV8 was sent, at no cost, to primary level hospitals and clinics in malaria-epidemic districts in Vietnam in 1999. This action gained great attention by the WHO. Since then, Prof. Li's team has developed and optimized several artemisinin-based compounds as new antimalarial drugs. Among them, new drug certifications for double hydrogen artemisinin-piperaquine phosphate tablet (Brand name Artekin) and artemisinin-piperaquine (Brand name Artequick, Yuetekuai) were issued in 2003 and 2006, respectively. Both were included in *The Principle and Scheme for the Use of Antimalarial Drugs* in 2009. Artekin was also included in the second edition of the WHO *Guidelines for the treatment of malaria* (March 2010).

In 2003, after reviewing the antimalarial history and the past 50 plus years' experience in China, Guoqiao Li suggested that the antimalarial strategy should be changed from eradicating the mosquito vector to eradicating the infectious source (malaria parasites) in the parasite-carrying patients

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or asymptomatic carriers. The new approach "Fast Elimination of Malaria by Source Eradication" (FEMSE) is capable of eradicating malaria in an area of one million plus population within two years, compared to the fifty to sixty years needed in the past.

In June 2003, the project leader signed a collaborative agreement on "fast control and elimination of malaria" with the national malaria center of Cambodia. To rapidly eliminate the infectious source, they successively carried out mass drug administration (MDA) from 2004~2006, using the artemisinin-based compound "Yuetekuai", plus a 9mg single dose of Primaquine. These administrations were carried out at 3 pilot sites where the G6PD deficiency rate was as high as 14.7%, with populations of 7,000; 3,000; and 18,000 respectively. These studies revealed quick-acting, safe and good results. Thus, the new approach, FEMSE, was proven to be effective.

Li's team transferred to Comoros, Africa at the end of 2006. After one year's malaria prevalence investigation and preparation, FEMSE was again carried out in Nov, 2007 on Moheli island which had a population of 36,000 at a high G6PD deficiency rate of 15.1%. This treatment led to more significant effects than those in Cambodia. After 4 months' implemention, the plasmodium carrier rate in the population decreased from 23.0% to 0.33%, and the plasmodium carrier positive rate in the mosquito vector declined from 3.1% (8/258) to 0% (0/400, 0/517). Death by malaria was stopped. This confirmed that the approach of eradication of infectious source and elimination of malaria was feasible for the rapid control of malaria. MDA was implemented in Anjouan island (with a population of 350,000) in October, 2012, and in the Grand Comoros (with a population of 400,000) from October to December, 2013. During one year of implemention of FEMSE on these two islands, malaria prevalence was effectively restrained, and parasite carrier rate and morbidity both declined by 95%. Nationwide morbidity in the 2nd year deceased to 2.8‰ (close to the control level). Comoros was changed from a high to a low malaria epidemic area within a short time and the expected goal of no malaria-induced death was achieved.

To clearly define the necessary steps in the rapid control and elimination of malaria, Prof. Li's team has pursued studies on rapid elimination of infectious source. After 12 years' continuous improvement, Prof. Li summarizes the following three major steps in FEMSE (Figure 1) to achieve rapid malaria elimination as follows: (i) Rapid malaria control relies on two rounds of MDA to the whole population with a high coverage rate (Li et al., 2010, 2015). (ii) Rapid malaria eradication relies on mass screening with polymerase chain reaction (PCR) technique for remnant infectious source detection and source elimination by treating all PCR positive individuals (Li et al., 2013). (iii) Thorough malaria infectious source eradication relies on the early diagnosis and early treatment policy and on joint action among neighboring districts against malaria re-entry.

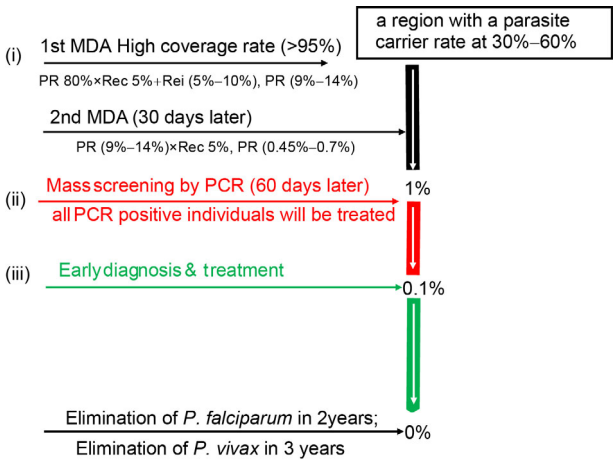

Figure 1 (color online) Three major steps in FEMSE to achieve rapid malaria elimination. PR, parasite rate; Rec, recrudescence; Rei, reinfection; *P. falciparum, Plasmodium falciparum*; *P. vivax*, *Plasmodium vivax*.

PCR technique has been around for more than twenty years, and has been widely applied in the biologic and scientific fields. From 2007 to 2013, we found the key reactive agent and optimized the detection method. Thus, we simplified the PCR operational procedure and lowered the cost, making PCR applicable for mass population screening in the FEMSE approach. This is a breakthrough in solving the difficult problem of the lingering low or re-surging population parasite carrier rate noted in the disappointing global antimalarial history. MDA was carried out on two large islands in 2012 and 2013. This action decreased the chance of transmission by migration to Comoros. We performed PCR mass screening in eleven selected villages on Moheli Island of Comoros in October of 2013. These villages were chosen because they had a few malaria cases in the previous two years. A total of 5,911 villagers were tested, and the PCR positive cases were numbered at 200 and the PCR positive rate was 3.4%. These carriers were treated 3 days with an artemisinin-based combination plus a low dose of 8mg primaquine added to the first dose. These drugs were dispensed by the antimalarial sub-center of the village and again sent by VMW to be taken by positive individuals. The PCR negative conversion rates were 92.7%, 93.9% and 100% respectively by days 5, 7 and 10. The results in 2013 suggested that the fastest and least costly technology to solve the problem of lingering low or re-surging population parasite carrier rate is to detect the infectious source and eliminate the infectious source by PCR. This technology creates an important condition for the rapid elimination of malaria.

After the implementation of FEMSE in a malaria-epidemic country or district (except for areas of political turmoil and civil war), the prevalence of malaria can be quickly controlled within half a year, death of malaria can

be stopped, and malaria can be expected to be eradicated within 2 years. Therefore FEMSE plays an important role in quickly suppressing and eradicating the first killer, malaria.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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