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Malaria – Antimalarial resistance

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Summary

The malaria parasites, *Plasmodium spp*, are among the most successful taxa ever evolved. Lizards have malaria, and so do frogs. Songbirds also have malaria, as well as penguins. Malaria is a major killer for mice and rats, but buffalos also suffer.

Human malaria, as far as we know, is as old as mankind itself; and human malaria parasites co-evolved together with their human hosts. Being such a big, widespread and old killer, it is not surprising that malaria had such a deep impact in human evolution. We are what we are also because we are descendents of malaria survivors.

Even if occasionally animal malarias infect and even kill human beings, human malaria is caused almost always by one of four specie-specialized *Plasmodium* parasites: *P. falciparum* (the major killer), *P. vivax* (as common as *P. falciparum*, but usually much less aggressive), *P. ovale* and *P. malariae* (less important). Malaria transmission is a mosquito business, and the mosquito vectors of human malarias, *Anopheles spp*, are their definitive host.

The fight against malaria started even before its transmission chain, its etiologic agents, and its vectors, were discovered at the turn of the XX century. But these discoveries facilitated and accelerated the fight. Two major findings at the time of World War II boosted malaria control: 1 – DDT and other residual insecticides, very effective against malaria mosquitoes; 2 – Chloroquine and other synthetic anti-malarials, very effective against *Plasmodium* parasites. Optimism ran high, and in a short time, for the first time in History, all of Europe, North America, North Asia, Australasia, South Africa and south South America were transformed into malaria-free areas. At the time, it looked like global malaria eradication could be achieved, and with wide national support the World Health Organization (WHO) launched a world eradication campaign.

But things went wrong. Wars, civil unrest, insufficient funding and politics intervened, and local programs were abandoned. Worse, in the 60s, *P. falciparum* developed chloroquine-resistance, and almost at the same time *Anopheles spp* developed DDT-resistance. Each new anti-malarial drug, as well as each new residual insecticide, was found, in a short time, to have to face widespread resistance. All over the World malaria control programs slowed down, and many stopped completely – therefore malaria made a comeback.

Areas that were previously malaria-free were re-invaded (Central Asia, South Africa, Turkey, etc), intensity of transmission went up almost everywhere, and malaria deaths started going up as well. Today there are more malaria deaths than ever – perhaps four times more than a generation ago: something like two to three million deaths a year[1]. In endemic areas, malaria is an opportunistic disease, so malaria death toll is concentrated in the most vulnerable members of the population: children, pregnant women, old or sick people. This enormous dead toll occurs even with 60-70% of the world population still living in malaria-free areas.

Global warming makes things even worse. Many temperate areas of the World, including Portugal, have now an enlarged (possible) malaria transmission season. In the last few years there were several reports of small chains of local malaria transmission, started by an imported case, in areas considered malaria-free: in South France or in New York City, in Italy as well as in Texas.

The future does not look bright. What can be done?

Some low tech measures do work fine: for example, widespread use of bed nets, or even better insecticide-treated bed nets, was repeatedly found to have a huge impact in lowering the disease and malaria death toll, a result completely out of proportion with its moderate cost.

At the drug treatment front, the new drug is an old drug: the Chinese traditional herbal medicine *Artemisia annua*, and its derivates, were found to be the most efficient and fastest *Plasmodium* killers ever. Their use can cut deaths in severe malaria by a third when compared with quinine-based standard treatment[2]. However, artemisin and related drugs have an Achilles' heel: because they act so fast, they are also washed out very quickly, and *in vivo* experience proved how easily the parasite became resistant to them[3,4].

Faced with this dangerous situation, the then new head of WHO's Roll Back Malaria Program, Arata Kochi, in trying to stop the spread of resistance, made a bold movement[5]: from now on, *falciparum* malaria must always be treated with drug combinations, in principle artemisin based combination therapy (ACTs)[6]. Furthermore, he made an *ultimatum* to the "big pharm": that WHO would consider as a public health menace the continuing commercialization of single-dose form of artemisin compounds, and its authors would be denounced as such.

It worked.

In a notoriously short time, almost all malaria drug developers changed to ACTs, and many developing countries also moved, at least in their official guidelines, to ACTs as standard everybody first line malaria treatment, for children as well as pregnant women, for HIV-infected as well as for old people.

However, the developed countries, including both EU and USA, became wrapped up in their own bureaucratic hyper-regulation, and have not yet approved this new malaria treatment paradigm.

So today, ironically, a severe *falciparum* malaria case may be better treated and have a better chance of survival if cared for in Manaus, Maputo or Bangkok, than in Boston, Paris or Lisbon.

Recommended reading

[1] – Molyneaux DH, 2004. Lancet 364, 380.
[2] – Dondorp A, *et al*, 2005. Lancet 366, 717-725.
[3] – Krudsood S, *et al*, 2005. Trans Roy Soc Trop Med Hyg 99, 142-145.
[4] – Baird JK, 2005. New Engl J Med 352, 1565-1577.
[5] – Arata Kochi, at the WHO Geneva Conference and Press Release, on 19 January 2006.
[6] – World Health Organization, 2006. *Guidelines for the Treatment of Malaria*. Geneva, WHO.