The resurgence of Malaria and the role of the Medicines for Malaria Venture

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Medicines for Malaria Venture

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Medicines for Malaria Venture (MMV) is a nonprofit foundation created to discover, develop and deliver new affordable antimalarial drugs through effective public-private partnerships.

Our vision is a world in which affordable drugs will help eliminate the devastating effects of malaria and help protect the children, pregnant women, and vulnerable workers of developing countries from this terrible disease.

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The worldwide resurgence of malaria has been extensively documented, and with 300 to 500 million cases occurring each year [1], it is likely that more people are infected with malaria today in sub-Saharan Africa than any other time in history [2]. This region of the world bears the brunt of disease burden: a heavy mortality toll that can reach up to 3 million lives – especially among children under age five and pregnant women – along with immense social and economic costs that hamper people's quality of life and perpetuate underdevelopment. Because access to effective medicines or even to basic preventive tools are often lacking, a child dies from malaria every 30 seconds-over 2,500 young lives lost every day.

These staggering statistics highlight the fact that malaria remains an enormous problem in developing countries, warranting this disease the same kind of urgency placed upon the HIV/AIDS pandemic. Sadly, however, the global community has to date failed to place malaria high enough on the geopolitical agenda to mobilise the resources necessary to combat this ancient scourge, one that is not only potentially readily curable, but also preventable using well-proven public health interventions.

Reasons for the resurgence

The recent resurgence of malaria cannot be attributed to a single factor. More likely it involves the interplay of diverse elements.

Floods associated with increased El Niño rains have led to an increase in local malaria epidemics in Africa, while support for the idea that global warming has encouraged parasite-harbouring mosquitoes to invade previously malaria-free regions has become more persuasive. Regional wars and civil disobedience have also contributed to the worsening situation by forcing migrations of people, often into highly malaria-endemic regions, that are also characterised by a collapsing public health infrastructure.

That general lack of funding underlies most public health problems in developing countries is not new: for malaria, however, even the most basic and effective preventive tools, such as insecticide-treated bednets, are still not widely enough distributed. Access to any effective treatment for malaria is inadequate, particularly in the poorest high transmission regions of Africa. Often healthcare facilities may not exist or are inaccessible, and they may be increasingly staffed by workers who have not been trained appropriately for malaria case management.

Most importantly of all, resistance against common antimalarial drugs has become a wide-scale problem in the most highly endemic areas leading to greatly increased mortality rates. Inexpensive and commonly used first-line agents such as chloroquine and Fansidar (SP) have lost their efficacy in many parts of the world, leaving few other affordable options available from the current limited arsenal of anti-malarial chemotherapy. The newer "travellers" drugs that still retain their efficacy against the malaria parasite are intrinsically expensive – prohibitively so in the African setting.

Lack of R&D activity

The extremely high costs involved in discovering, developing and registering pharmaceutical products to current regulatory standards requires that the returns on drug sales be very high to be commercially justified. On average, after taking into account the typically high rate of R&D failures, the research-based pharmaceutical industry spends around

Photo:WHO/TDR/Stammers

Figure 1. *Anopheles gambiae*: adult female bloodfeeding on human skin

Photo: WHO/TDR/S. Lindsay

Figure 2. A young girl experiencing a clinical attack of malaria in a Health Centre in the Gambia.

$800 million for every new drug that is registered. To justify such high levels of investment, potential annual sales of at least $200 million for a single drug is typically required, and the margins on these sales must be very high for many years. This R&D investment hurdle is currently only met by drugs with indications related to major medical needs in the USA, Europe and Japan.

For diseases of developing countries, the required high margin levels of revenue are simply not available. Thus, not surprisingly, in the past 25 years, only 1% of 1,393 New Chemical Entities (NCEs) approved for use were for tropical infectious diseases, and most of these were developed fortuitously by leveraging R&D allocated to veterinary or military programs [3]. Between 1975 and 1996, only three out of 1,223 new registered drugs were antimalarials [4].

This long-standing lack of drug discovery and development activity for malaria has emerged as a critical global public health issue. As a consequence we face the new millennium with an enfeebled armamentarium of anti-malarial drugs. Currently available first-line drugs used in endemic countries are, as mentioned, quickly losing their efficacy as drug resistance to them predictably accelerates.

Chloroquine, once considered a miraculous drug with stellar safety, efficacy and affordability, is now essentially useless in parts of the world most devastated by the disease. There is only a limited number of second-line antimalarials, but these all have significant safety liabilities or are currently too expensive for routine public health use in the highly impoverished countries that need them.

The very few new drugs and formulations recently registered for prophylactic use cannot be easily developed into truly affordable generic variants because of the intrinsic high cost of the pharmaceutically active ingredients they contain. This is alas also true for the now much favoured group of drugs (or drug combinations) based on chemically defined derivatives originating from extracts from the *Artemesia Annua* plant, the artemesinins. Though prices will likely come down as these drugs are scaled up, they nevertheless are unlikely ever to be cost-competitive with fully synthetic drugs. This fact serves to remind us that while innovation is expensive, lack of it can often be more so.

Thus, the tally of problems relating to antimalarial chemotherapy for public health is numerous. Many factors have led to a situation that can best be characterised as a major public health crisis. Most sadly of all, this crisis, coupled with the high demand for effective therapies has also led to increased criminal exploitation of the desperately sick by unscrupulous peddlers of low quality or counterfeit drugs.

Despite this rather dire picture there is also a new sense of hope emerging. Several recent events suggest that the malaria chemotherapy crisis, despite its multifaceted and cumulative origins, may have at last reached a nadir. The most publicised of these is the recent establishment of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. As a purchasing fund this globally supported financing mechanism should help with both the purchase of existing antimalarial drugs and also provide a "pull" mechanism at the end of the lengthy R&D value chain. Unfortunately it cannot, as currently established, support the R&D value chain itself – and it is arguably the decade's long innovation deficit which constitutes the real core of the malaria chemotherapy crisis. In this respect the malaria situation is very different from, say, HIV/AIDS therapy where commercial R&D has amassed a considerable number of recent products and is also driving a healthy pipeline of new ones. Thus a "one size fits all" financing mechanism such as the Global Fund leaves much to be desired – but is certainly much better than no global financing mechanism at all.

Somewhat paradoxically, the current malaria chemotherapy crisis is also taking place in a timeframe characterised by renewed scientific hope. Exciting scientific breakthroughs have occurred in our knowledge of the biology, immunology and particularly the molecular genetics of malaria. It is now known that *P. falciparum*, the most dangerous human malaria parasite, has 14 chromosomes, approximately 5,300 protein-encoding genes – almost two-thirds of which appear to be unique to the organism – and about 208 genes known to be involved in evasion of the host immune system [5]. Thus the stage is clearly now set to exploit this genomic information to yield new chemo-therapeutic targets, as well as antigens for potential vaccines. Innovation opportunities like these desperately need to be seized, but the question remains as to how, and who, will translate this knowledge into new treatments and prevention methods. As we have seen, commercial R&D activity in industry cannot be expected to provide the answer – at least not alone.

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The market-based business of healthcare innovation and provision has in large measure transformed the lives of the 10% of the world's population that have benefited, those living in the developed world – but what of the 'neglected' rest? There is an urgent need for creative sustainable solutions to stimulate R&D for their "neglected" diseases.

One creative solution to the lack of commercially driven innovation to improve antimalarial chemotherapy options is embodied in the work carried

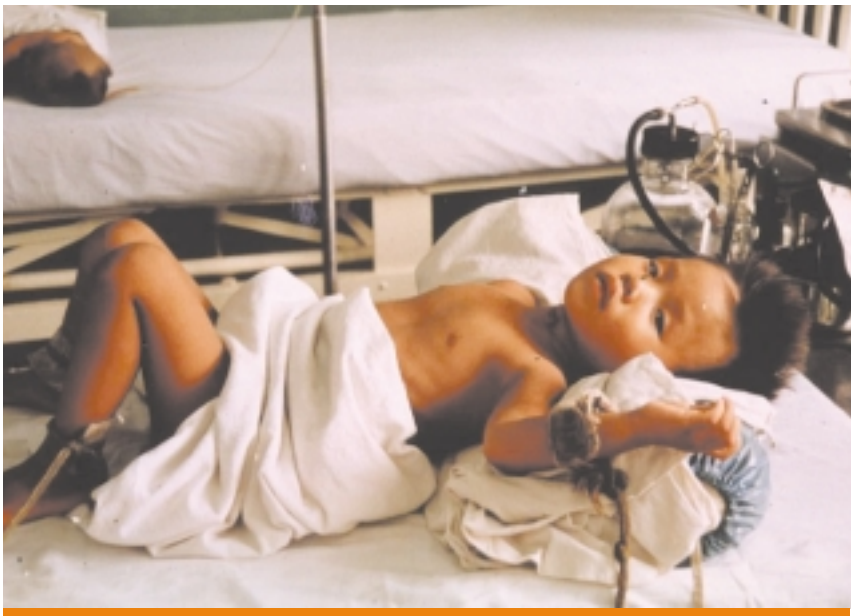

Photo: WHO/TDR/L. Maurice

Figure 3. An infant child with malaria in a bed in a hosiptal ward. Children are often restrained to prevent injury when they suffer convulsions.

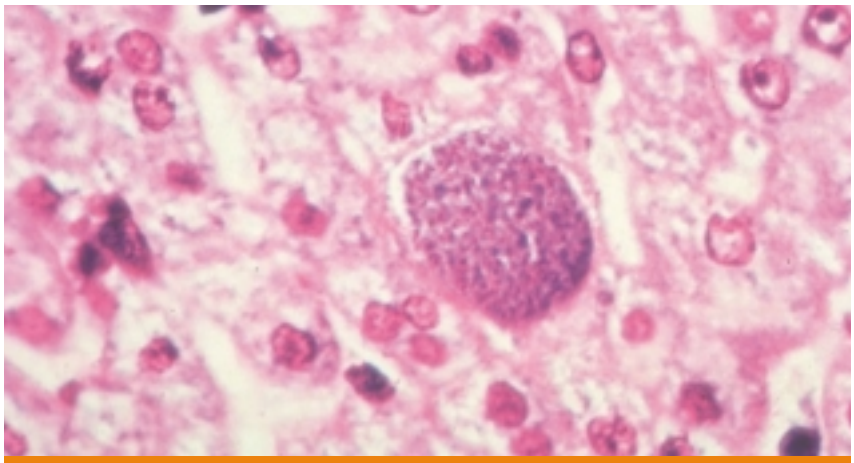

Photo: WHO/MAP/TDR

Figure 4. *Plasmodium falciparum:* Pre-erythrocytic liver stage.

out by a not-for-profit organisation, the Medicines for Malaria Venture (MMV) based in Geneva, Switzerland. MMV operates as a public-private partnership that seeks to discover develop and deliver new antimalarial drugs as "global public goods". The keyword illuminating its mode of operation is "partnership" – albeit partnership within a well established contractual win-win framework. MMV's partners include its donors (both public and philanthropic), its researchers (academic and pharmaceutical) and the many public health policy staff (from the UN/WHO network of organisations) who support it. Other NGOs are also likely to become increasingly involved where they have specific competences – for example in the downstream provision and distribution of drugs. Both public and private sectors are net contributors to the growth and development of the MMV drug pipeline and both get some rights to the fruits of the research, its newly developed antimalarial drugs. Crucially, from a public health perspective, MMV retains public sector distribution rights.

The ultimate measurement of MMV's success from the public health perspective is of course the positive health impact that will in due course be attributable to its newly developed antimalarial drugs – the impact on the lives of individuals in disease-endemic countries. Because product cost is a major concern that affects people's access to antimalarials, MMV has made it a priority to try to develop drugs with low intrinsic "cost of goods", in part by focusing manufacturing in low cost regions such as India. Low drug prices, though very important, are not sufficient when it comes to drug delivery and access. MMV is therefore supported by organisations like the World Health Organization, the Roll Back Malaria (RBM) Partnership, the World Bank, and the Global Fund, the key international players who can help it to navigate complex issue of drug policy and access in endemic countries.

While health impact is MMV's ultimate goal it is worth mentioning that some intermediary goals have already been achieved. The current MMV R&D portfolio is already the largest co-ordinately managed anti-malarial R&D portfolio since the Second World War, and certainly the largest ever managed for "public good".

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ABOUT THE AUTHORS

Dr Christopher Hentschel is a former bio-pharmaceutical executive with more than 20 years' international R&D and technology transfer management experience in both private and public sectors. He serves as a non-executive director of a number of biotechnology companies, as an advisor of a European Venture Capital Fund (PolyTechnos) and formerly a Senior Research Fellow of the Wharton Business School's Emerging Technology Program. Dr Hentschel is also a former Fogarty Fellow at NIH. He is now Chief Executive Officer of MMV.

Megumi Itoh recently graduated from Princeton University with a Bachelor of Arts degree in molecular biology and a certificate in African studies. Having worked as an intern at MMV and WHO during the summer of 2002, she wrote a senior thesis entitled "Medicines for Malaria: New Scientific and Policy Directions for Antimalarial Drug Development". She will be a first year medical student at the University of California Davis School of Medicine this autumn and hopes to pursue international medicine.

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