DEVELOPING EFFECTIVE MALARIA DRUGS

More malaria drugs are needed

Much money has been spent on finding a drug to fight malaria – almost USD1.2 billion by the Gates Foundation alone.(1) So why haven't we found a drug that works?

Historically there were several. Since 1945, a series of drugs, including chloroquine, proguanil, sulfadoxine - pyrimethamine, mefloquine, and andatovaquone were developed and used, only to be followed by resistance to the drug by the malaria parasite. In some cases this happened within 1 year of the drug's first use.(2)

One mechanism of emergence of resistance to antimalarial drugs is a spontaneous genetic change in a malaria parasite that interferes with the parasite's susceptibility to a drug.(3)

Malaria drugs are classified into several groups including the artemisinins, quinines, and antifolates. A mutation resistant to one drug may affect all drugs in its class. It is important to find new types of antimalarials instead of adjusting molecules within classes.

Also with malaria, researchers cannot count on immunity to bolster drugs they develop.

One of the reasons science has conquered diseases like smallpox and measles is that immunization against such viral diseases confers lifetime immunity. Malaria is not a viral disease and cannot be conquered in the same way.(4)

A DRUG THAT HAS IT ALL

Finding an effective drug to fight malaria is a complex undertaking. Any new treatment has to outsmart drug resistance, be powerful enough to kill the malaria parasite, but also must be safe enough for a child, who is likely to be malnourished. It has to able to attack cerebral malaria (when the parasite causes infected blood cells to stick to capillaries in the brain, restricting blood flow), but not destroy the liver, which the parasite uses as its base of operations. It should be a pill, rather than an intravenous drip, for easy distribution. It has to cure quickly since patients will often stop taking the drug when their fever goes down. And it must be cheap. People in places with high malaria prevalence live on less than USD3 a day.(4)

> "Most countries finally suppress malaria only when wealth arrives. Their houses have windows, their swamps are not just treated, but paved for malls. The disease could return to the United States. There are susceptible mosquitoes from Florida to Canada." – Donald G. McNeil Jr., NewsBank

> For resistance to spread, the spontaneous occurrence of a mutation in itself is not sufficient. In the absence of the drug to which it is potentially resistant, a parasite with the resistant mutation does not have a survival advantage and therefore does not reproduce faster than the non-mutants. There may even be a survival disadvantage, a so-called fitness cost to having the mutation. In the presence of the particular drug, the multiplication of the sensitive parasites is inhibited allowing the drug-resistant mutants to survive and multiply (this is selection), increasing the likelihood of transmission to the next host and therefore the spread of resistance. (Drs Yeung, Yeung S, Pongtavornpinyo, Hastings, Mills in 2004, ref 3)

Below left, Professor Wanjiru Waruingi (formerly known as SJ Dodgson) in a chemist (Americans call these shops pharmacies) in Surulere, Lagos State, Nigeria 29 Jul 2007. Right, a poster on a road to Lagos. Pictures courtesy of MJoTA's Pastor Osagie Edoro-Ighalo.

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Malaria is caused by one the over 100 species of Plasmodium. These single-celled parasites are injected into the blood stream by anapholese mosquitos and cause malaria in humans, animals and birds.

Four species of Plasmodium are known to cause malaria in humans. They cause different symptoms and can be distinguished microscopically. Since the mosquitos can carry more than one Plasmodium, clinical malaria can be caused by more than one Plasmodium. The 4 species are Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale.

Summarized from malaria page on National Institutes of Health website for the National Institute of Allergy and Infectious Diseases (NIAID) at http://www3.niaid.nih.gov.

Five new drugs showing the most promise are combination therapies involving artemisinin, a 2000-year-old Chinese herbal extract of *Artemisia annua*, the sweet wormwood plant.(5) Artemisinin, which acts quickly to lower fevers, is combined with amodiaquine or mefloquine, 2 established antimalarial drugs that act slowly but linger in the blood. This combination therapy helps ensure that all the parasites in the host are killed.

According to a report in *The New England Journal of Medicine*, the use of combination therapies with artemisinin does not preclude the onset of drug resistance, particularly since patients may not take the medication as directed. “Where more resources are available, including medications, resistant strains have been slower to develop. Where both medication and an effective health care infrastructure are present, resistance can be controlled.”(6)

THE MOST PROMISING MALARIA DRUGS

While there is much research being done on combination therapies, artemisinin combined with amodiaquine is already available in a treatment called Coarsucam, where 2 pills are packaged separately in blister packs. Evidence has shown that patients take the artemisinin-based pills, but leave the other because they do not like the taste. Relying too heavily on a single therapy encourages the growth of drug resistant strains of malaria.(4) Therefore, researchers have directed efforts to combining the 2 drugs into 1 pill. This process saw success first in 2006 with Coartem from Novartis, and this year with the introduction of ASAQ, made by Sanofi-Aventis.

Researchers at the nonprofit organization Drugs for Neglected Diseases Initiative, based in Geneva, discovered a way to combine the two drugs, and sought a corporate partner to conduct clinical trials, and produce and market the drug. Since ASAQ will sell for less than USD1, it won’t be especially profitable for Sanofi-Aventis, but according to a DNDi spokesperson, “It’s good for their image.” ASAQ is being introduced into West Africa and Kenya, but according to DNDi, it has not been registered in approximately a dozen countries and lacks prequalification from World Health Organization, which may delay its official launch.(7)

Coartem, a single-pill therapy already in use, was developed by Novartis in conjunction with the Institute for Microbiology and Epidemiology in Beijing. Coartem combines artemether, a traditional Chinese plant-derived remedy, with lumefabtrine, a synthetic. According to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Coartem destroys malaria parasites in 48 hours and has documented high cure rates.(8) During 2006, 62 million treatment courses of Coartem were delivered to 30 countries across Africa.(9) A new version, CoartemD will be launched by the end of 2008. CoartemD tastes like cherries and dissolves easily in water (or milk) making the drug easier to take for children, who, along with pregnant women, are the most common victims of malaria.

The Brazilian pharmaceutical company Farmanguinhos/ Fiocruz partnered with DNDi to develop a once-a-day, fixed dose ACT and released it in Brazil in April 2008. This therapy is called ASMQ is a combination of artesunate and mefloquine and is delivered in 1 small blue tablet.

Two more promising ACTs are currently in clinical trials. One set of Phase III clinical trials on dihydroartemisinin-piperaquine (DHA), developed by Sigma-Tau Industrie Farmaceutiche Riunite, Italy,

The author (white shirt) talking about malaria with Dr Kilama (second from left) and Dr Macharia Waruingi (sitting opposite). WW.

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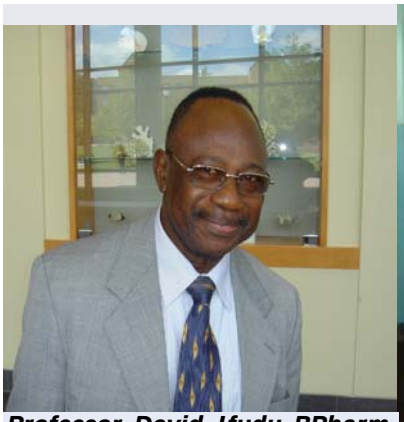

Professor David Ifudu BPharm, PhD, Dean of Pharmacy at University of Lagos, Nigeria.

Professor Ifudu is pictured far left on a visit to Philadelphia to give a talk to health professionals, and right, in front of a Pax Herbals outlet in a Catholic Church in Lagos.

Professor Ifudu was trained as a pharmacist at Unoversity of Lagos, and as a laboratory scientist at the University of Connecticut. He is strongly in favor of accountability by pratictioners of healing with plants that cure, and has been filmed pleading for more large pharmaceutical company investment in malaria therapies.

was completed in Africa in 2006. A second set of Phase III trials are being conducted now in India, Laos, and Thailand.

The second drug in clinical trials, and the final new ACT under development, is Pyramax, a combination of pyronaridine and artesunate produced by the Korean pharmaceutical company Shin Poong. Phase II clinical trials are currently underway in Africa and South East Asia. This drug will be tested in a combined tablet form for adults and children, as well as a special formulation for infants.(10) Pyramax will be launched late in 2010, and is carrying high expectations because its effects last long in the body.

"People can get a bite every month; we've seen infection rates of 300 to 400 a year," says Dr Tim Wells, Chief Scientific Officer with Medicines for Malaria Venture, a non-profit organization based in Geneva, Switzerland, that pursues partnerships necessary to discover, develop and deliver new anti-malarial drugs, "The longer a drug remains in the body, the more protection it provides. Many of the drugs we have now only protect for 6 to 8 weeks."

Professor Coker, a pharmacist with a PhD in pharmaceutics from the University of Glasgow, in the University of Lagos animal house, tending mice which will be used in animal toxicology testing. Below, he is accompanied by a traditional medicine practitioner.

Copy-cat Drugs Complicate the Process

One of the problems encountered on the way to finding an effective drug for malaria is the influx of drugs into Africa that have not undergone the stringent regulatory and compliance steps required by drugs coming out of the United States, Europe, Canada, and Japan. As an example, the development of DHA, above, has been impaired by the introduction into Africa of a similar drug by the Holley Pharmaceutical Company based in China. Holley's drug has not been approved by any western regulatory agencies, but is nonetheless being sold.

Dr Wells with Medicines for Malaria Venture points out how gathering enough data on a drug to ensure its safety is difficult in Africa.

"Thousands of patients need to be studied before the drug is released," says Dr Wells. "In Africa, there are not ways to measure adverse events. If you ask, people just shrug their shoulders. This is expected without an understanding of the importance of proper clinical trials and safety."

He also acknowledges that conducting those trials is a challenge.

"Who dies from malaria? Small children and pregnant mothers because the parasite is fiendish in that it lodges in the placenta," continues Dr Wells. "In safety studies we have to know if these drugs are OK for kids. Most pharmaceutical companies will avoid these parts of the population, because they are the hardest to study."

Professor Herbert AB Increase-Coker of the

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University of Lagos (former Deputy Provost, former Dean of Pharmacy, Professor of Pharmaceutics) sees the problem being fueled by poverty in Africa and the inability of people to pay for treatment.

"ACTs are very much available, but most people can't afford them," says Professor Coker, pointing out that a course of treatment costs USD10, while the average Nigerian salary is USD20 per month.

"There are versions of these drugs coming in from India and Pakistan that people are using because they are more affordable," he says. "They are also turning to alternatives. This is a backwards part of the world. People are treating themselves with all kinds of concoctions."

A VACCINE IN DEVELOPMENT

According to the briefing document prepared by GlaxoSmithKline for the Malaria Vaccine Financing Strategy Meeting in February 2008, "No vaccine has ever been developed for human use against parasites – pathogens with much greater complexity than viruses and bacteria".(11) Because immunity does not develop with malaria, the only way to see if a malaria vaccine might work is to go through clinical trials. Currently, 40 vaccines are under study, with 16 of the candidates now in clinical trials.(12)

The candidate that carries the most optimism is GlaxoSmithKline Biological's RTS,S, which is now in Phase III trials, and which the company is hoping to submit to regulatory authorities by 2011. Data published in The Lancet says that RTS,S "could have 35 percent efficacy against clinical disease in children for at least 18 months and 49% efficacy against severe malaria for the same timeframe." The company notes that even partial efficacy in preventing malaria would be a valuable public health tool.(11)

"The key question in developing an effective vaccine is how long do you protect a person, and what proportion of people do you protect?" says Dr Wells from Medicines for Malaria Venture. "Do you only inoculate babies during their first year of life?" He points out that developing an effective vaccine, and similarly, developing an effective drug to treat the disease, is just 1 piece of the total treatment picture.

"The answer of course is not drugs versus nets versus vaccines," he says. "All of the above are needed at different stages."

"There is no instant solution [to malaria in Africa]," says Dr Wells. "We have tools, but we need new tools, better tools. This is going to be a really long battle that will take us into the next decade."

Dr John Kilama, left, a pharmacist and scientist from Uganda, runs a biosciences development company in Delaware.

Dr Kilama and MJotA's Dr Waruingi gave talks on health business in East Africa to the USA-Kenya Chamber of Commerce at a Saturday conference at Villanova University, on 30 May 2008.

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