Where is chloroquine now?

It was called 'the magic bullet' in its heyday, but resistance issues led to it being replaced with combination drugs centred on *artemisia annua*, or at least that is what was supposed to happen. But as William R Brieger reports, it remained in use in some countries and studies are once again seeing value in the old medicine

For decades chloroquine (CQ) served as the mainstay for malaria case management. It was cheap, easily available and had minimal side effects aside from itching in a small portion of patients. Being cheap and available CQ was used for presumptive treatment of people with malaria-like symptoms in settings with minimal laboratory investigative capacity. The common path for differential diagnosis then was that if the patient did not recover after three days of CQ regimen, healthcare providers would start to look for other potential causes of febrile illness.

In the 1990s, malaria treatment became a bit more systematic under integrated management of childhood illness (IMCI) regimens.[1] Algorithms helped guide the health worker through signs and symptoms that could quickly distinguish between suspected malaria and febrile illnesses like pneumonia. Microscopy investigations were reserved for more severe presentations or patients that did not recover in three days.

This led to a natural inclination for health workers to depend on their 'clinical judgement' in determining whether to treat for malaria. If they were mistaken, the cost of the medicines was minimal. They also were told that it was better to presume malaria and save a life, especially in your children. This was especially true in Africa where *Plasmodium falciparum* dominates.

The evolution from chloroquine to artemisinin-based combination therapy

Since CQ required a three-day regimen, compliance issues were common. This may have one of the triggers that started development of CQ-resistant parasites in Southeast Asia and spread across the world. Thus between 1978 and 1988 CQ resistance arose across all African countries. In the 1990s malaria endemic countries in Africa began a series of CQ efficacy trials. Experts noted that, 'The dramatic impact of CQ-resistance on malaria mortality has long been underestimated' pointing to the fact that, 'There is an urgent need to change treatment policies in Africa'.[2] This led initially to a switch from CQ to sulfadoxine-pyrimethamine (SP) in the 1990s, but ultimately SP met the same fate in terms of *P. falciparum* resistance.

The scientific community offered two important insights for next steps. First, the herbal medicine *Artemisia annua* was found to be a stronger medicine, and secondly, if it was combined with another antimalarial drug, resistance could be delayed. The most common of these combination regimens, known as artemisinin-based combination therapy (ACT) were artemether-lumefantrine (AL) and artesunate-amodiaquine (AA).

Countries began adopting ACTs as their first line malaria medicines as early as 2001, and in Africa the early adopters were South Africa, Zanzibar, Zambia and Burundi. In its first malaria policy statement, the World Health Organization's (WHO's) Technical Consultation on Antimalarial Drug Combination Therapy[3] stated that, 'The conclusions and recommendations of the meeting strongly endorse the potential of combination therapy for use in Africa. Appropriate national and regional based studies should be initiated with all possible speed to assess their potential for incorporation into National Policies in preference to monotherapy'.

By 2004, the WHO established ACT use as its official position,[4] and then in 2006 the use of ACTs became the official malaria treatment policy of WHO.[5] Although WHO stated a clear preference for parasitological diagnosis of malaria to save costs of unnecessary treatment, it did recognise that clinical diagnosis was still the main option in many places. Specifically, the 2006 guidelines stated that, 'To counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome, combinations of antimalarials are now recommended by WHO for the treatment of falciparum malaria'.

Clinical diagnosis meant more treatments and challenges in terms of the much higher cost of ACTs. Fortunately the Global Fund for the fight against AIDS, TB and Malaria (GFATM) in 2005 indicated that for countries receiving malaria grants, the GFATM 'has given countries that have in place signed grants covering proposals for malaria treatment during rounds 1, 2, and 3 the option to consider reprogramming their requests for funds for treatment to be directed for ACTs'.[6]

The 2006 WHO malaria treatment guidelines specifically noted that non-artemisinin based combinations (non-ACTs), including sulfadoxine-pyrimethamine with CQ (SP+CQ) or amodiaquine (SP+AQ), were not appropriate because of the prevailing high levels of resistance, having compromised the efficacy of at least one of the drugs in these combinations. Clearly, CQ was no longer acceptable in terms of safe and efficacious malaria treatment.

Chloroquine did not disappear

It is not uncommon to see CQ on the shelves of medicine shops. Discussions with shops owners in Sokoto

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Figure 1: This medicine shop owner explains the economics of consumer demand and stock purchases of chloroquine

State, Nigeria in 2011 (see Figures 1 and 2) revealed very practical reasons for this. First, the shop owners themselves tended to respond to customer demands, and customers liked CQ first because of its low price, and secondly, because it came in syrup form which was easy to administer to children. The initial effects of the drug in reducing fever and pains led people to believe it was still effective. The other side of the story was that shopkeepers themselves, contrary to public opinion, are not rich. They said they could afford to stock higher priced drugs like ACTs if there was no market.

When asked if they had heard of the Affordable Medicines Facility for malaria drugs (AMFm), which was geared in part to medicine shops, the response was twofold. First, the planners only involved a sample of medicine shops, and even then they did not have the capital to invest in the specially marked ACTs, even at the reduced prices. One of the medicine seller association's leaders bemoaned the fact that he had helped some colleagues obtain initial stocks of ACTs, but most did not pay him back.

What was ultimately most surprising was that large stocks of CQ tablets and syrups were also found in local government primary healthcare facilities. Even though health staff had been trained on updated malaria case management, they shared that the local government budgets that buy essential drugs could not afford ACTs. The State at that point in time was unfortunately not benefitting from the global donor malaria drug provision programmes.

A 2012 report by ACT Watch in Nigeria found from a household survey that 54% of children who received an antimalarial drug were given CQ even though the national malaria drug policy had changed to ACTs seven years previously.[7] In 2013, a former WHO country representative in Nigeria revealed that, 'In spite of

Figure 2: Chloroquine tablets and syrups stocked in a local government primary healthcare centre

the ban it placed on the use of CQ, artesunate (AS), SP, and other monotherapies, the drugs continue to thrive in Nigeria'.[8]

Most recently, an April 2017 investigative report in *Premium Times* found that Nigerians were still using CQ. The reporter explained that, '… since most drugs are dispensed over the counter in Nigeria without prescription notes, many Nigerians, unaware of the limitations of the drug, have continued to use CQ for malaria treatment'.[9] When asked, the national drug authority told the reporter that since CQ was also used for other ailments, its sales were still approved. This represents a communication challenge between the national drug authority and the national malaria programme.

CQ is still being sold in Ghana, but not necessarily in the expected form. Wilmot and colleagues found that two out of five tested commercially available herbal products had possibly been adulterated with CQ or compounds with chemical properties similar to CQ.[10]

It is important to note that since most malaria episodes in Africa are caused by *P. falciparum*, which is the strain that has lost any sensitivity to CQ, we tend to forget that treatment of *Plasmodium vivax* has until recently been effectively treated with CQ. Unfortunately, Nyunt and co-researchers documented that, 'Although clinical failure rate was low, widespread distribution of CQ and antifolate resistance molecular makers alert to the emergence and spread of drug resistance vivax malaria in Myanmar'. It should be noted that resistance of *P. falciparum* to CQ, SP and even now AS has previously arisen in Southeast Asia. Thus effective treatment of *P. vivax* with CQ in Africa is also at risk.[11]

New research around chloroquine

Researchers and epidemiologists have continued to monitor the sensitivity of *P. falciparum* to CQ. In 2007 Nkhoma and colleagues looked at CQ sensitivity ten years after the withdrawal of CQ from malaria case management in Malawi. They measured in vitro antimalarial drug susceptibility of 84 *P. falciparum* field isolates. They learned that, 'most isolates are now sensitive to CQ and none is CQ-resistant'.[12] Frosch et al again looked at the situation in Malawi in 2009. They reported that, 'This study demonstrates near fixation of CQ-sensitive *P. falciparum* genotypes over a broad geographic range in Malawi in 2009, including rural areas and areas bordering Zambia, Mozambique, and Tanzania'.[13]

A recently published study conducted in southeast Cameroon also noticed positive changes in CQ sensitivity in the parasites. Based on their findings the researchers concluded that, 'Even though the proportion of CQ-sensitive parasites seems to be increasing in southeastern Cameroon, a reintroduction of CQ cannot be recommended at present in Cameroon'.[14] Caution is clearly the necessary approach, and if CQ were to be reintroduced, it would need to be in combination with another drug that also shows sensitivity.

Recently, Seon-Ju Yeo and colleagues examined the antimalarial effect of novel CQ derivatives as agents for the treatment of malaria. Two novel derivatives or 'hybrid molecules' were synthesized based on the CQ template and demonstrated enhanced antimalarial activity against CQ-resistant strains.[15] The team will be engaging in more mouse-based studies.

A recent review by Parhizgar and Tahghighi provides a more detailed look at the future directions of CQ-related research. They explain that, 'Antimalarial drugs with the 4-aminoquinoline scaffold such as the important drugs, CQ and AQ, have been used to prevent and treat malaria for many years'.[16] They point out that recent research has shown that the 4-aminoquinoline scaffold is active moiety in new compounds synthetic with anti-plasmodial activity. They observed that because of the progress made using these analogues researchers hopefully will 'achieve a new, efficient, cheap, and safe antimalarial drug with a 4-aminoquinoline structure as the next-generation of CQ/AQ analogues in clinical development'.

The goals of finding 'efficient, cheap, and safe' antimalarial drugs whilst ensuring efficacious combinations is needed to fight the threat of growing artemisinin resistance. It appears that CQ and its analogues may have a second chance at saving lives.

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