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EDITORIAL

A link between poor quality antimalarials and malaria drug resistance?

Paul N. Newton[a,b,c], Céline Caillet[a,b,c] and Philippe J. Guerin[b,c]

[a]Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao PDR; [b]Centre for Tropical Medicine & Global Health, NDM Research Building, University of Oxford, Oxford, UK; [c]WorldWide Antimalarial Resistance Network (WWARN), Centre for Tropical Medicine & Global Health, University of Oxford, Oxford, UK

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1. Introduction

Malaria remains a major public health problem for most of the world. The tragedy remains that many more malaria patients would survive if they had timely access to good quality, affordable and efficacious medicines. Antimalarial resistance has been a major impediment to malaria control. Since the 1950s, *Plasmodium falciparum* parasites have developed resistance to the main antimalarials used in national and international policies, including chloroquine, sulphadoxine-pyrimethamine (SP) and these have spread globally and increased mortality [1]. Recently, resistance to the artemisinin derivatives, associated with falciparum parasite kelch13 mutations, has been described in mainland South East Asia [2], but not yet confirmed in other endemic regions.

With few new antimalarials in the development pipeline, concern that key artemisinin-combination therapies (ACTs) may fail is of great public health alarm, with both resistance to artemisinin derivatives and partner drugs reported [3,4]. The risk of geographic spread is very high and would have dramatic consequences for many aspects of society, including health, education, and economy. Suboptimal antimalarial use both poor prescribing and poor adherence, has been invoked as a driver for poor patient outcome and parasite resistance, although see the caution of Noranate et al. (2007) [5]. Improved use, through better prescription and discussion with patients so that they know why and how to adhere will be important. Here, we argue that poor quality antimalarials also contribute to drug resistance.

2. Antimalarial quality

Over the last decade there has been increasing concern that much of the antimalarial supply in the developing world, especially in the private sector, is of poor quality. This problem is not new; falsified antimalarials were a severe problem in the seventeenth century when fakes of the first potent antimalarial drug, cinchona bark (the source of quinine), were widely marketed in Europe [6]. Over the last decade, it has become increasingly apparent that both falsified and substandard antimalarials are an important but largely unrecognized public health problem, but their prevalence varies widely in time and space [7].

Despite much debate, there has been considerable confusion over definitions of different types of poor-quality medicine. We use the term 'falsified' (i.e. produced by criminals fraudulently), which is more appropriate to address public health issues rather than the term 'counterfeit' that refers to trademark concerns [8], and substandard (i.e. unintentional but negligent errors in factory processes).

Poor-quality mefloquine, chloroquine, and doxycycline, SP, sulphalene-pyrimethamine, quinine, mefloquine, halofantrine, tetracycline, artesunate, artemether, artemether-lumefantrine, dihydroartemisinin, and dihydroartemisinin-piperaquine have been described [9]. As far as we are aware, poor-quality parenteral artesunate and atovaquone-proquanil have not yet been reported, but few have looked [7].

Reported information are often of poor quality [10], but some are very striking, suggesting important hotspots of poor quality – e.g. the seizure of ~1.4 million packets of falsified ACTs in Angola [11] and that in 2003 88% of oral artesunate monotherapy in the private sector in Laos was falsified [12]. Substandard medicines, often containing reduced percentage of active pharmaceutical ingredients (%API), have been found in all recent large surveys [13,14]. To date, only 11 surveys of antimalarial quality have used randomized sampling, the expected methodological standard. There are no convenience or random surveys of antimalarial quality for 53% of the 96 malaria endemic countries. The extent of the problem for patient outcome has been recently estimated [15], using the available evidence, suggesting that ~122,000 under-five malaria deaths were associated with consumption of poor-quality antimalarials in Africa.

3. Antimalarial quality and resistance interaction

How may poor-quality antimalarials impact on antimalarial resistance? Although it is a logical presumption, there is very limited field evidence that they are major contributors to resistance, because it is very difficult to tease apart the effects of sympatric poor prescribing, patient adherence and poor-quality drugs. The likely importance of subtherapeutic

CONTACT Paul N. Newton paul@tropmedres.ac

medication in the emergence of drug resistance is illustrated by the addition of chloroquine to salt on the Thai/Cambodia border in the 1950s, which probably contributed to the emergence of chloroquine-resistant *P. falciparum* parasites [16] and the beginning of the loss of the efficacy of this important medicine.

There have been alarms of malaria drug resistance that were actually due to poor-quality antimalarials and not parasite resistance [17,18]. However, ironically such antimalarials may engender future resistance if they contain subtherapeutic %API. For example, an epidemic of malaria on the Pakistan/Afghanistan border, thought to be due to SP resistance, was due to SP that contained the correct %API but with low bioavailability that would have resulted in low drug blood levels [18]. The classification of poor-quality medicines as falsified, substandard, and degraded is not immediately relevant for discussions of resistance; the key is whether reduced %API and/or reduced dissolution lead to inadequate blood levels. When resistance is suspected, the quality of the antimalarials used should be checked.

The selection of drug-resistant pathogens depends on a wide variety of factors, the parasite biomass, host immunity, relationship between the pharmacokinetic profile of the drug and pharmacodynamic effects on the parasite, their antimalarial susceptibility, and the fitness of resistant mutants. The dose absorbed is a key determinant of cure [19,20]. If resistant pathogens encounter sub-lethal concentrations of a slowly eliminated antimalarial, they will have a survival advantage and multiply faster than sensitive parasites. This will be especially important for poor-quality ACTs as they risk the spread of resistance to both the affected API and the 'unprotected' partner APIs [19]. White et al. (2009) [19] discuss the 'window of opportunity' for the selection of *de novo*-resistant parasites during which blood concentrations of antimalarials are below the minimum inhibitory concentrations (MIC) for the new resistant mutants but above the MICs for the drug-sensitive parasites. In this window, the net growth of drug-resistant mutants outstrips growth of the drug-sensitive organisms to reach the density required to produce gametocytes. Therefore, for slowly eliminated drugs, poor-quality medicines that produce blood concentrations within this selective window will be prone to select resistance. Antimalarials with very low API and/or dissolution that produce blood concentrations below this 'window', which is specific for different APIs, host immunity, and parasite sensitivity, are unlikely to select for resistant parasites. However, once resistance has arisen and been transmitted to other patients, different relationships will apply. Long elimination half-lives will strongly select for resistant parasites, amplifying resistance, and poor-quality drugs with long half-lives may be important in the spread of resistance, irrespective of the quantity of API [19,20].

With good evidence that parenteral artesunate reduces mortality from severe malaria [21], this is increasingly used. Hence, the supply is at risk of substandard products with reduced %API and of falsification. As patients receiving parenteral artesunate are likely to be hyperparasitaemic and as modeling strongly suggests that these patients are key for the spread of resistance [19], improved monitoring of the parenteral artesunate supply is needed, both to ensure optimal patient outcome and to reduce the risk of resistance.

At first sight, falsified antimalarials containing no stated API cannot be important in engendering resistance. However, this may not be the case for two reasons. First, especially in communities where patients 'shop' around when treatments fails, falsified antimalarials without API may aid and abet resistance by increasing the risk of hyperparasitaemia, recrudescence, and hypergametocyopaenia. The co-circulation of substandard and falsified medicines may be especially prone to engender drug resistance when patients take a medicine with no API, followed by, say, a 50% API medicine [22].

Second, falsified antimalarials frequently contain wrong APIs [7,23], such as artemisinin in fake halofantrine, which without chemical analysis will be 'invisible' to investigators but not to parasites. Pyrimethamine, as hidden monotherapy in fake antimalarials, will engender the further spread of *P. falciparum* dihydrofolate reductase mutations in Africa, increasing therapeutic failure and reducing the useful life of SP for intermittent preventive treatment in pregnancy. Consumption of antimalarials without patients and healthworkers being aware will also confuse our understanding of changes through time of the frequency of clinical failure and molecular markers of resistance [22]. This is especially important as inadvertent consumption will presumably reduce the probability that parasite susceptibility will return for chloroquine [24], as parasites will still 'see' chloroquine, without policy makers knowing about it.

It is not only chemical quality that is important but also the language, font size, and understandability of instructions, so that prescription and adherence are enhanced. Dose must be optimized, especially for children and pregnant women. The widespread continued use of artesunate oral monotherapy, despite WHO's call to abandon it a decade ago [22], is likely to have been important for the spread of artemisinin resistance and should be replaced by ACTs.

There is an urgent need for data, with sufficient sample size and appropriate sampling design, that can estimate reliably the prevalence of falsified and substandard drugs within countries so that the extent of the problem can be gauged objectively, the effectiveness of interventions assessed, and change through time measured. There is a need for innovative modeling to understand the relationship between medicine quality and resistance, with variables informed by better field data.

In the meantime, there is a great need to ensure that quality-assured ACTs are used wisely to reduce the risk of resistance. Key organizations to ensure this are national medicine regulatory authorities working with national malaria control programs. However, as only 20% of WHO member states are reported to have well-developed drug regulation [22], much greater national and international investment for those that lack functionality is essential.

Declaration of interests

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