Evidence-based resistance management?

Prof. Andrew F. Read
Centre for Infectious Diseases, Penn State

Introduction

Evolution is the major challenge for malaria control in the 21st Century. Malaria parasites repeatedly evolve resistance to front line drugs, and mosquitoes have evolved resistance to all classes of insecticides approved for malaria control. The standard response to this evolution is to search for new formulations and new active ingredients, with the expectation of replacing those when they in turn fail. The vision is of drug and insecticide discovery pipelines that last as long as malaria. Even allowing that there is an endless supply of new products to be discovered, these evolutionary treadmills cost. People suffer and die as interventions fail and national policies adjust. Additionally, more than US$1 billion per decade is required for an adequate anti-malaria drug discovery pipeline. And bringing a new insecticide to market may cost up to $ 200 million (1).

I argue that we could slow these evolutionary treadmills—and in some cases even stop them—if we better understood the forces involved in resistance evolution. These forces are created by our drugs and insecticides and the way we use them. In other words, the problem is completely in our control.

Current situation

Of course, many malaria control policies are designed to manage resistance; indeed, they represent some of humanity's greatest attempts to shape the future evolution of any organism. It is widely appreciated, for example, that drug use should be minimised where possible. This is why anti-malarials are normally not dispensed unless a patient is parasite positive. Likewise, the WHO has mandated that artemisinin and derivatives should always be combined with other drugs, on the theory that the probability of a single parasite being spontaneously resistant to two drugs is very, very much smaller than the probability of being resistant to just one. And great efforts are made to ensure patient compliance with treatment regimens, in the belief that incomplete drug treatment promotes drug resistance (2).

However, I think we lack the evidence to assess how much extra time on the evolutionary treadmill these policies buy our products. For instance, if we believe (rightly I think) that unnecessary drug use should be avoided in a community so as to impose no more selection for resistance than is absolutely necessary, why do we insist that patients continue chemotherapy after they feel better? Continuing to treat the patient until every last sensitive parasite is dead simply maximizes the evolutionary advantage of any resistant parasites that are present (3). There may be clinical benefits to full course chemotherapy (impact on relapses and infectiousness, for example), but is overwhelming chemical force an effective resistance management tool – or does it actually make the problem worse? Chloroquine failed in Africa because resistance imported from elsewhere spread across the continent (4, 5). Those resistant parasites enjoyed maximum evolutionary advantage in people who adhered to the recommended drug regimens.

Brief Introduction of Andrew Read

Professor Andrew Read is Professor of Biology and Entomology, and Director of the Center for Infectious Diseases Dynamics at Penn State. He was born in New-zealand and did his Ph.D. in evolutionary biology at the University of Oxford, U.K. After a Junior Research Fellowship in Oxford, he moved to the University of Edinburgh in 1993, becoming Professor of Natural History there in 1998 before moving to Penn State in 2007. He is a co-investigator on the 'Center for the Study of Complex Malaria in India'— an International Center of Excellence for Malaria Research recently funded by the NIH led by Prof Jane Carlton (NYU) and the Director NIMR, and involving many NIMR faculties and Officers-in-Charge. As part of that program, Read will be working on studies of drug resistance, insecticide resistance and mosquito ecology together with NIMR colleagues and Dr Matt Thomas, also at Penn State. His Penn State research program concerns the evolution of pathogen virulence and adaptation by disease causing organisms to drugs, vaccines and insecticides. He works with malaria parasites, mosquitoes, Marek's disease in chickens, and myxomatosis in rabbits. He has published around 170 research papers. For further information, see www.thereadgroup.net.

'Natural' selection

I use that example not to advocate changes in current policy (I am not), but rather to illustrate that as a matter of some urgency we should try to better understand the 'natural' selection imposed by our drugs and insecticides. This means trying to quantitate the evolutionary advantage drugs and insecticides give to resistant parasites and mosquitoes. I see a number of gains.

First, small changes in the relative fitness of resistant parasites or mosquitoes can substantially affect the rate of spread of resistance alleles (6, 7). This means that even subtle changes in the way we use our current malaria-control tools could prolong their useful life spans by decades – and conversely that, without knowing it, we could be unnecessarily shortening those life spans.

Second, we need to identify situations where immediate clinical or public health needs are at odds with resistance management. Failing to recognize that aggressive chemotherapeutic regimens are imposing extraordinarily strong selection for any resistant parasites present in an infection obscures a serious evolutionary problem in need of solution.

Third, it is often not clear from first principles what the best evolutionary management strategy is. Should we aim to prevent mutations by suppressing parasite and mosquito densities as best we can? Or should we suppress only when strictly essential, thus minimizing selection for any resistance that is present? From a resistance management perspective, suppressing the densities of target organisms is a double-edged sword (3).

Finally, understanding how selection is acting can suggest for ideas 'evolution-proof' products, those whose short-term efficacy is less likely to lead to their long-term downfall. The emphasis on mosquito control leads to enormous selection for resistant mosquitoes. Focusing instead on those few mosquitoes that actually transmit malaria (the old, the infectious) would achieve disease control with greatly reduced or even no selection for resistant mosquitoes (7). Similarly, some drug targets might be more evolution-proof than others (8, 9).

Empiricism

A sound knowledge base is required to rationally manage evolution. Ideal would be quantitative measurements of the impact of contrasting strategies on resistance evolution. This is possible. The relative transmission success of resistant parasites can be measured in animal models (e.g. 10), and to some extent in humans in field settings or in clinical trials (e.g. 11). Hospital-level experiments have been done for bacterial resistance (e.g. 12, 13), and it is possible on a village-scale for malaria. For example, 24 Mexican villages were randomly allocated to one of four different methods of applying insecticides for malaria (14). None of the putative resistance management strategies slowed the spread of phenotypic insecticide resistance in the local *Anopheles* (7). That example emphasizes that resistance management strategies need testing. Intuition (expert opinion) is a very poor guide to evolutionary outcomes.

There is also much mileage to be had from analyzing the natural spatial and temporal dynamics of resistance in the field. There are immense opportunities for this in India. Why is insecticide resistance frequent in some areas and not others? Why did chloroquine resistance in *P. falciparum* spread more rapidly in some parts of the country? Chloroquine is still highly effective against *P. vivax* despite perhaps more than half a century of intense use. Why?

Most research to combat resistance evolution goes to reformulations, product discovery, molecular mechanisms, surveillance and reconstructing evolution history. All that is vital work. But curiously little effort goes to studying the actual forces involved. Unless we properly understand the forces of evolution we impose on parasites and mosquitoes, it is difficult to rationally design and assess resistance management strategies – and equally serious, to avoid evolutionary mismanagement.

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