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Antimalarial therapies

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The tiny parasitic protozoan *Plasmodium falciparum*, the major cause of malaria, is possibly the most dangerous stow-away in history. One bite from an infected, female Anopheles mosquito can send hundreds of the parasites into the human bloodstream and they swiftly infect host cells, starting with liver cells and moving on to erythrocytes. The proportion of infected erythrocytes can reach 10%, by which time the hapless host experiences fevers, chills, anaemia and, possibly, cerebral damage. With a second bite, the mosquito picks *P. falciparum* up in gametocyte form, thus returning the parasite to its original host. Gametes fuse in the insect's gut forming a zygote that migrates across the gut wall, where it becomes an oocyst. Sporozoites are released when the oocyst bursts, they make their way to the mosquito's salivary glands to await transfer to the next human host and the process continues. Malaria is one of the world's biggest killers; it is estimated that one person dies from malaria every 30 seconds.

The plasmodial life cycle is as effective as it is elaborate. ~300–500 million people worldwide are infected every year and over one million of these cases result in death. Populations in sub-Saharan Africa are worst affected – deaths from malaria in this region account for >90% of the global total. Tragically, the majority of deaths occur in children under the age of five, the next most-at-risk population comprises pregnant women. Africa finally has the attention of politicians from the developed world, attention it has long deserved. With several global initiatives underway to combat the problem, the eradication of malaria is now under serious discussion.

Emerging resistance

The traditional antimalarial is quinine – a bitter-tasting compound, extracted from the bark of the cinchona tree, that came to prominence in Europe in the 17th century. A tonic made from quinine became popular (when mixed with gin and lemon for ease of consumption) among British colonials; few of today's imbibers of gin and tonic realise its original antiprotozoal purpose.

The end of World War II heralded a new dawn in malaria control. Synthetic pesticides, most notably DDT, were hugely effective in controlling mosquito populations and new antimalarial compounds, such as chloroquine and mefloquine, were less toxic and more effective than all of the preceding medications. In the early 1950s, these new measures culminated in the eradication of malaria in the USA and this was followed by the initiation of eradication efforts in other countries across the world. Not all countries, however, have been able to replicate the results that were achieved in the USA. In Africa, for example, this is blamed on a combination of social, political and biological factors, including civil war, lack of funding, poor coordination of efforts and the emergence of resistant vectors and parasites.

Resistance to whole classes of structurally similar compounds is now common among plasmodial populations and unfortunately this applies to the quinine analogues. Chloroquine resistance was reported as early as the 1950s and is now widespread. Mefloquine was introduced in the 1970s, in response to emerging chloroquine resistance, but mefloquine-resistant strains were reported within six years of its introduction. Resistance also emerged rapidly for members of the other major class of antimalarials, the antifolates. Understanding resistance mechanisms is important for the design of new control strategies but much is still unclear.

The most recent addition to the global antimalarial arsenal is also one of the oldest. Artemisinin, extracted from sweet wormwood (*Artemisia annua*), has been a component of Chinese herbal medicine for >2000 years but was only used on a large scale when it was discovered as a result of an antimalarial research programme, undertaken by the Chinese army in the 1960s. Because of the secrecy of the communist government in China at the time, it remained largely unknown to the rest of the world; the Chinese government refused to give western scientists either the plant or the refined drug. A worldwide search for the shrub was instigated, resulting in success in the most improbable place: the bank of the Potomac river in Washington DC, USA. It turns out that sweet wormwood is a very common plant.

Artemisinins have an antimalarial action that is unparalleled with regard to their speed of onset and their efficacy. They are currently very effective as second-line treatments against resistant strains of plasmodia but there is a feeling that uncontrolled use will inevitably lead to resistance. Combining different classes of drugs is now a popular strategy because the probability of a single

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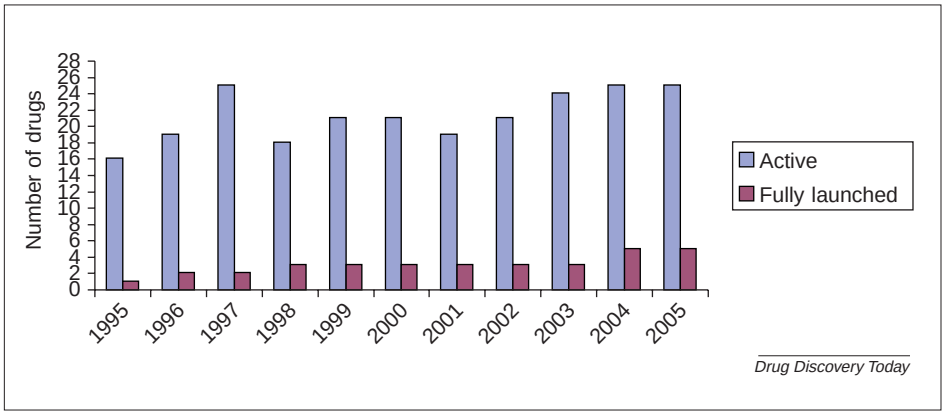

FIGURE 1

The number of antimalarials launched and in development between 1995 and 2005. A comparison between the number of antimalarial drugs that have been fully launched and the number in development (active) over the past ten years.

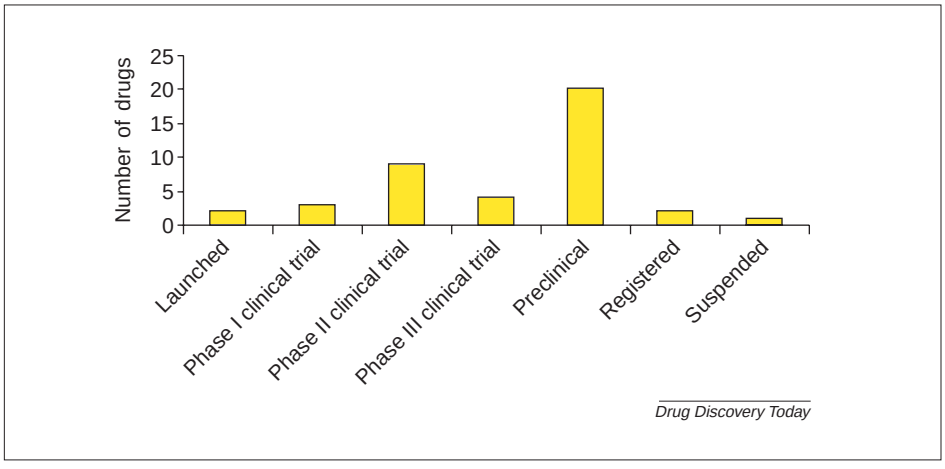

FIGURE 2

The developmental status of current antimalarial projects. Of the active antimalarial projects, the largest number are at the preclinical stage of development.

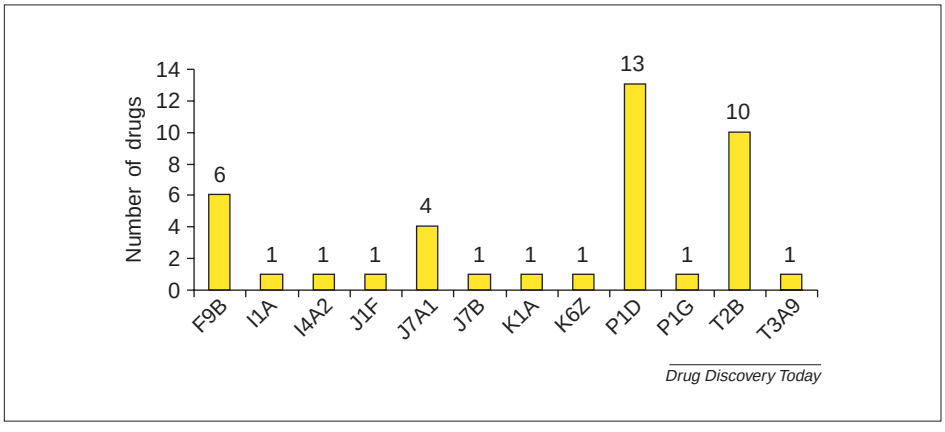

FIGURE 3

The primary therapeutic activity of current antimalarial and antiprotozoal projects. Key: F9B, formulation, fixed dose combinations; I1A, immunostimulant, anti-AIDS; I4A2, immunoglobulin, non-monoclonal antibody; J1F, macrolide antibiotic; J7A1, prophylactic vaccine; J7B, immunomodulator, anti-infective; K1A, anticancer, antibiotic; K6Z, anticancer, other; P1D, antimalarial; P1G, protozoacide; T2B, recombinant vaccine; T3A9, monoclonal antibody, other.

point mutation, resulting in resistance, is considered to be very low. However, the emergence of multiple resistance, already reported in many areas of Asia, is a possible worry for the future.

In the pipeline

Analysis of the trends in antimalarial research depicts a slow growth in launched products since 1995 (Figure 1). This highlights a particularly quiet five or six years spanning the turn of the millennium. However, 2002 saw the completion, after ten years, of the malarial genome project and an upsurge in products entering active development can be seen at the end of this period.

From the list of launched products, the three therapies that are indicated for malaria prophylaxis consist of mefloquine and two formulations of other well-established antimalarial compounds. These types of products are needed to treat the millions already diagnosed with malaria and they can also be used as preventive medicine for travellers on safari. However, the need for antimalarial vaccines in sub-Saharan Africa cannot be underestimated, especially because infants are hit so hard by the disease; this demographic, above all others, requires early prophylaxis. Encouragingly, *Pharmaprojects* reveals that almost half of the antimalarials currently in development are primarily prophylactic.

Figure 2 displays all of the active drug profiles currently under development for malaria treatment (ordered by world status). The outlook appears to be positive and several clinical and preclinical programmes are underway. In fact, products with vaccine-therapy codes account for almost as many of the total number of therapies as the therapeutic antimalarials and antiprotozoals combined (Figure 3), indicating that there is plenty of innovation in the prophylactic field, as well as with the putative cures. Notably, recombinant vaccines (code T2B) are booming in this area.

With six projects currently underway, GlaxoSmithKline (GSK) is the undisputed leader in antimalarial R&D in terms of pipeline size. This is partly as a result of GSK's collaborations with the Malaria Vaccines Initiative and the Medicines for Malaria Venture (MMV) and partly because of a strong

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pipeline of in-house products covering formulations of known antimalarials as well as vaccines. These products include a combination of chlorproguanil and dapsone, approved in several sub-Saharan African countries including Zambia and Malawi, and vaccines based on plasmodial proteins that are in Phase II trials.

In contrast to GSK, the majority of other companies involved in this area have antimalarial pipelines consisting of single projects. 40% of the compounds under investigation are immunostimulants designed to boost the host's natural ability to fight off the parasitic invasion. These are predominantly vaccines but also include the ABC-120 antibody (AERES biomedical), that targets parasitic invasion of the host's erythrocytes, and HE-2000 (Hollis-Eden), an anti-infective compound. Regarding the vaccines, surface proteins presented by the sporozoite and merozoite forms of the protozoan are the antigens of choice.

The sporozoite infects liver cells in the very early stages of disease, therefore, preventing this would be a truly protective prophylaxis. Radiation-attenuated sporozoites have been shown to protect individuals effectively against malaria, although the technical challenge of creating a vaccine based on whole sporozoites has traditionally been seen as prohibitive. However, Sanaria has taken up this particular challenge and they have a product in preclinical development.

The merozoite form of the parasite is released by infected liver cells and invades erythrocytes, causing systemic malaria. Vaccines based on merozoite antigens will prevent the development and clinical presentation of the disease and could also have greater potential for therapeutic use than sporozoite-targeting vaccines. They could benefit travellers returning from areas where malaria is endemic and could also benefit cases where traditional anti-malarials have failed, as well as benefiting chronically infected locals. One vaccine under development (Berna Biotech), and currently in Phase I clinical trials, combines sporozoite and 'blood-stage' antigens – a double defence against a two-pronged attack.

The remaining compounds are those designed to kill the parasite inside the host by inhibiting the function of essential plasmodial proteins. Variety in this area is particularly important for future efficacy because of the parasite's proven ability to evolve resistance rapidly. It is known that mutations in the gene that encodes the dihydrofolate reductase (DHFR) enzyme have rendered many antifolates ineffective and that single point mutations or multiple gene copies are suspected of giving rise to chloroquine resistance. To stay ahead of the game, new compounds with novel targets (and new combinations of these drugs) must constantly be developed to prevent resistant protozoa from accumulating in the population.

Looking to the future

The problem remains that the poorer people in Africa cannot afford the best medicines and the continent is not a key market for pharmaceuticals. This is not the fault of the pharmaceutical companies (R&D investment has to be recovered in the wealthier parts of the world so that they remain solvent) but their technical expertise will be desperately needed if the efforts of the G8 are going to make an impact. As it happens, malaria-focused collaborations between private companies and government-backed directives are on the rise. In particular, the MMV helps to fund several projects in addition to the GSK projects listed earlier. Examples include DB-289 (Immtech), that was entered into Phase II trials in Thailand in May 2005 (in the trial it is compared with standard artemesinin therapy), and RBx-11160 (Ranbaxy), also in Phase II trials. This public funding of private enterprise removes a major barrier to the development of medicines for the world's poorest people.

If Bob Geldof is right, a host of the problems faced by African countries will be helped by cancelling debts owed by the third world to the world's richest nations. A move such as this could benefit the pharmaceutical industry directly, by freeing up funds in these countries for the clinical development and marketing of drugs in the areas where they are needed most, or indirectly, by relieving the crippling poverty that keeps the markets closed. The unmet need is clear and, whichever course of action is chosen by the G8, hopefully a move towards a more prosperous Africa will allow big pharma to deliver some solutions.

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