Making malaria research bite

An audit of international activity in malaria research highlights the need for a more concerted research effort.

In the time it takes you to read this article 23 people will have died of malaria. The disease threatens 40 percent of the world's population — 2400 million people — in more than 90 countries. It causes an estimated 300–500 million clinical cases and 1.5–2.7 million deaths per year¹. If these figures alone aren't worrying enough, incidences of the disease are on the increase. Efforts to develop a malaria vaccine have so far been unsuccessful, and the effectiveness of most antimalarial drugs has greatly decreased. However, a recent study has shown that total identifiable global expenditure on malaria research is markedly less than on some other major diseases. Furthermore, while research contributes to improvements in health, much more can be done to put the results of scientific investigation to work. An international survey of malaria experts highlights the barriers to exploiting research results, identifies possible measures to tackle those obstacles, and assesses the prospects of various subfields of research for advancing knowledge over the next five years.

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ceutical industry)⁶. Based on global mortality figures from the literature⁷, expenditure per fatal case can be calculated as \$3274 for HIV/AIDS and \$789 for

asthma⁵. These figures are one to two orders of magnitude greater than the equivalent malaria figure, and they indicate that global research funding disproportionately prioritizes high-profile diseases in the West.

International organizations, philanthropic foundations and governments of some developed countries are the major funders of malaria research. The PRISM report revealed that more than half of the 1993 funding came from the USA, particularly the US Agency for International Development (USAID) and the National Institute of Allergy and Infectious Diseases (NIAID). Much of the remainder came from Europe — notably from the United Kingdom where the Wellcome Trust and the Medical Research Council (MRC) are very active — and from the Programme in Research and Training in Tropical Diseases (TDR). The TDR Programme is cosponsored by the United Nations Development Programme, the World Bank and the World Health Organization (WHO) as well as several governments, especially in Scandinavia.

The trend in worldwide funding over the last decade has been downward, largely reflecting decreasing investment from the USA, especially USAID. Meanwhile, malaria research funding from the TDR Programme has remained relatively constant as the UK has increased its contribution. Clearly, the UK has an increasing presence in the funding of malaria research. But what have been the results and broader outcomes from these investments?

Current disease situation

The *Plasmodium* parasite is becoming increasingly resistant to antimalarial drugs, including multidrug cocktails, in several countries². Control has become more difficult because of insecticide resistance of the *Anopheles* mosquito vectors and because of activities such as mining, changing agricultural practices, armed conflict and refugee movements³. Furthermore, recent trials of an experimental vaccine have not been encouraging⁴, and severe side effects from the use of the relatively new drug mefloquine (trade name Lariam) have been identified⁴.

Malaria is principally a disease of less developed tropical countries in Africa, Asia and Central and South America. The governments of many of these countries spend their limited resources fighting disease at the front line, leaving little or no money to invest in medical research. Pharmaceutical firms are aware both of the expense of developing new antimalarial drugs and vaccines and of their limited financial reward: who, after all, will buy pharmaceutical products for the world's poor?

Funding research

There is a pressing need for research in the field of malaria and for the effective translation of research results into practical application. A study published recently by the Unit for Policy Research in Science and Medicine (PRISM) at the Wellcome Trust has estimated that total identifiable global expenditure on malaria research in 1993, from both public and nonprofit sectors, was only about \$84 million⁵. Although data on investment from industry were not available, it is evident that there are a limited number of companies active in this area.

International malaria research expenditure equates to approximately \$42 for every death worldwide (based on a figure of 2 million deaths per year). In other disease areas, estimates for global annual expenditure on research and development were \$919–985 million for HIV/AIDS and \$127–158 million for asthma (over the period 1990–1992 and including the pharma-

Publication of research results

An analysis by PRISM revealed that the number of international papers in malaria published per year is only about 1000, a figure that mirrors the low funding. Furthermore, publication output from different countries and funding bodies largely reflected the balance of funding. The USA is currently the largest single contributor to the malaria research literature, but its share of world publications has declined over the past ten years (from 42 percent in 1984 to 34 percent in 1994). Meanwhile, the UK contribution has moved from 14 percent to 18 percent of the total world publications concerning malaria. These figures indicate the strong UK presence in the field of malaria relative to other biomedical fields where the UK share of global publications ranged from 6.9% to 16.1% (ref. 8). Although this analysis excludes literature published in national and non-English language journals, it clearly identifies the international players. All well and good, but what are the broader impacts of the research?

Health-care impacts

In a survey of more than 100 malaria experts, PRISM canvassed the opinions of both researchers and users on the role of malaria research in health care. Included in the survey were scientists, health services practitioners/advisers, administrators/policy makers and industrialists/manufacturers in both malaria-

endemic and nonendemic countries. The survey showed that more than two-thirds of respondents had personal experience of projects where research results were developed to improve disease prevention, treatment or control — a very high percentage, indicating the direct impact of malaria research on health care. Furthermore, the survey also indicated that the benefits of research were largely expected within the relatively short time span of 1–5 years.

Respondents' experiences of the practical use of results mainly focused on involvement in some stage of the development and testing of antimalarial drugs, in optimization of treatment or prophylactic drug dosage regimens, or in improving methods for the clinical management of malaria. Experience in developmental projects was also frequently cited in research related to intervention trials and health services research. Other respondents indicated research experience leading to vaccine development and vaccine trials.

However, the most worrying aspect of the survey was the

results of malaria research, and new mechanisms to develop novel products from the results of research were recommended. Respondents also suggested increasing investment in problem-solving or operational research, standardizing methods in field trials, and creating more training opportunities for researchers based in malaria-endemic countries.

The World Health Organization already plays a role in these initiatives. Also, an organization known as the Cochrane Collaboration has started to analyze the results of malaria research through its systematic reviews of randomized, controlled trials⁹. However, more can still be done and it is important to ask which research shows the most potential.

Promising research areas

The PRISM survey highlighted a number of research subfields likely to increase knowledge substantially over the next five years (see figure). Parasite genetics and biology were identified most frequently by respondents as having very good prospects

Prospects in each research subfield, expressed as a percentage of survey responses, for substantial advances in understanding over the next five years (n = total number of responses).

finding that almost half of the respondents were aware of valuable research results that were not being developed further or utilized.

Making research work

Several key obstacles to the development of existing research results were identified by the respondents. They felt that research programmes were not sufficiently oriented to public needs in malaria-endemic countries. Furthermore, they expressed the view that there was inadequate standardization of scientific methodology in field trials, and that there were insufficient means either to evaluate research results or to develop products to market. Less surprisingly, resource limitations in malaria-endemic countries were also cited as an obstacle.

A number of measures for tackling the barriers were identified. Respondents called for increased communication between researchers and users in malaria-endemic and nonendemic countries as a priority. A new center (or centers) was proposed to prepare, maintain and disseminate systematic reviews of the

for making substantial advances in understanding. Three other subfields were also perceived as having very good prospects for advancing knowledge in the medium term: epidemiology and mathematical modeling; intervention trials and health services research; and immunology and vaccine development. Some respondents also anticipated that the probable sequencing of the malaria genome within the next five years may lead to entirely new opportunities.

A review of the recent scientific literature identifies a number of promising developments for the practical control or prevention of malaria. Encouraging results have been published in operational research where the use of bed nets treated with the insecticide permethrin reduced childhood mortality by 33% and the risk of developing severe, life-threatening malaria in children by 44% (ref. 10). In the area of drug development, the use of wormwood (*Artemisia*)-derived artemether afforded a similar survival rate of patients with cerebral malaria as quinine, but caused less irritation and cleared the parasite from the body more quickly^{11,12}. Another development is the genetically engi-

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neered mosquito designed to transmit selected proteins and to encourage the production of antibodies against *Plasmodium*¹³. Finally, results published in this issue of *Nature Medicine* (pp. 80–83) indicate that injection of monkeys with recombinant human interleukin-12 can stimulate the immune system and protect against malaria¹⁴. Further studies of this factor for immunoprophylaxis of human malaria appear warranted.

The need for more concerted research effort

Scientific research underpins improvements in health care. Some international organizations, charities and governments are actively engaged in malaria research, but it is clear that more public investment is required. In addition, incentives to encourage investment by the pharmaceutical industry are needed. The renewal of the "Orphan Drug Tax Credits" in the USA (Public Law 104-188, 20 August 1996) allows American companies to deduct half of the costs of clinical testing of drugs that target diseases that are rare in the American population¹⁵. It is hoped that this law will encourage industrial investment in malaria research and will raise the issue of whether other countries should introduce similar measures to encourage industrial research and development.

In the meantime, the incidence of malaria has moved upward. The number of cases in Eastern Europe is increasing rapidly as a result of the economic collapse in countries of the former Soviet Union¹⁶, and both international migration and travel have caused mortalities in the United Kingdom¹⁷. In addition, global climate change has the potential to alter the distribution of vector-borne diseases, potentially causing 50–80 million additional cases of malaria per year¹⁸. These developments make it even more urgent that greater attention be paid to malaria research and to translating the results of such investigation into practice.

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