Malaria research : an audit of international activity / J. Anderson, M. MacLean and C. Davies.

MALARIA RESEARCH

AN AUDIT OF INTERNATIONAL ACTIVITY

UNIT FOR POLICY RESEARCH IN SCIENCE AND MEDICINE

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IN SCIENCE AND MEDICINE

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CONTENTS

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This study of the global malaria research effort over the past decade had its origins in the simple wish of the Wellcome Trust to obtain an objective review of the research outputs from its overseas units. That objective was subsequently expanded to accommodate the valuable suggestions made by members of the Steering Committee established for this 'audit' and by the Trust's Tropical Medicine Interest Group. Particularly important were the suggestions to seek opinion from 'users' as well as from the practitioners of malaria research and to examine the effectiveness with which research findings have been translated into practice.

Many individuals and organizations have collaborated in this project and hopefully they will find this report both of interest and of value. The authors have shown remarkable persistence in their pursuit of the data needed for this study and few organizations have failed to respond to requests for information. It is hoped that they also will find the study of value.

Some researchers have expressed a concern that the objective of the 'audit' might have been to reduce the funding for malaria research. However, at a time when the synthetic antimalarials developed in the middle years of this century are approaching the end of their useful life and the malaria vaccine remains a desirable yet unachievable goal, the report reveals that the support for malaria research by several of the major funding agencies has fallen significantly in recent years and highlights the very low level of industry-based research on this disease. It is to be desired that this report will stimulate a greater level of malaria research activity in both the public and private sectors.

The authors merit comment for their enthusiasm for this project and for the diligence and care with which the report has been constructed. The complexity of the exercise has presented both a major challenge and a very large workload but the final report more than justifies their efforts.

R E Howells
Programme Director
The Wellcome Trust

INTRODUCTION

Malaria is recognized as a major and increasing threat to world health. Disease prevalence is escalating and distribution expanding as resistance to antimalarial drugs and insecticides spreads. New and improved approaches to disease prevention, treatment and control are required and present an urgent challenge to the underpinning sciences. There is a pressing need for research in the field of malaria, and for the effective translation of research results into practical application.

The limited availability of funds for research, in any scientific field, dictates that support must be focused, and it would seem self-evident that future funding policies of organizations investing in biomedical research need to be information-led and evidence-based. An effective, overarching approach to the assessment of research activity in a field can help inform the decision-making process. This report presents the results of one such study, which examined international research activity in the field of malaria.

The study was undertaken using a set of novel analytic techniques developed by the Unit for Policy Research in Science and Medicine (PRISM). The purpose was to generate information that could help the Wellcome Trust in its policy decisions on the most effective means of supporting malaria research in the future. During the course of the study, it became clear that the information produced may also be of some value to individuals and other organizations which fund, manage or conduct malaria research. The key findings are therefore being published to provide a factual base of evidence to help inform discussions on malaria research policy more broadly.

The study examined the funding inputs to malaria research internationally, as well as the published outputs and broader outcomes, such as improvements in clinical treatment and development of new therapeutic products. In addition, the study examined research opportunities and also research areas requiring an input of resources. Opinion was sought on barriers perceived to be limiting the translation of research results into practice, and on measures to tackle these obstacles.

MAIN STAGES OF THE STUDY

The study comprised five analytical stages.

- A survey of international funding for malaria research over the past decade.
- An analysis of malaria publications and citations, over the same time period, to identify relative outputs and scientific impact by different countries and funding bodies.
- An assessment of publishing activity in the subfields of malaria research to elucidate the balance of effort between subfields.
- A qualitative assessment of the portfolio of publications arising from research supported by the Wellcome Trust to identify the achievements as well as the balance of the Trust's portfolio of malaria research output.
- An opinion survey of the malaria community – involving researchers as well as funders and users of research – on the main issues of research, the translation of research results into practice and key future opportunities.

MAIN FINDINGS

Funding

Total identifiable global expenditure on malaria research in 1993 was approximately US$84 million. Over half the total came from the USA (especially 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 the Wellcome Trust and the Medical Research Council, MRC, in the UK), or from the Programme in Research and Training in Tropical Diseases (TDR) which 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.

Funding has declined in some organizations over the past decade, most notably in USAID. However, there have been increases elsewhere, especially at the Wellcome Trust, NIAID and the US Department of Defense (DoD). Support went mainly to researchers in Europe and the USA. The exceptions were to be found in the funding initiatives of the TDR programme, the Wellcome Trust, the UK MRC, the European Union (EU) and USAID, which encouraged international cooperation. Notable among these were the overseas units supported in malaria-endemic countries by the Wellcome Trust and the UK MRC.

The overall conclusion to be drawn is that global investment in research is very low compared with other disease areas over the past 10 years, and appears to be declining further. Expressed as investment in research per death, malaria research (at approximately US$42 per fatal case) receives markedly less funding than other diseases such as cancer, HIV/AIDS or asthma.

Research outputs

International publishing activity largely reflected the pattern of funding and was very low compared with other biomedical fields. The USA is currently the largest single contributor to the malaria research literature (34 per cent of the global total in 1994), but its world share of publications has been declining over the past 10 years (from 42 per cent in 1984). Meanwhile, the trend from the UK is up, from 14 per cent of the world total in 1984 to 18 per cent in 1994. The world share of malaria publications from France, Australia and Thailand also increased.

UK centres for collaborative research located in malaria-endemic countries appeared to foster international coauthorship. A total of 38 per cent of UK output was internationally coauthored and largely reflected the work at the overseas units of the Wellcome Trust and UK MRC.

Citations to papers supported by the six funding bodies contributing most to malaria research were more numerous than citations to papers supported by other organizations. In 1989, the most recent year for which citation analysis was conducted, NIAID and the UK MRC appeared to have the greatest citation impact. For five organizations, the production of high-citation-impact papers remained more or less stable over time. These were the NIAID, the US DoD, TDR, the Wellcome Trust and the UK MRC. For one funding body (USAID), there was an apparent decline in its proportion of high-impact papers over time.

Activity in different subfields of malaria research

The field of malaria research was divided into 14 subfields, and research publications were assigned to each of these. 'Clinical' research papers accounted for 42 per cent of the world total, describing studies of malaria in humans ranging from clinical management and pathophysiology to human immune response and genetic susceptibility. 'Non-clinical' papers accounted for 58 per cent of the world total, describing studies of malaria in animal models or *in vitro* and basic studies on mosquito vectors.

International research activity, as measured by publication output in three selected years, was evenly distributed across most categories of malaria research. Publications were most numerous in two major research categories: (i) clinical treatment and pathophysiology, and (ii) basic science studies of the parasite. Research into antimalarial drugs, immunology, epidemiology and mosquito vectors were also well represented by publications. Intervention trials and health services research appeared to have less publishing activity.

Based on the address of the first author only, the USA dominated all subfields excepting those relating to clinical medicine and pathophysiology. UK authors published most frequently in pathophysiology and disease symptoms, whereas Thailand was the world leader in clinical management of malaria and drug trials. High coauthorship between researchers in the UK and Thailand suggested that the UK also had an important role in that area.

The Wellcome Trust portfolio of malaria research

Papers acknowledging the Wellcome Trust were sent out for review by 13 subfield experts. The portfolio of papers included publications in 11 subfields, two of which were especially well represented: pathophysiology and clinical disease symptoms, as well as clinical treatment and management of malaria. Basic studies of the parasite were also well represented.

Outputs in different subfields largely reflected funding inputs. However, publications were low relative to expenditure in three subfields: immunology and vaccine development, epidemiology, and intervention trials and health services research. Conversely, outputs were high relative to inputs for studies on both the biology and the biochemistry of the parasite.

The Wellcome Trust's research outputs were considered by reviewers to make a contribution both to advancing basic knowledge, and to improving malaria treatment and control. Realization of practical benefits from Trust-funded research was largely expected by the reviewers within five years of publication.

Current practice and future directions of malaria research

The views of over 200 members of the malaria community were sought on issues concerning current practice and future directions in malaria research. A total of 115 individuals responded to the survey, including researchers, clinicians, health services managers and practitioners, industrialists and administrators in both malaria-endemic and non-endemic countries.

Of the 14 subfields analysed, parasite genetics and parasite biology were identified most frequently as having very good prospects for advancing knowledge over the next five years.

The subfield concerning intervention trials and health services research was considered to be most under-resourced, consistent with the low publication output identified in that subfield. Increased resources were also considered necessary for research on: basic studies of the parasite, epidemiology, immunology and vaccine development, and antimalarial drug development. Investment was recommended in these subfields and in human capital.

However, research is characterized by uncertainty, and respondents anticipated that the probable sequencing of the malaria genome within the next five years may lead to new challenges and opportunities hitherto unidentified.

More than two-thirds of respondents indicated experience in projects where research results were developed to improve the treatment or control of malaria. However, half of all the respondents also indicated that they knew of research results that might have influenced malaria treatment or control but were not developed or utilized.

Respondents further identified a number of key obstacles to the uptake of research results for practical application in malaria treatment and control. These obstacles included: insufficient orientation of research programmes to public needs in malaria-endemic countries; inadequate standardization of field techniques; inadequate assessment of research results and development of applications; and resource limitations in malaria-endemic countries.

Several possibilities emerged from the survey for overcoming the perceived barriers to research uptake. One approach would be to strengthen existing mechanisms for evaluating research results for their potential uptake in programmes of malaria treatment and control. This might involve establishing a centre to prepare, maintain and disseminate systematic reviews of the results of malaria research. Related to this was the perceived need for a mechanism to develop new products from the results of research that would contribute to the treatment and control of malaria. The survey also indicated a need for improving active communication between professional groups with an interest in malaria (both researchers and non-researchers), and for creating more training opportunities for researchers based in malaria-endemic countries.

The challenge

This study has demonstrated the potential that malaria research has to make a significant contribution to the treatment and control of one of the world's most threatening diseases. Given this, the low level of funding globally is striking.

This report points to some of the areas of greatest need and opportunity for the field: scientific subfields with promise are highlighted, as are opportunities for improving the management and organization of the research enterprise. However, the challenge is too great for any one funding body. In reaching to meet the various needs and seize the opportunities identified in this report, there is a clear need for an international, collaborative approach, involving all of the main national and international organizations with an interest in malaria. The challenge is clear, and this study calls for a coordinated response from the international malaria community.

LESSONS FOR FUTURE STUDIES

The study has described a number of both quantitative and qualitative methods used to produce an evidence-based report on the status and future options in malaria research. In order to guide similar studies which might be conducted in the future, a number of general points should be made concerning the approach and techniques used in this study.

Assessing funding inputs

Direct contact with funding agencies provided detailed information on funding and permitted confirmation of the data once they had been analysed. However, this approach was time-consuming and limited by the extent of the response. An analysis of funding acknowledgements in publications rapidly and comprehensively identified the larger contributors to malaria research, as well as the smaller contributors, but did not provide data on the amount of support from each organization.

Analysing publications outputs

The limitations of commercially available databases – such as the Science Citation Index and Medline – suggest that the choice of one database or the other, or indeed the use of both databases, must be carefully considered according to the aim of a particular analysis. Furthermore, the effects of using a small number of publications in an analysis, such as for the citation analysis of particular funding bodies, should be recognized.

Defining subfields

The development of a classification system for dividing the field of malaria into a number of

subfields usefully identified differences between subfields. It is important to recognize the subjective nature associated with the definitions of the subfields, although every effort was made to use precise definitions and to minimize subjectivity.

Conducting an expert review of publications

The use of an expert review of published papers provided a retrospective analysis of the achievements of research and the identification of opportunities arising from that research. It provided a complementary approach to citation analysis and allowed for a detailed qualitative assessment of the publications in a field. The use of subfield experts allowed for an informed assessment. However, in this particular case, the small number of both publications and experts per subfield, limited by the size of the portfolio itself, suggest that caution is required in the interpretation of the findings.

Conducting a community-wide survey

A key feature of the community survey was its breadth across professional groups and geographical boundaries. Ideally, such surveys should aim to sample opinion from researchers as well as the users of research results, and from professionals based in malaria-endemic as well as those in non-endemic countries. This process can provide an opportunity for all groups to express their opinions and raise mutual awareness of broader issues of policy as well as of research.

1 INTRODUCTION

1.1 BACKGROUND TO THE MALARIA STUDY

This report presents the results of an international study of past activity and future options in malaria research. The origins of this work lay in a study commissioned by the Wellcome Trust, to help inform its policy decisions on the most effective means of supporting this field of research in the future. During the course of the study, it became clear that the large quantity of original data and information being collected might also be of some value to individuals and other organizations which fund, manage or conduct malaria research. The key findings of the study are therefore being published to provide a factual base of evidence to inform individual investigators and to support organizations developing future policies for malaria research.

There have been previous reviews of malaria research and control. The most significant recent attempt to review this field and gather hard data was undertaken by the Institute of Medicine in the USA (Oaks *et al.*, 1991). The aim of that study was primarily to make recommendations to the US government, and it therefore focused mainly on gathering data from US funding organizations. Valuable qualitative information was produced concerning the status of malaria research and control worldwide, as well as identifying the decline in support by the US government over the period from 1987 to the report's publication in 1991. Another recent study by an ad hoc committee convened by the World Health Organization (WHO, 1996) has a broader focus on tropical diseases. The report on that study reviews investment requirements to tackle global health problems, and provides a valuable context for more focused studies on single tropical diseases such as malaria.

While the Institute of Medicine study successfully achieved its objectives, it did not attempt to produce data on malaria funding in other countries, and acknowledged the substantial difficulties of doing so. However, the availability of such data is crucial when developing a balanced international strategy for research funding, and one of the goals of the present study was to attempt a survey of malaria research funding internationally.

An additional need, not covered by previous reviews, is for data on the outputs from malaria research; funding data, of course, only represent an input to the research system. Finally, previous reviews have not attempted to canvass opinion systematically from a wide base of professionals with an interest in malaria research (both researchers and those who use the results of research). Again, the information generated by a large-scale, systematic consultation of the malaria community can be important when developing policies.

1.2 SCOPE OF THE MALARIA STUDY

This study encompassed the full spectrum of malaria research from basic science through clinical studies, epidemiological studies of malaria prevalence, field trials, operational research and studies of the delivery of malaria treatment and control measures by health services and other organizations.

Specifically, the study included the following:

- A survey of financial support for malaria research internationally.
- An analysis of malaria publications and citations to assess the relative outputs from different countries and funding bodies.
- A scientific subfield analysis of papers published in 1984, 1989 and 1994, with the aim of determining the balance of effort between different areas of research within the field.

- A qualitative assessment of the scope and achievements of papers acknowledging the support of the Wellcome Trust with the aim of identifying the strengths and weaknesses of the Trust's portfolio, within the context of the international malaria research effort.

- An opinion survey of a diverse group of malaria researchers and users of the results of malaria research. The aim of the survey was to identify communication networks, mechanisms of dissemination of research results, barriers to the uptake of results, measures to strengthen the field, means of effectively transferring research results into practice, and key research topics and opportunities for the future.

The study was carried out over a period of 12 months and drew on a variety of data sources, published and unpublished, and a range of expert opinion. The work was carried out by the Wellcome Trust's Unit for Policy Research in Science and Medicine in collaboration with staff from the Trust's Tropical Medicine Science Division, and overseen by a Steering Committee. The overall aim was to present a data-driven analysis of the field of malaria research to inform debate on future priorities. It is being published here in order to contribute to broader debate on priorities for malaria research.

1.3 PUBLIC HEALTH SIGNIFICANCE OF MALARIA

The global significance of malaria, in terms of both health and economics, is described principally in several WHO documents (WHO, 1993; 1995a, b, c, d).

Malaria is a major killer which threatens 2400 million people, or about 40 per cent of the world's population. It is responsible for 300–500 million clinical cases and between 1.5 and 2.7 million deaths per year. Even these large numbers are, however, likely to be underestimates because of the problems associated with recognizing and reporting the condition.

The disease has its major impact in sub-Saharan Africa where over 90 per cent of the worldwide cases are reported. Approximately 10 per cent of hospital admissions and 20–30 per cent of outpatient consultations in Africa are due to malaria. Asia and the Americas are thought to have some 5–20 million cases per year. Most of these, about 80 per cent, occur in Asia. The most serious areas of risk for contracting malaria in Asia and in Central and South America are at the frontiers of economic development, such as in the Amazon basin where colonization and mining have greatly affected the environment, and in regions of social disruption, such as war zones in Afghanistan and Cambodia.

The incidence of malaria is on the increase. There is growing resistance to current anti-malarial drugs in many areas, including multidrug resistance in several countries of Southeast Asia and Africa. Increasing insecticide resistance is also a major threat, as are changing agricultural practices, especially irrigation programmes in many malaria-endemic countries.

Children are particularly at risk in rural Africa where the disease is one of the major childhood killers and responsible for the death of one in 20 children before the age of five years. It is also the most common disease among school children and young adults in Africa where it tends to strike at harvest time, affecting productivity. The disease causes anaemia in children and pregnant women, and increases their vulnerability to other diseases.

1.4 ECONOMIC SIGNIFICANCE OF MALARIA

In 1987 the estimated annual direct and indirect cost of malaria in Africa was US$800 million, and this figure was expected to rise to more than US$1800 million by 1995. The worldwide cost associated with malaria is undoubtedly higher, however, possibly reaching US$2000 million in 1995 (assuming that Africa has 90 per cent of the worldwide malaria cases).

For the control of the disease alone, the WHO Action Plan for Malaria Control, 1995–2000 (WHO, 1995c) has estimated that approximately US$28 million per annum of external investment in malaria control will be needed in Africa. Outside Africa, malaria control programmes cost an estimated US$175–350 million a year.

1.5 THE DISEASE

Excellent reviews of the disease and its history are provided by Bruce-Chwatt (1985), Oaks *et al.* (1991), and the WHO (1993). An outline of certain biological and historical aspects of the disease is given here, but readers are referred to the above texts for further information.

Malaria is a disease caused by four species of protozoan parasites of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. *Plasmodium falciparum* is responsible for the most severe manifestations of the disease. The parasite matures and reproduces sexually in the mosquito *Anopheles*, and is transmitted through that vector to humans.

Transmission occurs through the female mosquito, which requires a blood meal for the development of her eggs. The parasite sporozoites, which enter the human blood with the saliva of the biting mosquito, invade the liver cells where they develop and multiply. Merozoites, released into the blood from the liver, invade the red blood cells and initiate the cycle of development and multiplication that brings about the clinical symptoms of the disease.

Malaria is best thought of as a collective name for different diseases, since the epidemiology of malaria transmission and the severity of the disease vary greatly from region to region, village to village, and even from person to person within a village. Some of these differences will be due to the particular species of the parasite, the degree of compliance with a drug regimen, local patterns of drug resistance, and an individual's immunity.

1.6 HISTORY OF RESEARCH AND OF MEASURES AIMED AT CONTROL AND TREATMENT OF THE DISEASE

In the fifth century BC, Hippocrates discarded superstition as a cause for the fevers which afflicted ancient Greeks. He recognized the seasonality of the fevers, and described the early clinical manifestations and complications of malaria.

However, it was not until the seventeenth century that a breakthrough occurred in the treatment of the malarial fevers. The bark of the Peruvian tree, *Cinchona*, was discovered as the first therapy for the disease. The active principle of the bark, quinine, was later isolated. The devastating effects of malaria during the First World War stimulated research for synthetic antimalarial drugs, which were first discovered in the 1920s (pamaquine) and 1930s (chloroquine).

Also at this time, a major discovery in the control of malaria, through the use of a natural insecticide, established the cornerstone of malaria control. Pyrethrum, an extract of the chrysanthemum, was mixed with kerosene and sprayed on the walls of houses. Several

synthetic alternatives (dichloro-diphenyl-trichloroethane or DDT, and dieldrin) were discovered in the 1940s and became the standards for control programmes worldwide.

Serious attempts to eradicate malaria began in the mid-1940s, and following the Second World War there was a high level of international cooperation devoted to eradicating malaria from endemic regions. The United Nations Rehabilitation and Relief Administration, an international emergency organization formed in 1943, was very active in malaria control measures. The first Expert Committee on Malaria, established by the Interim Commission of the World Health Organization, met in 1947, and the World Health Organization was officially formed in 1948.

The programme was targeted to the eradication of the mosquito vectors, thus preventing transmission of the parasite. The insecticide DDT emerged as the most effective intervention tactic, although sub-Saharan Africa was excluded from the eradication programme because it was felt that its malaria problem was too large, and that this region lacked the technological capability. From the beginning it was realized that insecticide resistance would be a problem, and there was the fear that the mosquitoes would develop resistance before the disease could be wiped out.

Although the eradication programme produced some dramatic results in many parts of the world, it became clear by the mid-1960s that eradication was not technically or economically feasible in many other regions. In 1969 the World Health Assembly revised its global malaria eradication strategy, and its new approach encouraged control where eradication was not feasible. This emphasis on control required a long-term commitment of personnel and financial resources and also encouraged malaria control strategies to be integrated into the basic health services programmes of individual countries. The change in policy did not, however, increase funding for malaria control. Nonetheless, there was a dramatic increase in research into new antimalarial drugs by the US Armed Forces, which, at war in Vietnam, had encountered the major problem of chloroquine-resistant *P. falciparum*.

In recent times, there has been considerable pressure to restrict the use of DDT on environmental/health/conservation grounds. This has also had an adverse effect on malaria control efforts. In addition, drug resistance for the prevention and treatment of malaria has become increasingly prevalent, with multidrug resistance a major problem in many endemic areas of the Old and New World.

It was recognized in the late 1980s that the malaria situation in most parts of the world was deteriorating, largely because of relaxation of control measures and increased drug resistance. As a result, a WHO Ministerial Conference was held in Amsterdam in 1992, with the participation of ministers of health and other health workers from 102 countries, as well as representatives of the UN, other intergovernmental organizations and the scientific community. The outcome of the conference was support for a global malaria control strategy (WHO, 1993).

It is increasingly recognized that malaria treatment and control are issues which may have practical implications beyond the current geographical delineation of the disease. Increasing global temperatures have a potential impact on the prevalence and incidence of tropical diseases such as malaria (Kerr, 1995). Without adequate control of the disease in the future, it can be anticipated that malaria will spread beyond its current geographical boundaries.

The increased prominence and distribution of malaria, as well as its current prevalence, indicates a need to take stock of the current international effort in malaria research. The present study will, hopefully, contribute both by providing hard data and clear evidence of past trends, and by offering insight to future needs and opportunities in this field of research.

2 FUNDING INPUTS TO RESEARCH

This chapter presents the results of a survey of national and international funding support for malaria research. The survey aimed to identify the main sources of funding for research into the disease and to analyse trends over the past 10 years, drawing on original data provided by research funding organizations around the world.

For the purposes of this study, malaria research included the following: all research ranging from fundamental cellular and molecular studies to applied clinical, epidemiological and operational research studies (relating to the implementation of malaria treatment and control methods), and research on mosquito vectors of malaria.

2.1 METHODS

Over the 10 year period covered in the study, there have been significant differences in the relative rates of research cost inflation and living cost inflation. The much higher rate of research cost inflation has meant that the decrease in research purchasing power has been much faster than that for general commodities. This has meant that less research can be purchased now than before, relative not only to absolute money but also to other commodities. In what follows, an attempt has therefore been made to take account of these effects when drawing comparisons between funding bodies in different countries.

Funding organizations were identified through literature searches and scientific attachés in London-based embassies. Each organization was contacted for information on its overall research expenditure and on malaria research expenditure for the 10-year period 1984/85–1993/94. Organizations were asked to search their grant records (titles or abstracts) for awards relating to malaria or mosquito vectors of malaria, and, where possible, to provide a list of all grants identified. Lists of grants, where provided, were analysed by the audit team to ensure consistency of analysis. However, in some cases, organizations provided data in a pre-processed form. All funding bodies that contributed data were given an opportunity to check the accuracy of their coverage in the report, and most did so.

The following points should be noted:

- Although every effort was made to obtain comparable data, it cannot be assumed that all funding organizations classify their grants in the same way. Many organizations do not have computerized record systems and even within organizations, changes in classification systems may have occurred over the time period studied.

- The specific period covered in any financial year may vary between organizations. For example, whereas the financial year for one funding body may run from 1 January to 31 December, another agency may use the period from 1 October to 31 September.

- The approach to classifying the allocated funds over time also varies between organizations. For example, annual expenditure may be given as either the amount spent or the amount awarded in any one year.

- There may also be an element of double counting.[1] For example, some organizations allocate funds to the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and as a consequence such funding may appear in both the TDR data and the funding agency in question. This was taken into account where possible.

- Most of the funding identified is extramural support.[2] Intramural support for malaria research is generally not included, but may be significant in countries where research is mostly funded through ministries of health and block grants[3] to institutes.

To allow for inflation all data were adjusted using the appropriate Price Index[4] to express spending in 1992 figures. Data were then converted to US dollars ($) using Purchasing Power Parities.[5] The conversion factors were supplied by the Organisation for Economic Cooperation and Development (OECD) and were the most up-to-date figures available in January 1995.

2.2 RESULTS

All data presented are in 1992 US dollars and expressed in financial years (FYs). For the purposes of this report, FY 1993 has been identified as that which is quoted by each organization in one of the following four manners: FY93; 1993; 1992/93 when 1993 forms the greater portion of the year (e.g. October 1992–September 1993); or 1993/94 when 1993 forms the greater portion of the year (e.g. April 1993–March 1994). Data for the six largest contributors to malaria research, based on 1993 expenditure, are presented first. These are followed by data for the medium-sized and smaller contributors (see Table 2.1).

2.2.1 Larger contributors

US Agency for International Development[6]: $15.1 million in FY 1993

The US Agency for International Development (USAID) is the foreign assistance arm of the US government and provides more financial support to malaria research activities than any other US agency. Between financial years 1985 and 1993, USAID's budget for health, child survival and AIDS activities increased from $450 million to $564 million, but then decreased in FY 1994 to $549 million. The total annual sum allocated to malaria research and field programmes decreased from $49 million to $15 million over the period FY 1985 and 1993, and to $9.7 million in 1994 (see Figure 2.1). As a proportion of USAID's total expenditure on health, this represented a decline from 11 to 3 per cent, and finally to 1.8 per cent in FY 1994.

Figure 2.2 shows how USAID funding for malaria is divided between bilateral projects and central projects of which the Malaria Vaccine Development (MVD) project is a major component. In the USAID context, bilateral projects target malaria control and are country-based projects managed by USAID Missions in the field. Central projects are managed by USAID/Washington. The most marked change over the period FY 1985–1994 has been a substantial decline in support for bilateral projects; between FY 1985 and 1991, almost two-thirds (63 per cent) of USAID malaria funds went to support bilateral projects, but by FY 1994 this had declined to 25 per cent. Funding for MVD was, in absolute terms, quite stable to FY 1993. However, as a percentage of the total malaria

[1] Double counting refers to the overestimate of funding by a factor of two as a result of attributing the same research funds to two separate funding bodies.

[2] Extramural support is that which is acknowledged in a publication from a source that is different from the address of the researcher. Intramural support is defined as that funding which is not acknowledged as extramural funding and which is apparent from the address of the researcher (e.g. support to an institution established and managed by a funding body).

[3] Block grants are grants which are given to fund a number of projects.

[4] Price Indices are used to inflate or deflate actual financial data, effectively normalizing the data to a constant base year. The base year selected in the current report was 1992 (see National Science Board, 1993).

[5] Purchasing Power Parities are the preferred standard for calculating international expenditure in research and development. They account for the variable costs of buying goods and services in different countries, including the wages of scientists and other personnel (see National Science Board, 1993).

[6] Many governmental bodies in the USA employ a financial year which runs from 1 October to 30 September. Thus, FY 1993 = October 1992–September 1993.

Table 2.1 Summary of identified funding support for malaria in financial year 1993 (FY 1993)

Funding organization	Funding for malaria research ($ million 1992 base year)
United States Agency for International Development (USAID)[7]	15.1
National Institute of Allergy and Infectious Disease (NIAID) (USA)	13.1
Department of Defense (DoD) (USA)[8]	~11.6
Research and Training in Tropical Diseases (TDR) Programme[9]	9.0
Wellcome Trust (UK)[10]	7.1
Medical Research Council (MRC) (UK)	6.8
European Union (EU)	2.6
National Institute of Health and Medical Research (INSERM) (France)	2.3
Centers for Disease Control (CDC) (USA)[11]	2.2
National Health and Medical Research Council (NHMRC) (Australia)	1.8
Overseas Development Administration (ODA) (UK)[12]	1.6
International Development Research Centre (IDRC) (Canada)[13]	1.4
The Mexican government[14]	1.2
Directorate General for International Cooperation (DGIS) (The Netherlands)	1.1
MacArthur Foundation (JCM) (USA)	1.0
Institute for Scientific Research for Development and Cooperation (ORSTOM) (France)	1.0
Others	~5
Total	**~84**

[7] The USAID figure is for research and field programmes.

[8] DoD data for FY 1993 were not available. The data presented here are for 1995 (adjusted to 1992 US dollars).

[9] The TDR programme is supported by voluntary contributions from governments, international organizations, charities, other non-governmental bodies and the three co-sponsors of the programme – the World Health Organization (WHO), the World Bank and the United Nations Development Programme (UNDP). The figure of $9 million given represents malaria funding only, and not the additional tropical diseases covered in the Programme.

[10] Funding for malaria research at the Wellcome Trust increased markedly in FY 1994 to $10.6 million.

[11] The CDC figure is for research and control activities.

[12] ODA data for FY 1993 were not available. The data presented here are for FY 1992, which is to say April 1992–March 1993.

[13] IDRC reported that its funding of malaria in FY 1993 was unusually high.

[14] This figure, which is for FY 1994, is believed to be an underestimate of government expenditure as it represents the support given to one research organization only.

allocation, the MVD portion fluctuated and has decreased by more than half in FY 1994. This reflected the overall decrease in malaria funding in that year, although the large loss of funds to MVD was partially offset by a small increase in funds to other central projects.

A geographical analysis of USAID's support for malaria research and field programmes is made difficult by the fact that the Agency's funding organization structure does not directly reflect the location of expenditure. For example, central funds managed by Washington may, and often are, reallocated and spent at the country level. Consequently, the specific allocation of malaria support on a geographical basis is not readily available.

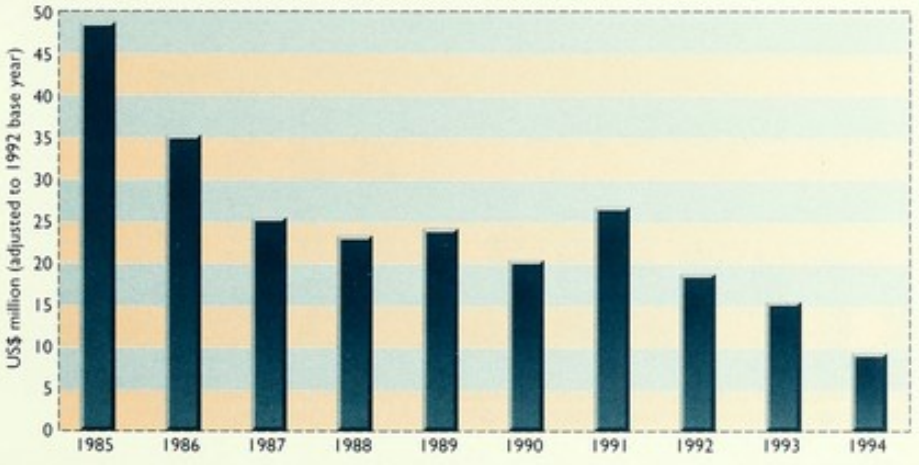


Figure 2.1: Funding for malaria research and field programmes by USAID

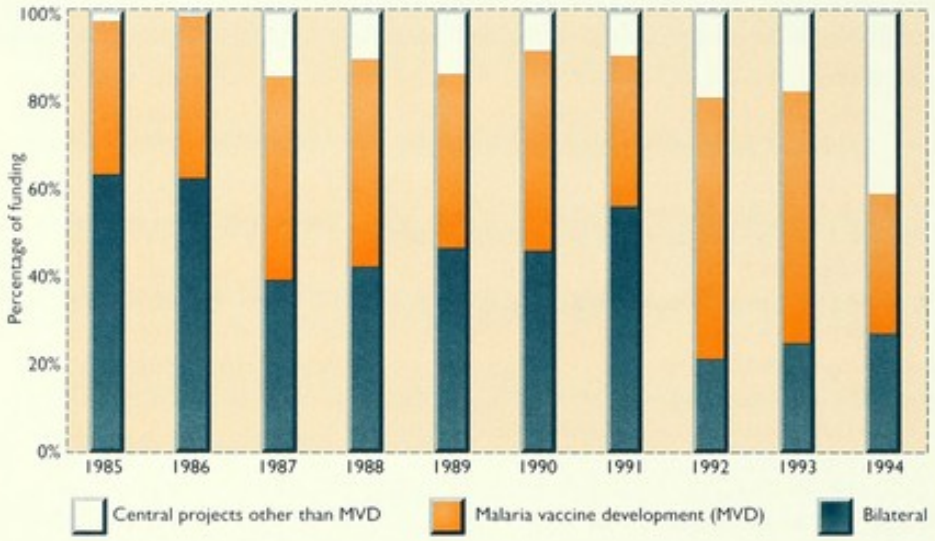


Figure 2.2: Funding for USAID malaria projects by allocation type

National Institute of Allergy and Infectious Disease:

$13.1 million in FY 1993

The US National Institute of Allergy and Infectious Disease (NIAID) is one of two dozen institutes, centres and divisions at the National Institutes of Health (NIH). Within the NIH, NIAID has lead responsibility for activities related to tropical diseases. Grants, in support of research on malaria and other tropical diseases, are awarded to extramural institutions on a competitive, peer-reviewed basis. In addition, NIAID supports research on malaria in its intramural laboratories in Bethesda, Maryland.

Over the 10-year period between FY 1984 and 1993, NIAID's annual budget increased from $420 million to $960 million. During that same period, support for malaria research increased from $6.4 million to $13.1 million, and increased further to $15.2 million in FY 1994 (Figure 2.3). Approximately 30 per cent of the funding awarded in this period was in support of intramural activities. The proportion of funds allocated to malaria research has remained reasonably constant at just over 1 per cent of NIAID's total budget.

The bulk of NIAID malaria support is allocated for research within the USA. A total of

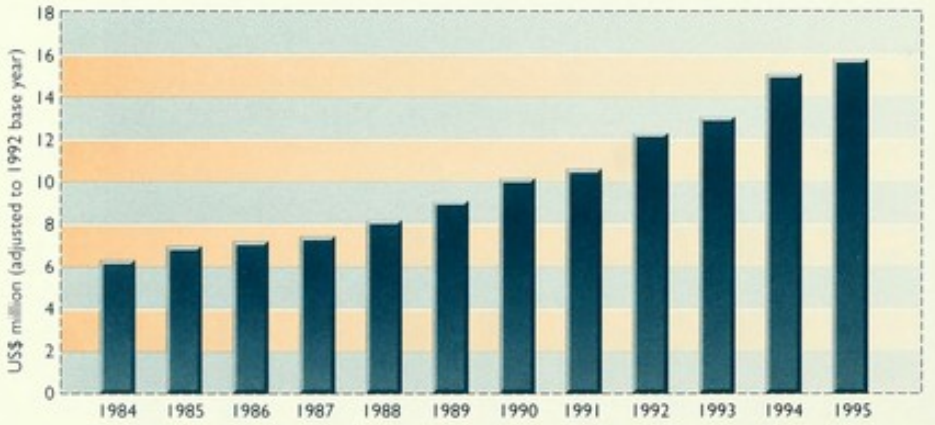


Figure 2.3: NIAID funding of malaria research

3 per cent of the awards made between FY 1984 and 1993 were made to institutions outside the USA. This represented just 2 per cent of the total funds allocated.

The Department of Defense:
estimated $11.6 million in FY 1993

The US Department of Defense (DoD) supplied data for the 1995 financial year which indicated that approximately $6.9 million was spent on malaria vaccine research and $4.7 million on research into antimalarial drugs. This appears to represent an increase over previous years according to data provided in the Institute of Medicine malaria report (Oaks *et al.*, 1991). According to that source, the DoD allocated almost $38 million, or roughly $7.6 million per annum, to malaria activities between FY 1986 and 1990. Malaria activities were defined in the Institute of Medicine report to include vaccine development, drug development and vector biology research and control.

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR):
$9.0 million in FY 1993

The Special Programme for Research and Training in Tropical Diseases (TDR) is cosponsored by the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). TDR is supported by voluntary contributions from governments, international organizations, charities, other non-governmental bodies and the three cosponsors of the Programme. The largest contributors to TDR, over the period FY 1974–1994, include the following: Denmark, Norway, Sweden, the USA and the cosponsors (WHO, 1995b). The Programme, which commenced in 1975, has two objectives: to research and develop new tools to control tropical diseases; and to train individuals and strengthen institutions to increase the research capability of developing tropical countries. As well as malaria, the TDR Programme also includes schistosomiasis, filariasis, trypanosomiasis, Chagas disease, leishmaniasis and leprosy.

Figure 2.4 shows TDR's commitment to research and development, and research capability strengthening (e.g. training and institutional strengthening) over a 10-year period. The total budget rose from $20 million in FY 1984 to $22 million in FY 1993, peaking at $28 million in 1991. Of this, malaria research accounted for an average of 38 per cent. In FY 1993, the budget for malaria activities was $9 million. This figure increased in FY 1994 to $9.6 million out of a total TDR operational budget of $19 million. Consequently, malaria accounted for almost 50 per cent of all TDR spend in that year, thus representing the highest proportion of the total budget ever dedicated to the disease.

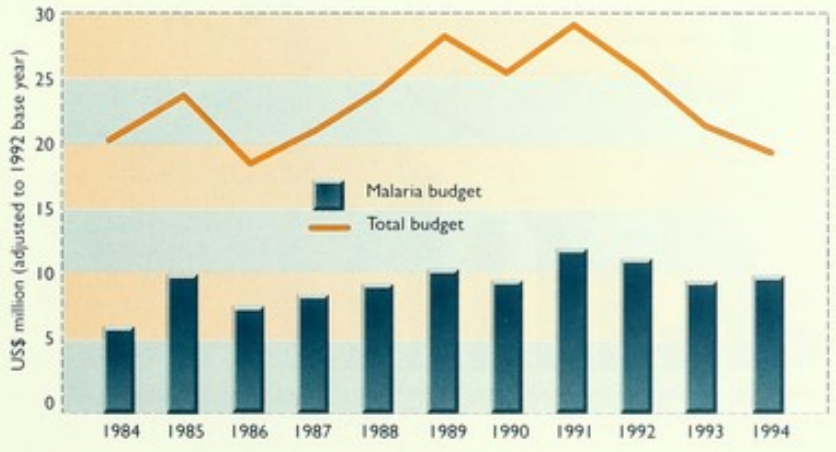


Figure 2.4: TDR Programme malaria budget and total operational budget

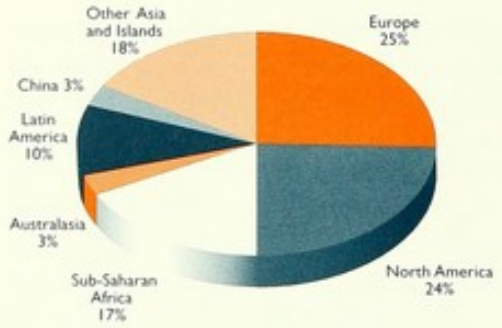


Figure 2.5: TDR Programme malaria funding by region
(% of funding 1984–1994)
(other Asia and Islands includes Japan, Middle Eastern Crescent, Indian subcontinent)

Almost one-half of the grants awarded between FY 1984 and 1993 went to researchers in Europe and North America (Figure 2.5). Sub-Saharan Africa received 17 per cent of the total with 'Other Asia and Islands' receiving 16 per cent. However, these ratios have changed over time, and by FY 1993 the portion received by sub-Saharan Africa had increased to 24 per cent per year.

The Wellcome Trust:

$7.1 million in FY 1993

The Wellcome Trust is the world's largest charitable foundation. It was established in 1936 by the will of Sir Henry Wellcome, the successful industrialist and philanthropist. Wellcome decided that, on his death, the share capital of the pharmaceutical company, The Wellcome Foundation Limited – later Wellcome plc and now part of Glaxo Wellcome – would be held in trust to create a research-funding charity.

The objectives of the Wellcome Trust are to support research in the biomedical sciences including veterinary and tropical medicine and the history of medicine. All types of research are funded, from the basic sciences related to medicine to the clinical aspects of medicine. The greater part of the Trust's income is currently used to support the work of researchers in the UK and the Republic of Ireland. However, through its International and Tropical Medicine Programmes, the Trust supports scientific exchange between the UK and the rest of the world and provides certain types of support for research projects in other countries.

Total science funding and malaria support

The funding commitment of the Wellcome Trust both for science as a whole and for malaria have increased substantially over the past 10 years (Figure 2.6). In FY 1993,[15] $7.1 million was allocated to malaria research, out of a total research budget of $277.2 million. A large increase in funding occurred in FY 1994, when expenditure on malaria research increased to $10.6 million and total expenditure to $353.2 million. In FY 1995, the funding commitment to malaria increased to $12.7 million. Malaria research, as a proportion

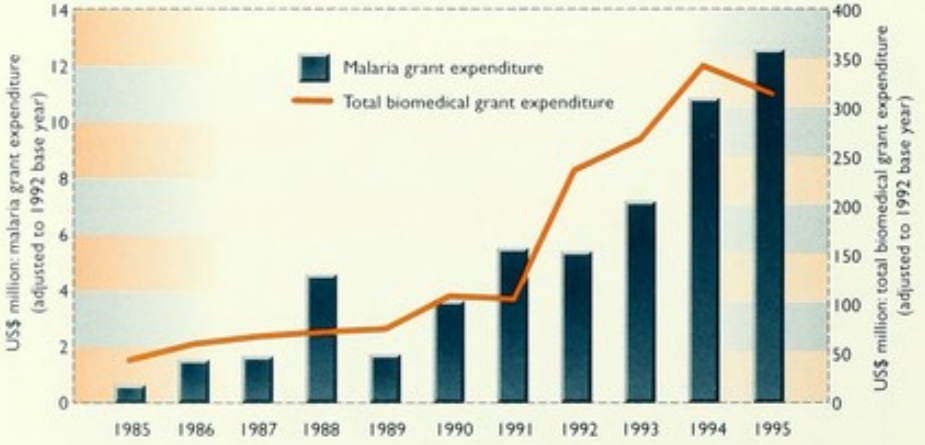


Figure 2.6: Wellcome Trust funding for all biomedical grants (excluding History of Medicine and Public Understanding of Science) and for malaria grants

[15] The Wellcome Trust employs a financial year consistent with the UK academic year running from 1 October to 30 September. Thus, FY 1993 = October 1992–September 1993.

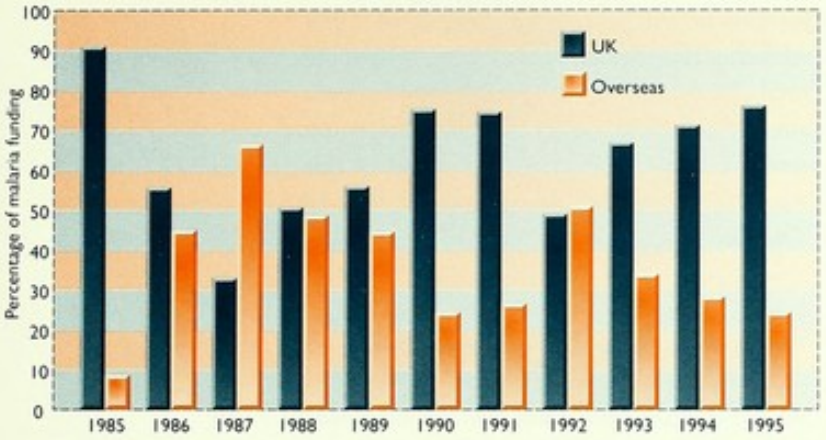


Figure 2.7: Wellcome Trust funding for malaria in the UK and overseas

of the funding portfolio of the Trust, has been approximately 3–4 per cent since FY 1993.

Funding for malaria overseas

In this study, 'overseas' support was defined as all funding provided for the support of research in Trust overseas units, regardless of the point of administration, and all grants with an overseas address. Grants awarded to UK universities but that involved field research in tropical countries were not included in the definition of overseas. Most of the increased support for malaria in the past five years has gone to institutions or individuals in the UK (see Figure 2.7). The proportion of research funding going overseas varied from 9 per cent of the total support for malaria research in FY 1985 to 67 per cent in FY 1987, with a mean of 38 per cent.

Support by the Trust for malaria research overseas over the period FY 1985–1994 (Figure 2.8) was greatest in Thailand and Kenya, followed by Australia and Vietnam. In Australia, most funding was through the Australian–New Zealand Fellowship Scheme. In Thailand, Kenya and Vietnam the support was principally for research units. Support was <5 per cent in each of Brazil, Switzerland, Germany, Sweden and the USA.

Funding for malaria by type of support

The breakdown of support for malaria by type of funding over the period FY 1985–1994 is shown in Figure 2.9. Just over one-third of support for malaria research was through personal fellowships that provide for both research costs and salary support for individual researchers. A similar amount was allocated to Trust overseas units located in Thailand, Vietnam and Kenya that are predominantly concerned with research into malaria, but whose research programmes also include other infectious diseases. Expenditure that was classified as 'units' support included research equipment, consumables, local salaries and infrastructure costs for the field research as well as resources in the UK to provide logistical backup and transport between the unit and the UK. Just under one-third of support was allocated through project and programme grants that provide research expenses and technical or research assistance. 'Other' expenditure includes support for equipment in UK institutes as well as funding for meetings.

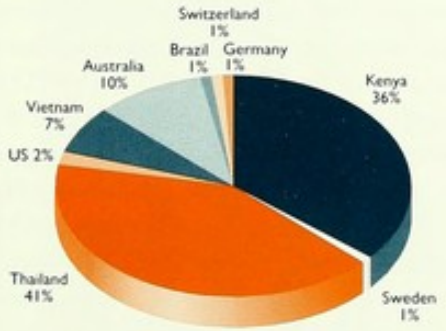


Figure 2.8: Wellcome Trust overseas funding for malaria by country
(% of funding 1985–1994)

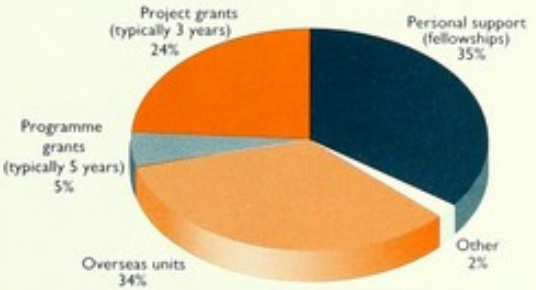


Figure 2.9: Wellcome Trust funding for malaria by funding mechanism type
(% of funding 1985–1994)

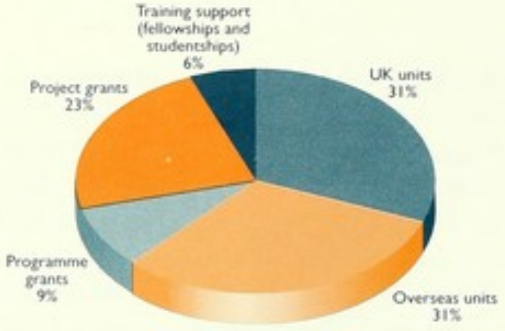


Figure 2.10: MRC funding for malaria by funding mechanism type
(% of funding 1993)

The Medical Research Council:

$6.8 million in FY 1993

The UK Medical Research Council (MRC)[16] is one of six government-funded research councils in the UK. The MRC supports research and training in biomedical and related sciences with the aim of maintaining and improving human health. It aims to meet the needs of the beneficiaries and users of biomedical research, including providers of health care as well as, for example, the pharmaceutical, biotechnology, food, health-care and medical instrumentation industries. Finally, the MRC provides advice on, and informs the public on, research issues in the biomedical sciences.

Table 2.2 MRC funding data

Year	Total science ($ million)	Malaria ($ million)	Malaria as % of total science
1983	286.4	4.2	1.5
1988	284.9	4.8	1.7
1993	377.0	6.8	1.8
1994	402.6	6.0*	1.5

*This does not include a figure for training.

In FY 1993, the MRC spent a total of $377 million on research. A total of $6.8 million of this was spent on malaria research. Thus, in FY 1993, the MRC spent 1.8 per cent of its budget on malaria. This represented a small increase on the proportion spent in FY 1983 when malaria accounted for 1.5 per cent of the total (Table 2.2). In FY 1993, the MRC spent almost one-third of its malaria budget on research overseas (Figure 2.10). Most of this was for the support of its overseas unit in The Gambia.

2.2.2 Medium-sized contributors

The Commission of the European Union:

estimated $2.6 million in FY 1993

In 1982, the Commission of the European Communities (now Union) implemented a research and development programme which aimed to mobilize science and technology in support of economic and social development in developing countries. Three generations of the Science and Technology for Development Programme (STD) have supported projects in agriculture and health, including malaria.

The third programme (STD3), with a budget of $56 million, covered the three years FY 1992–1994. Malaria was the largest single research topic, representing 14.1 per cent. Twenty-four projects costing $7.9 million, or about $2.6 million per annum, involved 109 partners from different countries.

The rationale of the STD programmes is strengthening research capabilities by forging collaborative links between research institutions in Europe and developing countries. The programme requires that each project has a minimum of two partners from different EU Member States and one partner from a developing country. An analysis of the geographical distribution of the funds allocated in STD3 to malaria research indicates that 75 per cent of the total awarded went to researchers in Europe, 13 per cent to researchers in sub-Saharan Africa and a further 7 per cent to researchers in 'Other, Asia and Islands' (Figure 2.11). However, an alternative analysis based on the number of countries involved in joint collaborative research indicates that European countries are included in 27 per cent of all partnerships, African countries in 43 per cent, and Latin America and

[16] The Medical Research Council has a financial year which runs from 1 April to 31 March. Thus, FY 1993 = April 1993–March 1994.

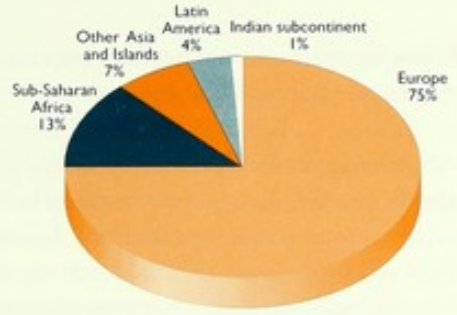


Figure 2.11: Destination of EU funding for malaria research between 1992 and 1994
(% of $7.9 million awarded during STD3)

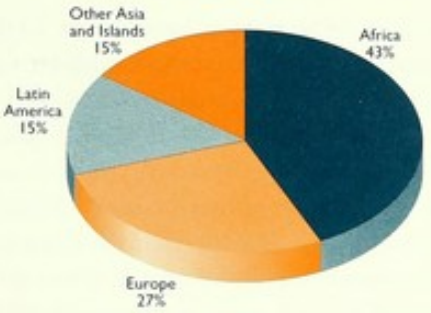


Figure 2.12: EU collaborative partnerships in malaria research between 1992 and 1994
(% of total number of countries collaborating in STD3)

'Other, Asia and Islands' each account for 15 per cent of all partnerships (Figure 2.12).

French National Institute of Health and Medical Research:

$2.3 million in FY 1993

The French National Institute of Health and Medical Research (INSERM) supports malaria research in France and abroad. The total budget for malaria in 1993, which represented approximately 1 per cent of INSERM's overall budget, was $2.3 million. Of this figure, $0.6 million was specifically for research and the remainder for salaries and equipment. Although the majority of projects being funded are located in France, INSERM provides grants to universities in Israel, Thailand and Mexico.

Centers for Disease Control:

$2.2 million in FY 1993

The US Centers for Disease Control (CDC), an agency of the US government, spent[17] an average of $1.5 million per annum on malaria research and control activities between FY 1984 and 1993. This represented approximately 0.3 per cent of CDC's total budget. In FY 1993, $2.2 million was allocated to malaria research and control. Over the past 10 years, there has been a doubling in support (Figure 2.13).

Malaria research at CDC over the past 10 years has been focused mainly on four areas: vaccine development and testing; field studies of malaria epidemiology and the effectiveness of population-based public health strategies; monitoring and investigation of domestic outbreaks and imported malaria cases; and the development of improved malaria diagnostic tools.

CDC has recently developed a programme of research on *Anopheles* biology and genetics that has received substantial support from the

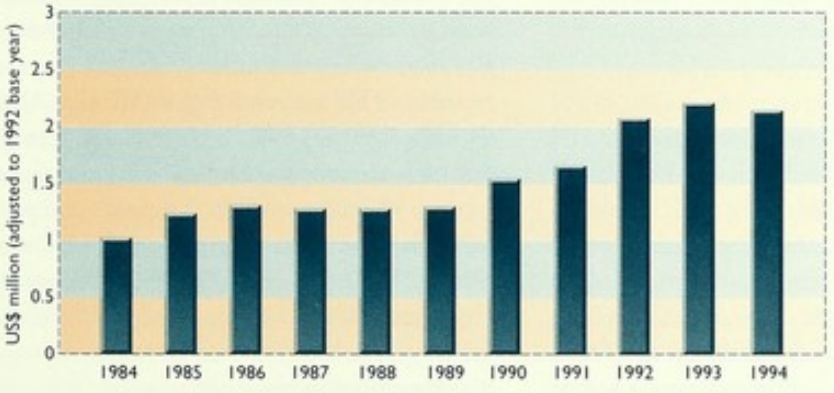


Figure 2.13: CDC spend on malaria research and control activities

[17] The CDC specifically indicated that 80–85 per cent of funds represent salary and related personnel benefits expenses for CDC employees engaged in malaria research and control activities, rather than for the activities per se.

MacArthur Foundation and the TDR Programme. CDC also provides support for staff and facilities at field research stations in Kenya and Guatemala.

Furthermore, the International Health Program Office (IHPO) of CDC has also supported malaria research and control. Given that these IHPO funds originated from USAID, they are not represented in the CDC data.

Australian National Health and Medical Research Council:

estimated $1.8 million in FY 1993

The Australian National Health and Medical Research Council (NHMRC) supported malaria research between 1986 and 1994 with a budget which increased from $0.18 million to $1.1 million. A block grant from NHMRC to the Walter and Eliza Hall Institute of Medical Research (WEHI) also supported research into malaria. In 1993, this grant was just over $5.4 million, of which approximately 12 per cent, or $0.7 million, went to the support of malaria research.

UK Overseas Development Administration of the Foreign and Commonwealth Office:

$1.6 million in FY 1992 (excluding another $1.6 million to the TDR Programme)

The Overseas Development Administration of the Foreign and Commonwealth Office (ODA) aims to promote the economic and social development of less developed countries. In so doing, it commissions and sponsors research on topics relevant to those countries receiving aid.

In FY 1992,[18] expenditure on medicine and health research in the Health and Population programme totalled $4.9 million. Two long-term projects within the programme were of particular relevance to malaria and had an annual combined cost of $1.6 million. Both of these were financed jointly by the ODA and other donors or institutions, most particularly the UK Medical Research Council. An analysis of data since FY 1989 showed that funding for medicine and health research and for malaria remained quite constant.

In addition to the Health and Population programme, the ODA supported research in the field of tropical public health at the London School of Hygiene and Tropical Medicine at a total cost of $17.8 million between 1990 and 1995 ($3.6 million in FY 1992). It also supported five work programmes at the Liverpool School of Hygiene and Tropical Medicine between 1990 and 1995 at a total cost of $7.4 million ($1.5 million in FY 1992). These work programmes covered other tropical diseases as well as malaria.

ODA also contributes to the TDR Programme ($1.6 million in FY 1992) and to the European Union's STD Programme.

International Development Research Centre:

$1.4 million in FY 1993 (excluding $1.0 million to the TDR Programme)

The Canadian International Development Research Centre (IDRC)[19] receives its core budget from the Canadian government, although increasing emphasis is being placed on generating co- and parallel funding.[20] Its total programming budget increased from $49.7 million in FY 1984 to $65.7 million in FY 1993. Between FY 1984 and 1993, malaria research was funded at a total cost of $4.4 million.

On average, 0.4 per cent of the IDRC's budget went to malaria projects. The exception was in FY 1993 when a total of $2.4 million was awarded. This included a grant of more than $1 million to the TDR Programme for the support of bed net trials. Over the 10-year period studied, 43 per cent of IDRC's support (as funds) for malaria went to countries in sub-Saharan Africa, 27 per cent went to Europe, 19 per cent to Latin America, and 10 per cent to Asia.

The Mexican Government:

$1.2 million in FY 1994

Data for the funding of malaria research in

[18] The Overseas Development Administration has a financial year which runs from 1 April to 31 March. Thus, FY 1993 = April 1993–March 1994. However, data were unavailable for FY 1993, and thus FY 1992 is presented.

[19] The IDRC uses a financial year from 1 April to 31 March. Thus, FY 1993 = April 1993–March 1994.

[20] The terms 'co-funding' and 'parallel funding' refer to funding provided by other donors to an IDRC-supported project. In the former, the additional funds are administered through IDRC. In the latter, the funds are provided directly to the recipient and are not administered through IDRC.

Mexico were obtained from the Pan American Health Organization (PAHO). The Center for Malaria Research in Mexico received over $1.2 million from the government in FY 1994. Data from other Mexican research funding agencies were not available.

Netherlands Directorate General for International Cooperation:

estimated $1.1 million in FY 1993

The Netherlands Directorate General for International Cooperation (DGIS), part of the Ministry of Foreign Affairs, supports research in tropical medicine. DGIS has estimated that it contributed approximately $2.4 million to the TDR Programme between FY 1987 and 1994. In the same period, approximately $7.6 million was allocated to malaria research, including the above TDR contribution which was earmarked for research into malaria. Given that these funds covered research over the period FY 1987–1994, an average annual expenditure on malaria may be estimated as $1.1 million.

John D and Catherine T MacArthur Foundation:

$1.0 million in FY 1993

The John D and Catherine T MacArthur Foundation (JCM) is one of the largest US philanthropic foundations. The Foundation supports programmes in mental health, tropical medicine, conservation, education, peace and international cooperation, mass communications, and individual creativity. It also supports cultural and community organizations. The expenditure of the Foundation rose from $96 million in FY 1984 to $148 million in FY 1993, of which an average of 15 per cent per annum was allocated to its Annual Health Program.

Between FY 1984 and 1993, two 10-year initiatives with relevance to malaria research were launched as part of the Annual Health Program. Support for the consortium and the network over the 10-year period FY 1984–1993 totalled over $38 million. Based on estimates given by individual grant holders, approximately 28 per cent of this, or an average of $1 million per annum, was allocated to malaria research. Over the 10-year period studied, 64 per cent of funds for malaria research went to groups working in North America. The consortium came to an end in 1993. The network is to continue until FY 1999 with an average annual budget of $1.2 million, although malaria will account for only a fraction of this sum.

French Institute for Scientific Research for Development and Cooperation:

$1.0 million in FY 1993

The French Institute for Scientific Research for Development and Cooperation (ORSTOM) allocates almost $1 million to malaria activities annually. Of this sum, approximately $0.85 million is expended in salaries, $0.02 million in training of people in malaria endemic countries, and only $0.08 million in research.

2.2.3 Smaller contributors

Rockefeller Foundation:

<$1 million in FY 1993 following the completion of a medium-sized funding project up to 1992

The Rockefeller Foundation is a private philanthropic organization. The Foundation's Health Sciences budget rose from $6.7 million in FY 1984 to $13.2 million in FY 1993. Two initiatives between FY 1984 and 1994 were relevant to malaria research. The Great Neglected Diseases (GND) supported research ranging from basic investigation in the laboratory to field studies. Between FY 1984 and 1987, the GND budget was in the region of $2.35 million per annum, of which an average $0.3 million was devoted to malaria research.

Between FY 1988 and 1992, the Health Sciences for the Tropics (HST) Programme aimed to transfer biomedical research competence for tropical diseases to developing countries. This was attempted through partnerships between countries from the northern and southern hemispheres. The TDR Programme funded the southern groups

with the Health Sciences Division of the Rockefeller Foundation supporting their northern partners. In its five years of operation, the HST budget averaged $1.8 million per annum, of which malaria received an average of $0.6 million per annum, or 4 per cent of the total Health Sciences budget. The HST Programme has not been renewed and the Rockefeller Foundation is not currently funding any large research programmes relevant to malaria.

Netherlands Organization for Scientific Research:

<$1 million in FY 1993

The Netherlands Organization for Scientific Research (NWO) is the largest Dutch organization in the field of fundamental and strategic scientific research, acting as the national research council in the Netherlands. In FY 1994, NWO received 10 per cent of the Dutch government's science budget with 37 per cent of the budget going directly to the 13 Dutch universities. The leading Dutch research institutes were funded from the remainder. NWO's budget in 1994 was approximately $181 million.

The NWO structure includes six Councils, representing different scientific fields, and two multidisciplinary foundations. One of these, the Netherlands Foundation for the Advancement of Tropical Research (WOTRO), promotes and coordinates research in tropical and developing countries. A search of WOTRO's records revealed that five grants had been awarded for malaria research in the past 10 years, at a total cost of approximately $0.5 million.

Danish Council for Development Research:

<$1 million in FY 1993

The Danish Council for Development Research is financed by the Danish Aid Organization (Danida) in the Ministry of Foreign Affairs in Denmark. Over the past four years (FY 1990–1993), Danida's budget for health research averaged $2.5 million per annum.

In FY 1988, a special programme administered by Danida was launched for developing countries, the 'Bilateral[21] Programme for Enhancement of Research Capacity in Developing Countries' (ENRECA). ENRECA's total budget between FY 1990 and 1993 was $7.6 million. Of this, $1.9 million, or roughly $0.6 million per annum, was allocated to four projects in the field of malaria. The objective of the ENRECA programme is to build up research capabilities in developing countries through the provision of training, equipment and other facilities, and by facilitating the participation of researchers from developing countries in global research cooperation. The remit of ENRECA covers health, agricultural, technical, social and natural sciences. All projects are awarded jointly between groups in Denmark and groups in a developing country. Two further malaria projects (not under ENRECA) were funded by Danida in FY 1993, at a cost of $0.3 million.

Danish Medical Research Council:

<$1 million in FY 1993

The Danish Medical Research Council (DMRC) has an annual budget in the region of $9 million per annum. The DMRC receives very few applications for malaria research; within Denmark, such research is handled by Danida. Over the past five years, the Council has funded four projects relating to malaria.

Swedish Medical Research Council:

<$1 million in FY 1993

The annual budget of the Swedish Medical Research Council[22] in FY 1995 was $37 million of which $21 million was used to fund about 800 research projects. Since FY 1987 the Council has given 63 grants for malaria research at an average annual cost of approximately $0.13 million, or a total cost of $1.3 million.

German Federal Ministry for Education, Science, Research and Technology:

<$1 million in FY 1993

An analysis of research funding in Germany is complicated by the fact that under the federal

[21] Bilateral projects are generally defined as those in which funding by the donor is made to a developing country.

[22] The Swedish MRC has a financial year which runs from 1 July to 30 June. The year 1994/95, which starts in July 1994, is referred to as FY 1995.

system, funding of higher education is the responsibility of individual states (Länder), while funding for research is the joint responsibility of the states and the federal government. Much of the basic research carried out in German universities and institutes is supported by funds from the state ministries.

At federal level, support for research may be provided by the Federal Ministry for Education, Science, Research and Technology (BMBF), the Federal Ministry of Health and the German Research Agency (DFG). Data from the DFG on support for malaria are not available at present. The Ministry of Health provides money to institutions for research; it does not sponsor individual projects on malaria research. Over the period FY 1985–1994, eight project grants in malaria research have been awarded by the BMBF at a total cost of approximately $6.6 million.

Swiss National Fund for Scientific Research:

<$1 million in FY 1993

The Swiss National Fund for Scientific Research (FNRS) had an annual budget in FY 1993 of over $100 million. Of this, just under half ($44 million) went to the Division of Biology and Medicine. However, between FY 1984 and 1994, only six malaria research grants were awarded and these totalled $0.55 million.

Swiss Tropical Institute:

<$1 million in FY 1993

The Swiss Tropical Institute also invests approximately $0.5 million per annum in malaria research. These funds originate from both the local and national governments, as well as through diagnostic and clinical services and research grants of bilateral/multilateral development projects. Research is conducted principally in Switzerland (35 per cent) and Tanzania (55 per cent), although there is also some support for Chad, Thailand, Papua New Guinea and India.

The Italian Government:

<$1 million in FY 1993

The Italian government allocates, on average, $0.3 million to malaria research per year. Of this figure, approximately two-thirds is spent in Italy. A total of some six to seven projects are funded annually, roughly half of which are located in the Istituto Superiore di Sanità. Research fields principally include epidemiology and diagnostics.

Canadian Medical Research Council:

<$1 million in FY 1993

The Canadian Medical Research Council (CMRC) introduced disease classification codes in FY 1988, hence statistics on support for malaria research are available from FY 1989 only. Since that year, the CMRC supported 11 grants in malaria research, at a total cost of just under $1 million (or an average of $0.18 million per annum). This represented approximately 0.1 per cent of the total annual budget. All grants went to Canadian universities or institutes.

The Pan American Health Organization:

<$1 million in FY 1993

The PAHO, which is part of WHO, has not been a major supporter of malaria research since the advent of the TDR Programme. Since FY 1988, eight malaria research projects have been supported at a total cost of $0.17 million.

Brazilian Funding for Studies and Projects:

<$1 million in FY 1993

Brazil has a large number of publicly supported research agencies, both federal and state, many of which conduct malaria research. However, most of these did not respond to requests for funding data. A survey of malaria research supported by the government department of finance for science and technology, Financiadora de Estudos e Projetos (FINEP), identified 10 projects over the past 10 years at a total cost of $1.2 million.

Venezuelan National Council for Science and Technology Research:

<$1 million in FY 1993

Data for the funding of malaria research in Venezuela were obtained from the PAHO. A survey of funding for malaria research by

national research organizations in Venezuela identified 45 projects between FY 1987 and 1993 at just over $1 million. The National Council for Science and Technology Research (CONICIT), a government research agency, supported 16 of these at a total cost of $0.85 million. A further 29 malaria projects were supported by assorted industrial concerns and the PAHO.

Australian Department of Industry, Science and Technology:

<$1 million in FY 1993

The Australian Department of Industry, Science and Technology (DIST)[23] funded malaria research at the Walter and Eliza Hall Institute over the period FY 1989–1994 at a cost of $2.6 million. Additionally, the DIST supported research in malaria vaccine development, principally through a programme named Saramane which is a joint venture between the Australian government and Roche of Switzerland for clinical trials in Brisbane and Papua New Guinea. Public funds devoted to vaccine development, mainly through Saramane, have totalled approximately $4.3 million over the period FY 1981–1994.

Australian Research Council:

<$1 million in FY 1993

The Australian Research Council (ARC) is funded by the Department of Employment, Education and Training (DEET). The ARC allocated approximately $0.24 million to malaria research over the period FY 1989–1993. Support for malaria is increasing at the Council and the malaria research allocation for FY 1994–1998 has already doubled the spend from the previous period.

South African Medical Research Council:

<$1 million in FY 1993

The South African Medical Research Council[24] (SAMRC) is the main source of funds in that country for biomedical research. One of eight research councils, its annual budget from the South African government increased more than threefold between FY 1985 and 1993. Prior to FY 1991, the proportion spent on malaria research stood at less than 0.1 per cent of the total. In FY 1992 and 1993, the proportion of the MRC's annual budget allocated to malaria rose to 1.9 per cent of the total public expenditure, equivalent to approximately $0.4 million. However, most of this figure represents salaries and other overheads. The annual public allocation specifically for grants in malaria research itself is typically around $0.06 million per annum.

In FY 1993 a new source of funds for malaria research was introduced through the SAMRC. The Health Systems Trust, which is funded from three sources including the South African government, the European Union and the Karzzer Family Fund in the USA, currently funds research in malaria with an annual budget of approximately $0.07 million. Malaria research at the SAMRC is also supported by commercial funds. Approximately $0.05 million is received direct from pharmaceutical and insecticide companies including Imperial Chemical Industries, Agroeva Insecticides, Biyer Pharmaceuticals, Merz Pharmaceuticals, Firmenich Pharmaceuticals, and Byk-gulden Pharmaceuticals.

South African Institute for Medical Research:

<$1 million in FY 1993

The South African Institute for Medical Research (SAIMR)[25] is a not-for-profit organization which funds malaria research principally through its Department of Medical Entomology. The average annual budget over the past 10 years for research in malaria is about $0.08 million. These funds derive principally from the provision of laboratory diagnostic services by the SAIMR to provincial and private hospitals. Malaria vector research comprises roughly 80 per cent of the annual budget of the Department of Entomology. Types of support include salaries, equipment, running costs and consumables for training. All projects are undertaken at SAIMR and field work is conducted in South Africa, Botswana, Mozambique, Zimbabwe and Tanzania.

[23] The DIST financial year is from 1 July to 30 June.

[24] The South African Medical Research Council utilizes a financial year which runs from 1 April to 31 March.

[25] The financial year at the SAIMR runs from 1 January to 31 December.

2.3 SUMMARY

Collecting comparable and reliable international funding data presented a difficult challenge. In this survey, organizations were asked to provide information on awards for malaria research over the past 10 years, and if possible to provide lists of specific projects. By adopting this approach, it was hoped that some of the pitfalls associated with this type of data collection would be avoided. Nevertheless, gaps and omissions were inevitable.

The total identifiable expenditure on malaria research worldwide for 1993 (using 1992 as a base year) is of the order of $84 million per year (Table 2.1). Even though this figure may not include sources of funding that were hard to detect, it is clear that funding for the field is very low in comparison with other major disease areas.

Malaria research funding in perspective

One way of looking at relative research expenditure on different disease areas is to calculate the number of deaths associated with a disease, and compare this with research investment. A recent estimate puts global malaria deaths in 1993 at 2 million (WHO, 1995d), and comparing this with the global research expenditure in the same year (from the present study) produces a figure of about $42 per fatal case. Comparative figures for other disease areas are difficult to obtain, but rough estimates may be made from data published by WHO, as shown in Table 2.3. This approach suggests that research expenditure on malaria was about $65 per fatal case in the early 1990s; a similar estimate to that for 1993 derived from the present study.

It should be noted that the main difference in these two estimates is that the $65 figure is produced by using an estimate of 926 400 malaria deaths per year, whereas the $42 figure is produced by using the more recent figure of 2 million deaths per year. Comparisons between data from the present study and from figures in WHO publications suggest that global research expenditure per death for tuberculosis is of the same order of magnitude as for malaria. However, research investment per fatal case is about 80 times greater for HIV/AIDS, and 20 times greater for asthma than it is for malaria. These differences are so great that they will not be markedly affected by using alternative published estimates of the global mortality rate for malaria.

Another way of putting malaria research expenditure into perspective is to compare it with well-documented data on research spending on an established disease in an industrialized nation. Taking cancer in the UK as an example, it may be estimated that the total public and non-profit expenditure in 1993 (including government and charitable sources) was about $225 million (based on data from AMRC, 1994; MRC, 1994; Department of Health, 1995). This equates to about $1525 per UK cancer death (using a mortality figure of 147 461: Office of Health Economics, 1995). If research funding from industrial sources were included, this figure would be

Table 2.3 Global expenditure on research per associated death for various diseases

Diseases	Annual global research expenditure ($ million) (estimated from data for 1990–1992)[26] (Michaud and Murray, 1996)	Global mortality (1990: thousands) (Murray and Lopez, 1994)	Estimated global research expenditure ($) per fatal case worldwide (circa 1990)
HIV/AIDS	952	290.8	3274
Asthma	143	181.3	789
Malaria	60	926.4	65
Tuberculosis	26	2015.5	13

[26] The figures for annual global research expenditure are estimated from data for 1990–1992 from all sources – government and public agencies, non-profit organizations, and the pharmaceutical industry.

much higher. The most striking conclusion to be drawn from this is that public research spend on this one disease, in one medium-sized nation, is more than twice the global spend on malaria research from all sources.

Taken together, the conclusion from these various (albeit imperfect) comparisons is clear. Diseases such as cancer, as well as HIV/AIDS and asthma, receive markedly higher levels of research funding than does malaria (and tuberculosis). This is true in terms of absolute levels of funding and research spend per death.

Trends in international support

Internationally, the USA is currently the largest contributor to malaria research. However, overall support in the USA has been decreasing over the past 10 years. Figure 2.14 presents the change over time in the malaria spend by the six largest investors, grouped by geographical region, in malaria research. The evident reduction in USA spend can be attributed to the decrease in the USAID budget. Total malaria expenditure in the UK has been increasing over the past decade, and the Wellcome Trust has become a major global sponsor of malaria research.

The UK also has an increasing presence in funding research carried out specifically in malaria-endemic countries. Indeed, the combined research expenditure in those countries by the Wellcome Trust and the UK MRC exceeds the combined expenditure of the TDR Programme and the EU in those same countries. The Wellcome Trust, with nearly twice the spend in these countries compared with the MRC, supports malaria research in endemic countries at an amount which is very similar to that of the TDR Programme.

Comprehensive data on expenditure by the private sector, such as the pharmaceutical industry, could not be obtained. However, private-sector funding of malaria research is expected to be small at present. Nonetheless, the increasing wealth in some tropical countries (in particular Asia/Pacific) may lead to greater research investment in tropical diseases by the drugs industry of both malaria-endemic and non-endemic countries.

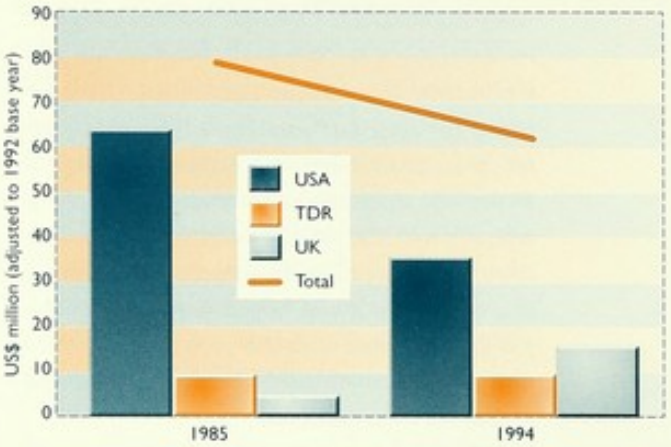


Figure 2.14: Funding for malaria research from the major contributors by geographical region
(the reduction in US spend can be attributed to a decrease in the USAID budget)

The current uncertainty in the USA over the future of the so-called 'orphan drug tax credit' (Wadman, 1996) may influence investment into malaria research by the American pharmaceutical industry. The credit, which has had broad support from the drugs industry, allows American companies to deduct half of the costs of clinical testing of drugs which target diseases that are rare in the American population (defined as affecting fewer than 200 000 Americans). However, the credit has now expired without a clear indication of its renewal. This can only reduce the incentive for industrial investment in malaria research.

In the previous chapter, an assessment of the funding provided for research was used as a proxy measure of scientific activity. An alternative approach to assessing activity is based on measures of research output. The two approaches are complementary, and together allow for a robust analysis of the state of scientific activity in a particular field.

3.1 BACKGROUND

3.1.1 Research outputs and research outcomes

The results of biomedical research include both outputs – such as new knowledge, papers and patents – and outcomes – such as the development of new products or improvements in health care. Measurements of the outputs of research, which are more accessible than measurements of the outcomes, are explored in the present chapter.

Direct outputs may be quantified by a number of methods which assume that for new knowledge to be of value to a wide audience, it must be published. The method of bibliometrics (measurements of publication output) is the accepted approach to assess direct output from scientific activity. Bibliometrics captures advances in codified knowledge[27] which are published in international journals. It does not measure advances in tacit knowledge, nor does it cover publications which are not included in peer-reviewed international journals. However, research has indicated that there is a high correlation between the findings of bibliometric analysis and other more qualitative approaches to assessing output (Narin, 1976).

3.1.2 Bibliometric analysis

The current analysis of malaria research employed three bibliometric measures: the number of publications, both internationally and nationally – a quantitative indicator of research activity; the number of citations to those publications – a qualitative indicator of the direct impact of the publications; and the extent of coauthorship – an indicator of international collaboration. Analyses were based on three years of publication – 1984, 1989 and 1994 – which permitted trend analysis over a 10-year period.

An assessment was also made, using acknowledgements quoted in the publications, of the sources of financial support for the research. Acknowledgements analysis is a valuable mechanism which enables funding organizations to identify, in an international context, the extent of their contribution to scientific outputs. This information helps the organizations to evaluate the research they support and to develop new policies for the future. In the present study, this analysis also provided a double check on the major sources of funding for malaria research identified in the funding survey.

3.1.3 Limitations of bibliometric analysis

The databases used for the analyses were the Science Citation Index (SCI), produced by the USA Institute for Scientific Information, and the Research Outputs Database (ROD), developed by the Wellcome Trust. Whereas the SCI includes citation rates of publications, the ROD links published papers to their acknowledged sources of support.

The SCI has been criticized as being biased towards the USA and Europe in terms of its journal coverage. Indeed, estimates of the omission in SCI of publications by scientists in developing countries is as much as 90 per cent (Sancho, 1992). The missing publications, the so-called 'grey literature', are published in local or non-English journals. This omission is an important consideration for the field of malaria, which predominantly affects developing countries and is of local interest to researchers in those countries.

[27] Codified knowledge is that which is systematically expressed in a language or number code. Tacit knowledge is that which is understood or implied without being stated.

An alternative database produced by the USA National Library of Medicine, Medline, is thought to cover a more comprehensive set of journals related to medical research, including those which are more clinically oriented as well as those written in a language other than English. Medline also has the advantage of providing abstracts for most of its articles. A comparison of the Medline and SCI databases in the field of malaria indicated that, over time, the number of publications specific to Medline was decreasing (Figure 3.1). Meanwhile, the number of malaria publications specific to SCI was increasing, as was the number of publications common to both Medline and SCI.

A major disadvantage of Medline is that it does not record all the addresses listed on a paper, but only that of the first author. Furthermore, Medline does not provide information concerning citations to published papers. For these reasons, the bibliometric analysis presented in this chapter relied on the SCI database. However, the Medline database was used in the subfield analysis of Chapter 4, where the benefits of the inclusion of an abstract, as well as the greater coverage of clinical and epidemiological journals, outweighed the disadvantage of a limited number of author addresses.

As a clearly defined clinical area, malaria presented fewer problems of definition than other more basic or multidisciplinary research fields. Published papers were therefore relatively easy to identify. As in all the analyses, the scope of the bibliometric studies included research on the malarial parasite and disease, as well as vector studies and operational research. For comparative purposes, some data on the fields of tropical medicine and biomedicine are also included.

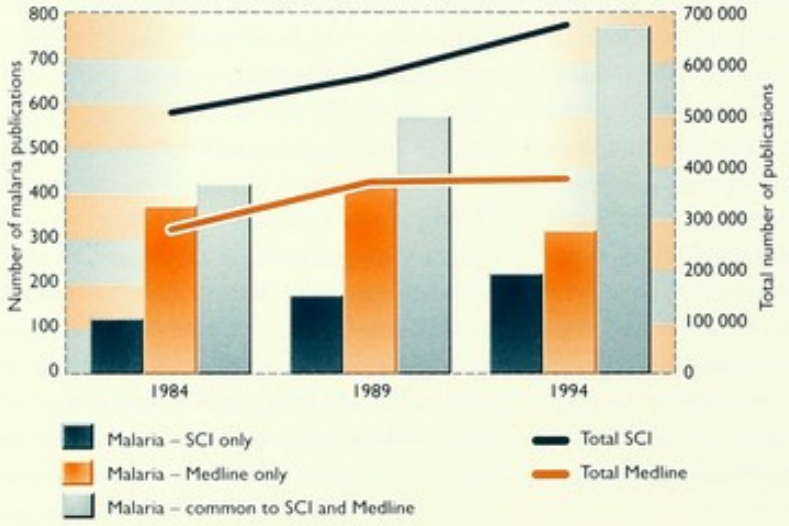


Figure 3.1: Trends in output of malaria papers relative to the total number of records in SCI and Medline databases (1984–1994)

3.2 METHODS

The first step in the analysis was to set the boundaries of the field of malaria research. A variety of methods exists to define a subject field for bibliometric analysis. These include identifying a specialist journal set or using a specialist subject database, using co-citation analysis, applying keywords to a general biomedical database, or using an international classification scheme (Balmer and Martin, 1991; Rogers and Anderson, 1993). The method used in the present study was the application of keywords to a general biomedical database.

The field of malaria research was defined in a two-step process shown below (Box 3.1). Three types of publication – articles, notes and reviews – were included in the analysis. These types are considered to contain substantial original scientific material (Anderson *et al.*, 1988; Leydesdorff, 1988). Letters (apart from those to *Nature*), meeting reports, news and editorials are viewed as peripheral and were thus excluded from the analysis.

In the first step, titles from the SCI were searched using a set of precise keywords relating to malaria research (antimalaria*, malari*, *Plasmodium* or Plasmodia*). This step produced a set of papers that were accepted unconditionally. In the second step, another set of keywords that related to antimalarial drugs and mosquitoes was employed in a search strategy that produced a broader range of publications, only some of which were relevant to malaria research. Irrelevant publications were excluded by searching for an additional set of keywords that related to other diseases transmitted by mosquitoes or treated with antimalarial drugs. The remaining conditional set of publications was then manually reviewed in order to eliminate those that were obviously beyond the remit of the study. The results of this two-step approach were combined to produce a final total set of malaria publications. The search strategy is shown in Annex 1. The field of tropical medicine was defined by a similar process (Lewison and Seemungal, 1995), and data on the size of the field were included for comparative purposes.

In order to determine the publication output for each country, malaria records identified from the three-year sample of the SCI were analysed on the basis of the addresses of their authors. Addresses were analysed using integer counts.[28] Consequently, the figures should be interpreted as the number or percentage of publications in which a country participated (rather than the number or percentage of publications exclusively produced by a country). This is a useful method of calculating and assessing publication data given increasing collaboration between institutions and between countries (Katz *et al.*, 1995).

Box 3.1 Two-step process for identifying malaria publications

[28] Analyses of publication numbers may be on the basis of integer counts or fractional counts. In integer analysis, each country address on a publication receives a whole, single number for the publication – e.g. if a paper has one UK address and two US addresses, each of the UK and the US receives 1.0 publication count. In fractional analysis, each country address on a publication receives a fraction of the total number of country addresses on the publication – e.g. for the above example, each of the UK and the US receives 0.5 of a publication count. NB: it is also possible to analyse publication output at the institutional rather than the national level.

Box 3.2 International collaboration/coauthorship index

$$\frac{\dfrac{\text{Number of UK papers coauthored with country X}}{\text{Number of UK papers internationally coauthored}}}{\dfrac{\text{Total number of papers with at least one country X author}}{\text{Number of world's papers – number of papers with only UK authors}}}$$

Patterns of coauthorship of malaria papers between the UK and other countries were also analysed. An index of coauthorship was calculated using the total number of UK–foreign collaborations and the number of papers produced by the UK and the country being studied (Box 3.2).

Financial support for research was assessed by analysing acknowledgements to funding bodies and, for intramural support, addresses on papers. This was done by manually examining, in libraries, the acknowledgements given on each malaria publication.

Citations to papers published in 1984 and 1989 were counted for the five years following publication – 1984 to 1988 and 1989 to 1993, respectively. The citation data were from all documents indexed in SCI rather than on just articles, notes and reviews. Reference or norm citation values were determined for each set (1984 or 1989) of malaria publications over each five-year period. These values defined three standards of citation frequency – the 10 per cent norm, the 25 per cent norm and the 50 per cent norm. The 10 per cent norm defined those papers which received the most citations – those which were in the top decile group of citation counts. The 25 per cent norm defined those papers which were in the top quartile group of citation counts, and the 50 per cent norm defined those papers which received more than the median number of citation counts.

A separate analysis was conducted of the citation counts of papers acknowledging support from each of the major funding organizations of malaria research. By comparing the citation profile for each major funding body with that of the combined sample of malaria publications, it was then possible to identify whether the research funded by a particular organization had a greater or lesser citation impact than the combined sample norm.

Given the limitations of the SCI database discussed above, the results presented below should be interpreted with the potential bias toward Europe and the USA in mind.

3.3 RESULTS

3.3.1 Publication output

The total number of malaria papers identified in the three-year sample was 2307, which represented an average of 17.8 per cent of all papers in tropical medicine (Table 3.1). The percentage increase in the number of malaria publications over the period was 82 per cent, significantly more than the 50 per cent increase in tropical medicine papers over the same period.

The country which participated in the largest number of scientific publications in the three years studied was the USA (Table 3.2). Just over 37 per cent of the world's output of

Table 3.1 The number of international publications in malaria and tropical medicine, and malaria publications as a percentage of tropical medicine publications (data based on SCI)

Year	Malaria (Number of publications)	Tropical medicine (Number of publications)	Malaria as a % of tropical medicine
1984	542	3317	16.3
1989	776	4500	17.3
1994	989	4960	19.9

Table 3.2 Number of published papers by country

Country	Number of malaria publications (1984, 1989 and 1994)	National malaria publications as % of world malaria publications (1984, 1989 and 1994)	National biomedical publications as % of world biomedical publications (1993) (Barre *et al.*, 1994)
USA	858	37	38.5
UK	378	16	11
France	178	8	5
Australia	136	6	2.4
India	122	5	N/A
Thailand	121	5	N/A
Germany	106	4.5	5.8
Switzerland	79	3	N/A
Netherlands	78	3	2.5
Kenya	59	2.5	N/A

malaria publications had at least one USA author. This value was similar to 1993 USA biomedicine publications as a whole. The UK had the second highest share of global output in malaria at 16 per cent. This was higher than the overall UK contribution to biomedical research in 1993. This finding is supported by other data which indicate that the UK percentage publication share ranges, for 16 broad areas of biomedicine, from 6.9 per cent in physiology to 16.1 per cent in psychiatry (Lewison and Seemungal, 1995). Relative to other areas of biomedicine, France and Australia were also relatively strong in malaria research. Three malaria-endemic countries – India, Thailand and Kenya – also had a high share of global malaria publications.

The malaria publication record for each country as a percentage of world total number of malaria publications is shown in Figure 3.2. It is evident that there was a decline in output from the USA from over 40 per cent of the world total in 1984 to <35 per cent in 1994. Publication share also decreased steadily in India. Countries whose share of the output has increased since 1984 included the UK, France, Switzerland, Australia and Thailand.

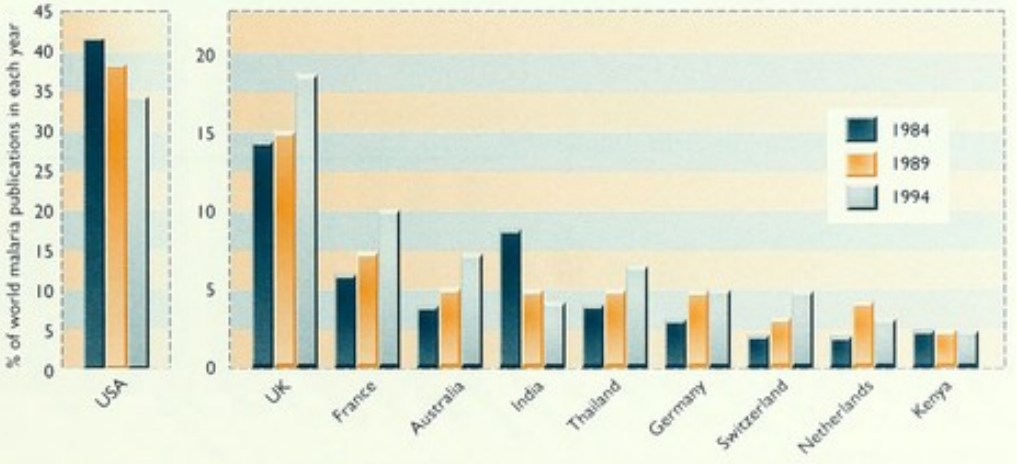


Figure 3.2: Analysis of malaria publications by year from the 10 countries with the highest publication output

3.3.2 International collaboration

Data on coauthorship in the publications of 1984, 1989 and 1994 were averaged to give an indication of the extent of collaboration over a 10-year period (Figure 3.3). A total of 142 out of 378 UK papers published in these years (38 per cent) were internationally coauthored. The coauthorship index indicated the strength of collaboration in malaria research between the UK and other countries. The higher the index, the stronger the association between the UK and that country. A value greater than 1.0 indicates that collaboration was greater than might be expected, given the number of malaria papers produced and coauthored by these countries internationally.

As might be expected, the results indicate that UK collaboration was very high with the three countries in which the Wellcome Trust and the MRC have their units overseas – Kenya, Thailand and The Gambia. There was also high collaboration with Malawi and Papua New Guinea, indicating that additional international links exist. High UK coauthorship with Papua New Guinea can be accounted for mainly by collaboration with Australian scientists who have established field research links there. Collaboration was lower between the UK and certain European countries and the USA. UK coauthorship appeared primarily to reflect collaboration with malaria-endemic countries, rather than geographical proximity. As the total number of UK malaria papers is relatively small, it should be recognized that collaboration by individual researchers may influence the levels of coauthorship with other countries.

3.3.3 Acknowledgements to funding organizations

The main funding bodies supporting malaria research are listed in Table 3.3 and Annex 2. A total of 2242 publications were examined for this analysis – 65 out of the 2307 malaria publications identified from the SCI were not located, hence funding acknowledgements for those publications could not be determined. An explicit acknowledgement to one or more funding bodies was identified in 78 per cent of the publications examined.

Overall, the greatest number of funding acknowledgements were to the TDR Programme, followed by NIAID, the USA Department of Defense, the UK MRC, USAID and the Wellcome Trust.

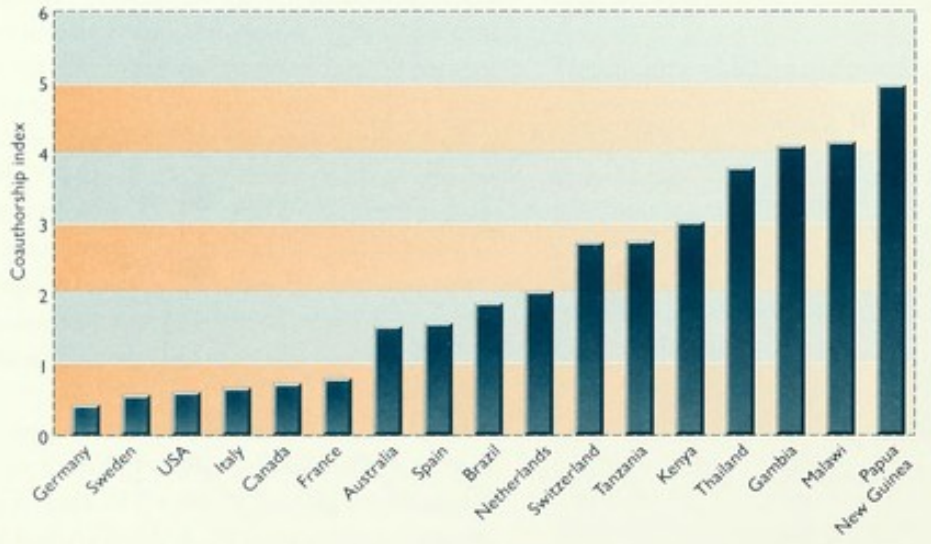


Figure 3.3: International collaboration with the UK in malaria research (1984–1994)

Table 3.3 Acknowledgements to funding bodies (1984, 1989 and 1994)

Funding body	Papers acknowledged
TDR Programme[29]	412
National Institute of Allergy and Infectious Diseases (NIAID) (USA)	294
US Department of Defense	206
Medical Research Council (UK)	160
US Agency for International Development (USAID)	149
Wellcome Trust (UK)	134
Australian National Health and Medical Research Council	85
Centers for Disease Control (CDC) (USA)	83
Institut National de la Santé et de la Recherche Médicale (INSERM) (France)	65

[29] The World Bank, the UNDP and the WHO co-sponsor the TDR Programme. However, many countries and organizations also make financial contributions to the Programme (see Chapter 2). The figure of 412 acknowledged papers is derived from a common 412 papers acknowledging each of the Programme co-sponsors. While both the UNDP and the World Bank had 412 papers acknowledged, the WHO had 507. The additional 95 WHO-acknowledged papers were considered to be funded through research programmes other than TDR.

The acknowledgements data compare well with the analyses of funding support (Chapter 2), with all the top funding organizations appearing as the most frequently acknowledged sources of support. However, a number of organizations appeared in the funding acknowledgements but not in the survey of funding. This was possibly a result of the difficulty in identifying the less obvious funding bodies located in developing countries. These included, among others, the Indian Council of Science and Industrial Research, the Kenya Medical Research Institute, the Papua New Guinea government, and the Health and Family Welfare Ministry of India (see Annex 2).

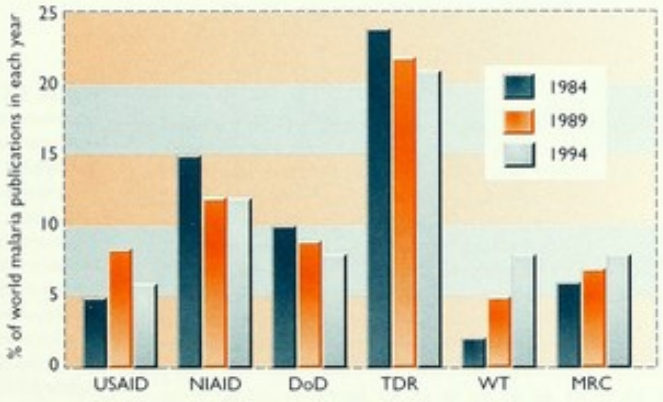


Figure 3.4: Publication acknowledgements by year for the six largest contributors to malaria research

Four industrial organizations were also identified in the acknowledgements analysis (see Annex 2). Hoffmann-La Roche, SmithKline Beecham, Wellcome Foundation / Wellcome plc (now Glaxo Wellcome plc) and Imperial Chemicals Industries were each acknowledged. These commercial organizations clearly had an interest in malaria research, but it is not possible with these data alone to assess the extent of their investment.

The acknowledgements analysis for the six largest contributors is shown in Figure 3.4. The results are expressed as the percentage share of the world's malaria publications in each year. The analysis indicated that both the Wellcome Trust and the MRC showed an increase in their percentage share of world publications over each of the two periods, from 1984 to 1989 and from 1989 to 1994. The percentage share of acknowledgements to the TDR declined over time, as did those to the US Department of Defense. There was some fluctuation in acknowledgements to both USAID and NIAID.

3.3.4 Citations to publications

Citations to malaria papers published in 1984 and 1989 were analysed for the five years following publication. The results of the analysis for the entire set of malaria papers published in 1984 are presented in Figure 3.5. This analysis

defined the reference or norm citation values for that year. Half of all 1984 malaria papers had five or more citations in the five-year period following publication – the 50 per cent norm. One-quarter of the publications had 11 or more citations – the 25 per cent norm. Finally, one-tenth of the publications had 23 or more citations – the 10 per cent norm. Thus, any papers which received 23 or more citations were in the top decile of the entire 1984 set. Papers which received between 11 and 22 citations were in the top quartile, and those which received between 5 and 10 citations were above the median of the entire 1984 set. A similar analysis identified the norm values for the 1989 malaria publications: 4 for the 50 per cent norm, 11 for the 25 per cent norm, and 22 for the 10 per cent norm.

The citations to those publications which acknowledged the six largest contributors were analysed separately in order to identify whether the research which they funded had a greater than expected impact in relation to these norms (Figure 3.6). As a consequence of the integer-counting method used in the analysis, those papers which acknowledged more than one funding source were attributed to more than one funding body. Thus, the analysis must be interpreted as the participation of a funding organization, and not necessarily the exclusive support of that organization. Furthermore, the small number of papers involved in parts of the analysis – for example, there were only 11 papers acknowledging the Wellcome Trust in 1984 – should be recognized. Citations to all funding organizations excluding the top six were aggregated and included in the analysis for comparative purposes. Likewise, citations to papers which did not acknowledge any funding body were aggregated and included in the analysis.

Papers acknowledging the support of the six largest investors in malaria research had more citations than the aggregated set of all malaria papers. These results indicate that the work of the six largest funding organizations had the highest direct impact in the published malaria literature.

Comparing these top six funding bodies, three organizations – USAID, NIAID and the MRC – had a particularly high proportion of their papers in the top decile. By definition, it would be expected that these organizations would each have only 10 per cent of their papers in the top decile, if their performance was in line with the world norm. However, all had more than 20 per cent of their papers in the top decile. The remaining three funding bodies – the DoD, the Wellcome Trust and the TDR Programme – were also well represented in the top decile. Each of these organizations had more than 10 per cent of their papers in the top decile.

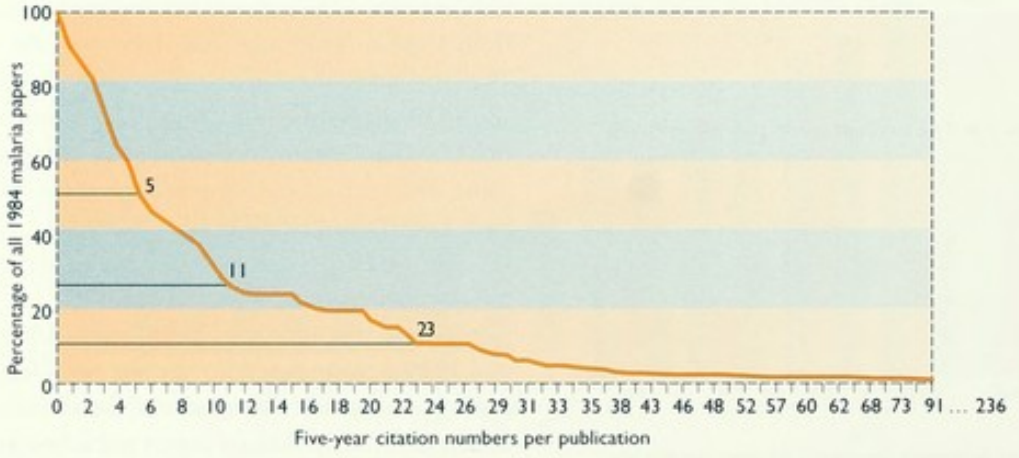


Figure 3.5: Norm citation values for malaria papers published in 1984.
The graph shows that 50% of all malaria publications had 5 or more citations in the five years following publication; that 25% of all malaria publications had 11 or more citations in the same period; and that 10% of all malaria publications had 23 or more citations in the same period.

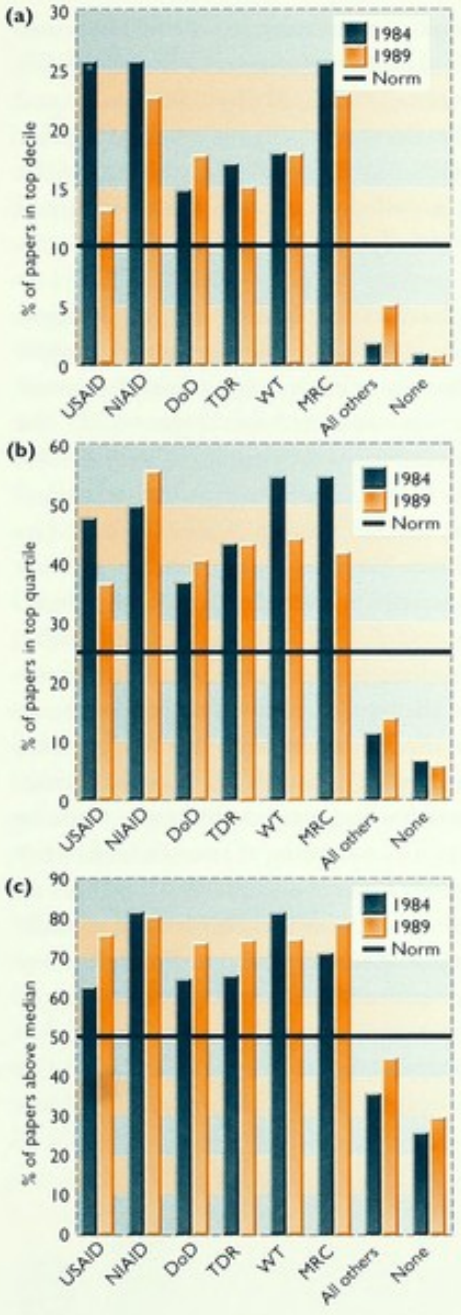


Figure 3.6: The percentage of papers with five-year citation numbers greater than or equal to the norm citation value for 1984 and 1989: (a) the top decile, (b) the top quartile, and (c) the top half of citations. The analyses include (i) those papers acknowledging each of the six largest contributors, (ii) those papers acknowledging all other funding organizations including those papers with no acknowledgements ('all others'), and (iii) those papers with no acknowledgements ('none')

Over time, the percentage of USAID publications in the top decile decreased in 1989 to half of what it was in 1984. Downward trends were also exhibited by NIAID, the TDR Programme and the MRC. An upward trend was exhibited by the DoD. The Wellcome Trust's representation in the top decile remained stable.

Full details of the 10 most highly cited malaria papers of 1984 and 1989 are given in Annex 3. The most highly cited paper of 1984 was supported by the DoD, the National Cancer Institute and NIAID. In 1989, the most highly cited paper was supported by the Burroughs Wellcome Fund, the FNRS in Switzerland, the National Institutes of Health, Sandoz Stiftung, the Wellcome Trust, and the TDR Programme cosponsors.

3.4 SUMMARY

The bibliometric analysis was based on publication records in the SCI. It excluded grey literature published in local or non-English journals. Estimates of the size of the grey literature are difficult to obtain, but work on the science and technology community in Thailand has suggested that international journal publications may form only 9–10 per cent of that country's total scientific literature (Anderson, 1991). This value is much in line with previous calculations that the SCI misses 90 per cent of publications by scientists in developing countries (Sancho, 1992). Unfortunately, a systematic analysis of outputs in the grey literature is not possible given that it is not included in any comprehensive database. The analysis in this chapter therefore only gives an insight to publication performance in the international scientific literature.

The number of malaria publications worldwide was low. However, their number increased by 82 per cent over the period 1984 to 1994. Compared with other fields of biomedicine, malaria publications accounted for

approximately 0.3 per cent of the world's total biomedical research output in 1994 (based on a PRISM estimate of 325 000 biomedical papers per annum). This figure can be compared with that calculated for cardiovascular biology, which contributes 18–19 per cent of the world's biomedical research (Rogers and Anderson, 1993).

The largest producer of malaria papers in the three years studied was the USA, but the trend in the USA over time is downward. The number of publications by the UK was strong on an international basis and the trend with time was upward. Papers supported by the Wellcome Trust and the UK MRC were increasing with time, thus accounting for much of the increase in the UK total. These trends in output mirror the trends in funding (Chapter 2), thus providing further confidence in the findings.

An average of 38 per cent of all UK papers were internationally coauthored. International coauthorship was very high between the UK and the three countries in which the Wellcome Trust and the MRC have their units overseas – Kenya, Thailand and The Gambia. However, collaboration was also very high with Malawi, Papua New Guinea, Tanzania and Switzerland – suggesting that additional collaborative links exist. Geographical proximity with the UK did not appear to be an important factor in determining coauthorship in malaria research.

International collaboration in scientific research has been identified more as a feature of tropical medicine research than of other areas of biomedical research (Narin and Whitlow, 1990). This feature is supported in the current analysis by the high coauthorship in malaria, compared with cardiovascular science (Anderson *et al.*, 1994). In malaria, the maximum coauthorship index was 5.0, as compared with 1.6 in cardiovascular research. As with the global pattern of outputs, the international collaboration pattern in malaria research is substantially different from that of other research areas.

The organizations receiving the highest number of acknowledgements were the TDR Programme, followed by the DoD and NIAID. Acknowledgements were also high for the MRC, the Wellcome Trust and USAID. The acknowledgement data identified several sources of support in the private sector.

A rough analysis of the acknowledged participation in published papers by the six largest contributors, relative to their financial investment, was conducted (see Figure 3.7). The analysis was based on papers published in 1994 and on funding in 1990. This four-year timelag was selected because of limitations in data availability. However, most research is probably published two to four years after receiving funding support (PRISM, unpublished data). Nonetheless, caution is urged in the interpretation of the results because there is no direct or simple relationship between input and output, especially over any delayed period of time. Furthermore, no attempt has been made to account for co-funding of research which may vary greatly between organizations. Likewise, no account was taken of variable overhead expenditures associated with research. These also vary with country and with funding-body type.

The analysis indicates that between three and 23 acknowledgements to the largest contributors

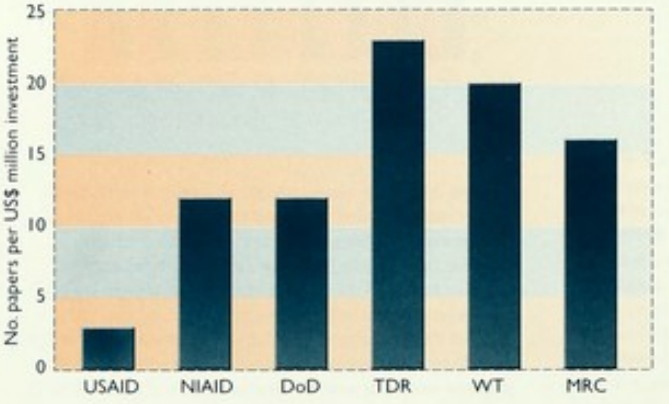


Figure 3.7: Ratio of the number of 1994 acknowledged papers to 1990 investment for the six largest contributors.
(NB. 1990 funding data were unavailable for the MRC; its 1988 figure has been used instead)

were made in the scientific literature for every million dollars they each invested. The TDR Programme and the Wellcome Trust had the highest number of acknowledgements per unit of investment. These were very closely followed by the MRC. The DoD and NIAID had fewer acknowledgements per million dollars. Finally, the USAID had the fewest acknowledgements – roughly sevenfold less than TDR and the Wellcome Trust per million dollars invested. However, interesting though these findings are, they should not be taken to represent greater or lower levels of productivity by different funding bodies. The costs and nature of the research supported by different agencies may vary greatly.

Citation analysis revealed that 1984 and 1989 publications which acknowledged the support of one or more of the six largest contributors were more frequently cited than papers which did not acknowledge these organizations. Indeed, these six funding bodies had on average twice the expected percentage of publications in the top decile.

NIAID and the MRC had more of their papers in the high-impact set (top decile) than other funding bodies. These organizations which had a high citation impact were followed closely by the Wellcome Trust and the DoD, which were in turn followed by the TDR Programme and USAID. For most of these six funding bodies, the proportion of their papers in the high-impact set remained stable over time. The exception was USAID, which experienced a decline in its proportion of high-impact papers over time.

Based on these analyses, it is evident that the research supported by each of the six largest contributors has had high citation impact internationally. However, this analysis is based on only a narrow interpretation of the term 'impact'. Publications and citation data can only indicate the influence of a piece of research within the scientific research community; that is, among other researchers and malariologists who publish papers. Bibliometric analyses say nothing about the broader achievements of malaria research, its potential impact for improving health care, or the nature of barriers to the implementation of research findings. These issues require a more qualitative approach based on expert judgements and systematic opinion survey. Chapters 5 and 6 report the results of attempts to undertake such survey work.

As a precursor to this, it is important also to stress that malaria research is not a homogeneous activity, and that a number of distinctive subfields of inquiry have become established over the years. Understanding trends in activity within these subfields is as important as understanding overall trends in malaria research as a whole, when developing funding strategies. The next chapter, therefore, reports the results from a detailed analysis of inputs to, and outputs from, a number of important subfields of malaria research.

4 SUBFIELDS OF MALARIA RESEARCH

Whereas the previous chapters have analysed research activity in the field of malaria as a whole, the current chapter examines activity in the main subfields of malaria research. A classification system was designed for the division of the overall field of malaria research into a series of defined subfields. Bibliometric analysis was based on papers published over a 10-year period in 1984, 1989 and 1994. Papers were classified into subfields to assess the relative productivity of the different research areas. An analysis of the first-author addresses gave an indication of the geographical spread of research activity within each malaria subfield and also highlighted the particular research strengths and weaknesses of individual countries.

4.1 BACKGROUND

The databases used for the current analyses were Science Citation Index (SCI) and Medline. The Medline database had the distinct advantage, in the current analysis, of including an abstract summarizing the contents of the paper and enabling its classification into a particular subfield. Papers which appeared only in the SCI database, where no abstracts are provided, had to be classified by title alone. As this analysis was restricted to first-author addresses, the results should be interpreted bearing in mind international collaborations. As indicated in the previous chapter, 38 per cent of all UK malaria papers recovered from the SCI involved international collaboration.

The use of both databases provided a robust subfield coverage. As mentioned in Chapter 3, the Medline database has the advantage of covering a more comprehensive set of journals relevant to malaria research, including some published in both local and non-English-language journals. A comparison of the two databases, which was required as a principal step in the analysis in order to eliminate any double entries, revealed certain differences in the coverage of both journals and subfields. Whereas Medline captured significantly more papers in the fields of clinical medicine and epidemiology, the SCI captured more papers relating to the chemistry of antimalarial drugs.

An input–output assessment of the subfields was made in the context of malaria research funded by the Wellcome Trust. To characterize the portfolio of malaria research supported by the Trust, the subfield classification procedure was applied to Trust grants awarded between 1984 and 1994 and also to papers acknowledging Trust support that were published in three selected years.

4.2 METHODS

4.2.1 Bibliometric analysis

The classification system for malaria research was designed by the scientific staff of the Wellcome Trust in consultation with the Steering Committee for the study. The overall field of malaria research was first divided into eight major categories (A–H). These categories were then further subdivided into a total of 14 minor subfields (1–14). Particular attention was paid to defining potential areas of overlap between subfields. The result was a classification system that consisted of a series of closely defined subfields that were, as far as possible, non-overlapping. Full details of the classification scheme and of the scope of each subfield are given in Box 4.1. Throughout the text in this chapter, letters in brackets refer to research categories (A–H) and numbers in brackets refer to subfields (1–14).

The search strategy described in Chapter 3 was applied to both the Medline and SCI databases. As before, original research was identified from SCI by selecting three types of publications – articles, notes and reviews. On the Medline database, original research was identified by selecting from one type of publication – articles.

Each malaria research publication was classified by inspection of the title and, where possible, on the basis of the information given in the Medline abstract. The subfields were defined in such a way that the majority of publications could be assigned to one subfield only. These publications were counted using integer counting.[30] However, there were inevitably some papers (0.9 per cent of all publications) that spanned more than one discipline and in this situation, fractional counts were assigned. Biology, biochemistry and genetics of *Plasmodium* had the most overlap between subfields.

Each paper was also identified as either 'clinical' or 'non-clinical'. For the purpose of this review, a broad definition of clinical was employed such that it included all studies of malaria in humans. Full details of this definition are given in Box 4.1.

The addresses of first authors on papers published in 1994 were examined to assess the contributions of different countries to particular areas of malaria research and to characterize national strengths and weaknesses. Analysis of the addresses of all authors was not possible because of the limited address information available on Medline records.

4.2.2 Funding analysis

Grants awarded by the Wellcome Trust between 1984 and 1994 in the field of malaria research were classified into the 14 subfields according to the research description on the original grant application. The majority of grants, awarded for research of 3–5 years' duration, had a broad scientific scope. Consequently, there was a tendency for grants to span more than one subfield. Fractional counts were assigned to subfields in this situation and no attempt was made to estimate the emphasis of the grant in different areas of research.

The distribution of Trust-supported research across the different subfields of malaria research was calculated on the basis of expenditure and on the basis of the number of grants awarded. For the analysis of expenditure, data are presented both including and excluding support for the overseas units. Research carried out at the units was judged to span a number of different subfields, but it was not possible to determine accurately the relative subfield emphasis of the research programmes. Hence, in calculations of expenditure, the costs associated with overseas units were divided equally between the relevant subfields. For the analysis of grant numbers, all awards in the form of fellowships, project grants and programme grants were included, but grants to support the Trust's overseas units were excluded.[31] However, research at the units is reflected, to a significant extent, in fellowship awards to principal

[30] See Chapter 3 for details on bibliometric techniques.

[31] Grants to units are not directly equivalent to the other award types since they may be for individual items, such as equipment, rather than for a defined research programme. See Chapter 2 for details of award types at the Wellcome Trust.

Box 4.1: Malaria research classification system

(A)1,2 **Antimalarial drug discovery and development *in vitro* and in animal models, and the biochemistry of drug action**

1. **Antimalarial drug discovery and development *in vitro* and in animal models**
Measurement of the activity of potential antimalarial drugs in **animal models and *in vitro* models** of malaria. Antimalarial drug pharmacokinetic, toxicity and metabolism studies *in vitro* and in animal models. Chemistry and synthesis of antimalarial drugs. Analytical tests for assaying antimalarial drugs.
Excluding: Antimalarial drug pharmacokinetic, toxicity and metabolism studies **in humans**, trials of antimalarial drugs and combinations of drugs in human malaria patients to establish efficacy (→8). Effects of drugs on immune status (→3).

2. **Mechanisms of drug action**
The biochemistry of drug action on *Plasmodium*. The mechanisms of parasite resistance to antimalarial drugs. Analysis of genes involved in drug resistance. Characterization of drug-resistant strains of *Plasmodium*. Tests for drug susceptibility of parasites.
Excluding: Epidemiology of drug resistance (→11).

(B) 3,4 **Immunology, vaccine development and vaccine trials**

3. **Immunology and vaccine development**
In vivo and *in vitro* studies on the protective immune response (cellular and humoral) of the mammalian host to malaria. Immune response to particular antigens, including variable antigens. Population studies of human immunity to malaria and the effects of antimalarial drug treatment on immune status. Vaccine development studies and studies of adjuvants for malaria vaccines. Studies on the genetics of the immune response to malaria.
Excluding: Vaccine trials (→4). Studies of the pathology of malaria (→9). Cloning of candidate vaccine antigens (→7). Epidemiology studies of the effects of specific host genotypes on malaria transmission and prevalence (→11). Biochemical characterization of vaccine candidate proteins (→6).

4. **Human vaccine trials and vaccine review articles**
Trials of antimalarial vaccines in humans to establish safety and efficacy. Reviews on the status of antimalarial vaccine development.
Excluding: Preliminary studies of malaria morbidity and mortality in vaccine study area (→11).

(C) 5,6,7 **Biology, biochemistry and genetics of *Plasmodium***

5. **Biology of *Plasmodium***
Structure and morphology of different developmental stages. Host–parasite interactions. Biology of invasion of host cells. Localization of parasite proteins or antigens. Culture of parasites. Purification of parasites or parasite stages. Descriptions of species of *Plasmodium* and characterization of malaria strains in animal models (course of infection, susceptibility of different hosts). Studies on rosetting, sequestration and adhesion of infected erythrocytes in which pathological consequences are not examined. *In vitro* studies of interactions between *Plasmodium* and other infectious agents (e.g. EBV).
Excluding: Studies whose primary focus is the pathology of malaria (→9). Studies of the molecular basis of host-cell invasion, rosetting and sequestration (→6).

6. **Biochemistry of *Plasmodium***
Metabolism and nutrition. Enzymology. Translation, processing and export of proteins. Protein sequences, protein and enzyme characterization (including antigen analysis). Glycosylation, GPI anchors, transporters, ion channels, mitochondrial metabolism, electrophysiology studies. Influence of parasite on host-cell biochemistry. Characterization of antigen/protein diversity in strains of *Plasmodium*. Characterization of proteins involved in sequestration and rosetting of infected erythrocytes and of molecular basis for host-cell invasion.
Excluding: Papers primarily on mechanisms of antimalarial drug action (→ 2). Immune response to particular antigens (→3). Pathological consequences of parasite sequestration (→9).

7. **Genetics of *Plasmodium***
Studies on chromosomes. Genomic maps. Genetic crosses. Cloning and sequencing of genes/cDNAs for functional Plasmodial proteins (including drug targets and vaccine candidates). Expression of proteins from cloned genes. RNA analyses. Control and timing of expression of genes. Post-transcriptional processing. Genetics of antigenic variability. Techniques for the genetic transformation of *Plasmodium*. Studies of genetic diversity and phylogeny. Tests for genotyping *Plasmodium*.
Excluding: Analysis of the genetics of parasite resistance to antimalarials (→2). Epidemiology of antigenic variability (→11). Diagnostic tests for detection of malarial parasites (→13).

(D) 8,9,10 **Clinical treatment and prophylaxis of malaria, and pathophysiology of malaria**

8. **Clinical management of malaria and antimalarial drug trials**
Antimalarial drug pharmacokinetic, toxicity and metabolism studies in humans. Trials of antimalarial drugs and combinations of drugs in human malaria patients to establish efficacy. Drug treatment and prophylaxis recommendations. Development of drug treatment regimens for particular clinical presentations of malaria (e.g. severe malaria, cerebral malaria or malaria during pregnancy, drug-resistant malaria). Case history reports and studies of antimalarial drug side effects.
Excluding: Malaria prophylaxis recommendations for non-immune travellers to endemic countries. Diagnosis and treatment of malaria in non-endemic countries (→10). Studies of social factors influencing drug treatment and compliance. Assessment of long-term prophylaxis in communities in endemic areas. Health service research (→12). Reports on drug-resistant strains of *Plasmodium* (→11).

9. Pathophysiology and disease symptoms of malaria
Clinical diagnosis of malaria and clinical observations of the disease presentation and pathophysiology of malaria in humans and in animals (e.g. observations on cerebral malaria, malaria during pregnancy, mild malaria). Interactions between malaria and other concurrent infections. The role of nutritional status in determining disease severity. Histopathology of malaria in humans and in animals. The mechanisms of pathology in malaria, including the role of the host immune system, expression of adhesion molecules etc. Studies of the mechanisms by which particular susceptible/resistant mammalian host genotypes exert their effect.
Excluding: Epidemiological studies of malaria prevalence in relation to human genotype (→11). Studies linking immunity to malaria to specific genotypes (→3).

10. Malaria treatment and prophylaxis in travellers and migrants
Malaria prophylaxis recommendations specifically for short-term visitors to malaria-endemic areas. Diagnosis and treatment of malaria in individuals in non-endemic countries. Case reports of malaria in non-immune travellers to endemic regions. Import of malaria by migrants to non-endemic areas. Prophylaxis in army personnel deployed to endemic areas.

(E) 11 Epidemiology of malaria prevalence and severity, and mathematical modelling
Epidemiology of the distribution of species of malarial parasites and mosquito vectors, and of the prevalence of morbidity and mortality due to malaria. Studies of the biological, environmental, social and economic determinants of malaria transmission dynamics and of malaria prevalence (e.g. roles of human behaviour; vector behaviour, ecology and epidemiology; inoculation rates, host genetic factors, *Plasmodium* strain variation etc.). Epidemiological studies of genetic factors influencing the prevalence of malaria, including sickle cell genes, thalassaemia, HLA type etc. The impact of malaria on selection for particular host genotypes. Epidemiology of resistant/susceptible strains of *Plasmodium* to antimalarial drugs and of mosquito vectors to insecticides. Mathematical modelling of malaria (e.g. of malaria transmission and of human immune response to malaria).
Excluding: Studies of the effects of control interventions on malaria transmission. Morbidity and mortality as a result of malaria (→12). Studies on the mechanisms by which specific mammalian host genotypes influence host immunity (→3) or pathology (→9). Studies of vector ecology and behaviour which are not in the context of transmission (→14). Cases of malaria imported to non-endemic areas (→10).

(F) 12 Intervention trials and health services research
Trials to test measures for the control of mosquito vectors (bed-nets, environmental and biological control measures, insecticides etc.) and to test other interventions, administered through health care services etc., for the control of malaria morbidity and mortality in communities (e.g. drug treatment and prophylaxis). Studies of community attitudes, knowledge and practice in relation to malaria treatment and control programmes. Health care service studies in relation to delivery of malaria treatment and control measures. Design of treatment and control programmes appropriate to local prevailing conditions. Implementation and evaluation of large-scale malaria treatment and control programmes operated through health care services, government ministries, non-governmental organizations etc. Operational research. Economic impact of malaria morbidity and mortality on communities and the economics of malaria control measures.
Excluding: Clinical trials of drugs or vaccines to establish safety and efficacy (→8 or 4).

(G) 13 Development of diagnostic tests for malaria
Diagnostic tests for the detection and identification of malarial parasites in humans: ELISAs, DNA probes, PCR tests, novel microscopy tests etc.
Excluding: Application of these tests in epidemiology studies (→11). Tests for genotyping parasites (→7).

(H) 14 Studies of mosquito vectors of malaria
Vector biology, biochemistry and genetics. Including studies of vector susceptibility to infection by *Plasmodium*, genetic transformation of vectors, insect transposable elements, genetics of insecticide resistance, tests for vector identification, taxonomy and systematics. Development of tests for the identification of *Plasmodium*-infected mosquitoes. Characterization of mosquito behaviour and ecology.
Laboratory-based studies to develop mosquito control measures. Studies of parasites and pathogens of mosquitoes, including those which might be applied as biological control agents.
Excluding: Studies primarily on biology of parasite interaction with mosquito host (→5). Studies in which the epidemiology and behaviour of vectors is specifically related to the transmission of malaria (→11). Field testing of mosquito control measures (→12).

Definition of 'clinical' and 'non-clinical' research
Publications or grant awards were classified as **clinical** if they included within them studies of malaria **in humans**. For example: clinical management and clinical observations of malaria in humans, the human immune response to malaria, human genetic susceptibility to malaria, the prevalence of morbidity and mortality due to malaria, malaria control and treatment studies in populations (including mosquito control programmes), epidemiology of antimalarial drug resistance, health services research.

All research into animal species of *Plasmodium* and studies of human parasites *in vitro* were classified as **non-clinical**. This category also included basic science studies of mosquito vectors of malaria, studies of clinical disease or pathology **in animals**, theoretical mathematical modelling of malaria, studies of the epidemiology of mosquito vectors and vector behaviour studies.

investigators at the units. SCI papers acknowledging the Wellcome Trust, and published in 1984, 1989 and 1994 (see Chapter 3) were also categorized by subfield.

4.3 RESULTS

4.3.1 Publication output

The number of publications in the field of malaria retrieved from both the SCI and Medline databases (the 'combined' SCI/Medline set of papers) increased from 918 in 1984 to 1302 in 1994 – a 42 per cent increase. On average, the number of publications identified by the combined search was substantially greater than that identified using SCI alone in Chapter 3. However, the increase in SCI output over the 10-year period was 82 per cent, indicating that over time an increasingly large share of the combined SCI/Medline malaria papers can be found in SCI alone.

The classification system which was designed for the analysis proved to be very specific. The majority of papers were classified into one subfield only, although 29 papers (0.9 per cent of the total output) were considered to span more than one subfield. The distribution of malaria research outputs across the broad categories of research, A–H, is illustrated in Figure 4.1. A detailed breakdown of the publications into subfields 1–14, and according to the 'clinical' or 'non-clinical' nature of the studies, is presented in Figure 4.2 and Annex 4.

Publications were most numerous in two major categories: clinical treatment and pathophysiology of malaria (D), and basic science studies of *Plasmodium* (C). The categories of drug discovery and development (A), immunology and vaccines (B), mosquito vector studies (H), and epidemiology and mathematical modelling (E) were also well represented by publications. One broad category that appeared less active than the others was that of intervention trials and health services research (F). The small number of papers relating to diagnostic tests (G) was not unexpected in view of the limited definition and extent of this category.

A substantial proportion of papers (15 per cent) related to the discovery and development of new antimalarial drugs *in vitro* and in animal models (1, 2). Of these papers, just over two-thirds described studies of the chemical properties or synthesis of antimalarial compounds; the activity, toxicity or pharmacology of drugs *in vitro* or in animal models; or the development of methods to detect antimalarial drugs in blood or urine (1). The remaining one-third of papers explored the biochemistry of antimalarial activity or the mechanisms of parasite resistance to drugs (2). Nearly 13 per cent of all papers described clinical studies of

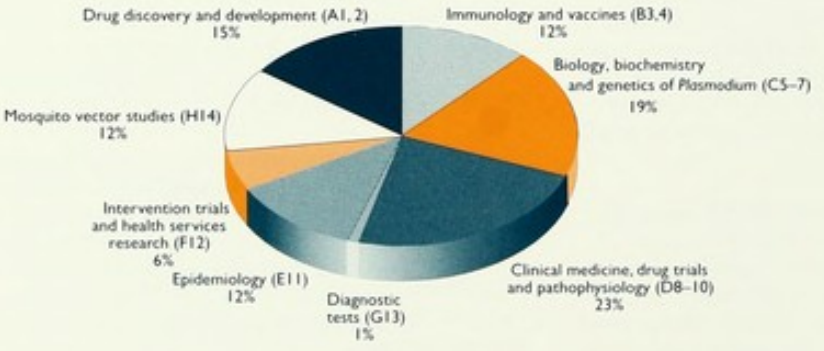


Figure 4.1: International malaria research publications (1984, 1989, 1994) by major research category (A–H)

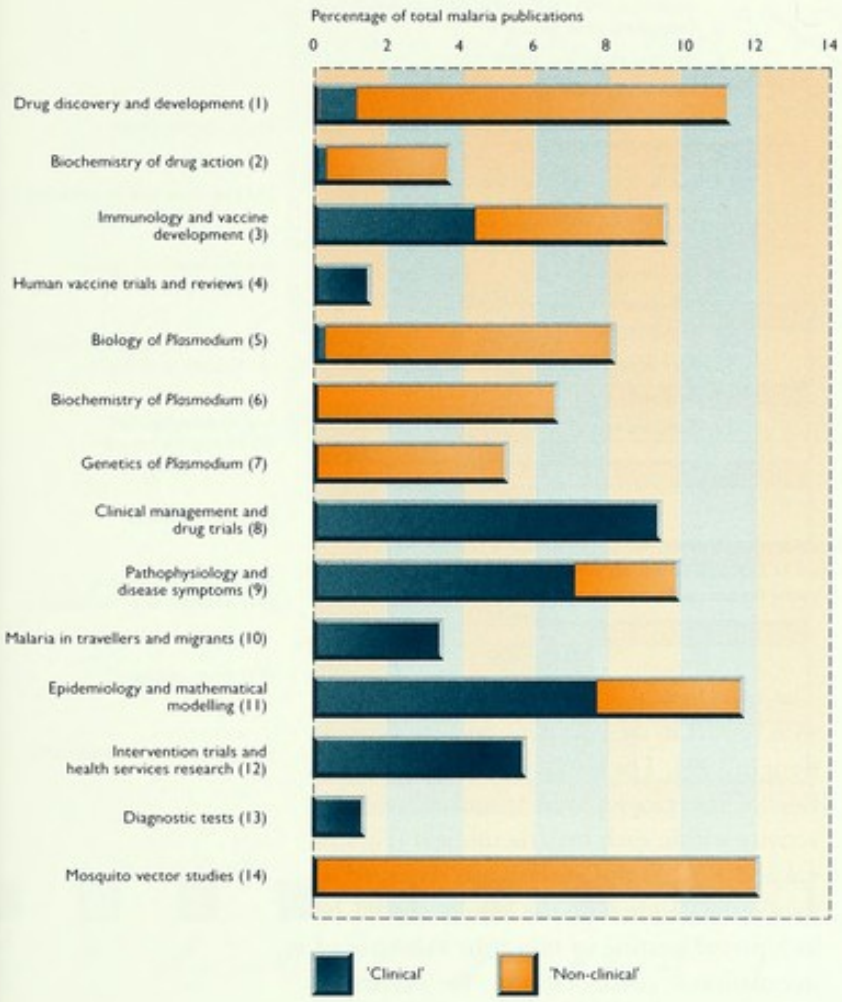


Figure 4.2: International malaria research publications by subfields (1984, 1989, 1994)

antimalarial drugs in humans, including research into the clinical management of malaria, clinical drug trials, optimization of drug treatment regimens and studies of prophylaxis and treatment of malaria in travellers and migrants (8,10). Thus, a total of 28 per cent of all malaria research outputs related to the development of new antimalarial drugs, from studies of drug chemistry through to clinical trials in humans (1, 2, 8, 10).

Overall, 42 per cent of the malaria research publications were classified as 'clinical', describing studies that involved humans. The remaining 58 per cent of publications were classified as 'non-clinical', describing research employing *in vitro* or animal models of malaria; basic science studies of *Plasmodium* or mosquito malaria vectors; epidemiological studies of mosquitoes; or theoretical mathematical modelling studies.

In the set of immunology and vaccine papers (3, 4), approximately half of the publications described studies of the human immune response, while the other half described research in animal models or *in vitro*. In pathophysiology and disease symptoms (9), about one-third of the studies employed animal models, while two-thirds were studies of disease in humans. About two-thirds of epidemiological studies (11) described the prevalence of Plasmodial parasites (including drug-resistant strains) and morbidity and mortality resulting from malaria, while the other third concerned the epidemiology of mosquitoes or mathematical modelling of malaria transmission dynamics.

Research trends examined over the past 10 years are illustrated in Figure 4.3, where the diagonal line represents no change in publication share between 1984 and 1994. Subfields that showed a marked increase in their percentage share of the overall malaria research output (>2 per cent) were genetics of *Plasmodium* (7) and clinical management of malaria and antimalarial drug trials (8). Those that showed a marked decrease (>2 per cent) in their percentage share of the total output were the biology (5), and biochemistry (6) of *Plasmodium* and mosquito vector studies (14).

4.3.2 Geographical patterns of output

The top publishing countries in the field of malaria research were also determined from the combined SCI/Medline set of papers. However, the analysis was limited to 1994 publications and based on the address of the first author only. The top 10 publishing countries are listed in Table 4.1. A more complete list is given in Annex 5, together with the top publishing countries determined in Chapter 3

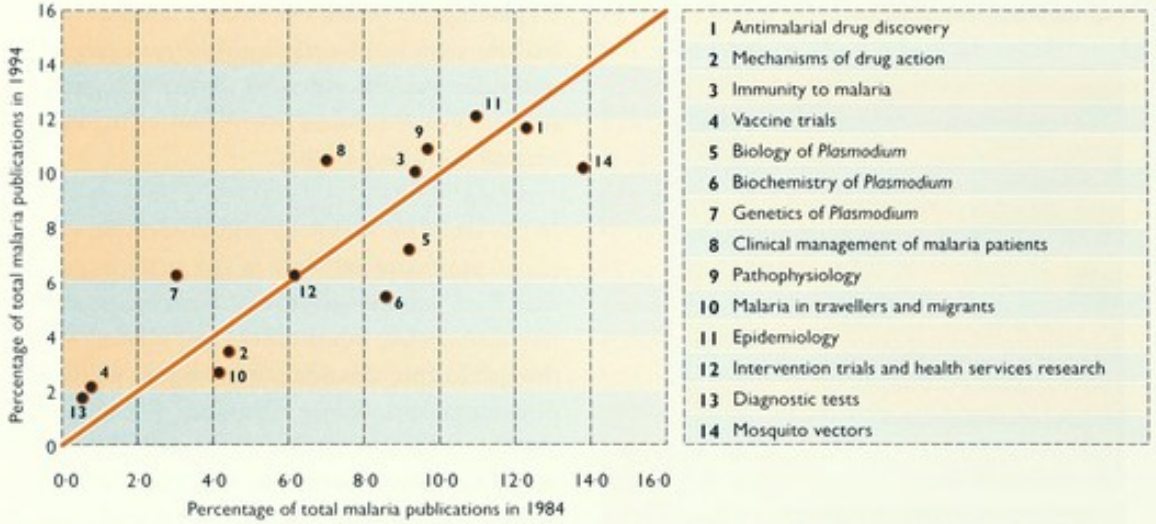


Figure 4.3: Changes in the distribution of malaria publications across subfields between 1984 and 1994.
The straight line represents the static situation in which the percentage share of each subfield was the same in 1994 as in 1984. Points located above the line thus represent subfields that have increased in prominence during the last ten years, while points below the lines are subfields whose share of the total output in malaria research has fallen.

by analysis of the addresses of all authors on 1984, 1989 and 1994 SCI publications (see also Table 3.2). The most notable difference between the two lists is that China and India, and also certain other countries such as Brazil, South Africa and Russia, had a higher ranking in the combined SCI/Medline data set, than that determined from SCI papers only. This was primarily the result of the inclusion within Medline of a greater number of national and regional journals and, in particular, of Indian and Chinese medical journals.

Of the combined SCI/Medline set of malaria publications (1994), 23 per cent had a first-author address in the USA and 12 per cent in the UK. In contrast, 37 per cent and 16 per cent of SCI malaria papers (1984, 1989 and 1994) had at least one author address in the USA or the UK, respectively (see Table 3.2). The lower percentage shares of the USA and UK of the combined publications set, compared with that of SCI papers alone, was partly the result of the different methods of analysis employed (i.e. all author addresses were taken into consideration in the SCI data set), but also reflected the greater representation of local and non-English-language journals in the combined SCI/Medline publications set.

The countries of first authors were analysed with respect to the research subfield classifications in 1994. The results provided an indication of the geographical spread of research activity within each malaria subfield (Figures 4.4 and 4.5). As this analysis was restricted to first-author addresses, the results should be interpreted bearing in mind the existence of international collaborations. For example, 34 per cent of the combined SCI/Medline set of papers with a first-author address in Thailand were found also to include at least one UK author. This is consistent with the results presented in Chapter 3, which demonstrated a

Table 4.1 Top publishing countries (SCI/Medline combined)

Country	Number of first-author papers from that country (1994)	% of total malaria papers (1994)
USA	307	23.6
UK	149	11.4
France	87	6.7
India	85	6.5
Australia	72	5.5
Thailand	56	4.3
Germany	39	3.0
China	35	2.7
Switzerland	28	2.2
Italy	26	2.0

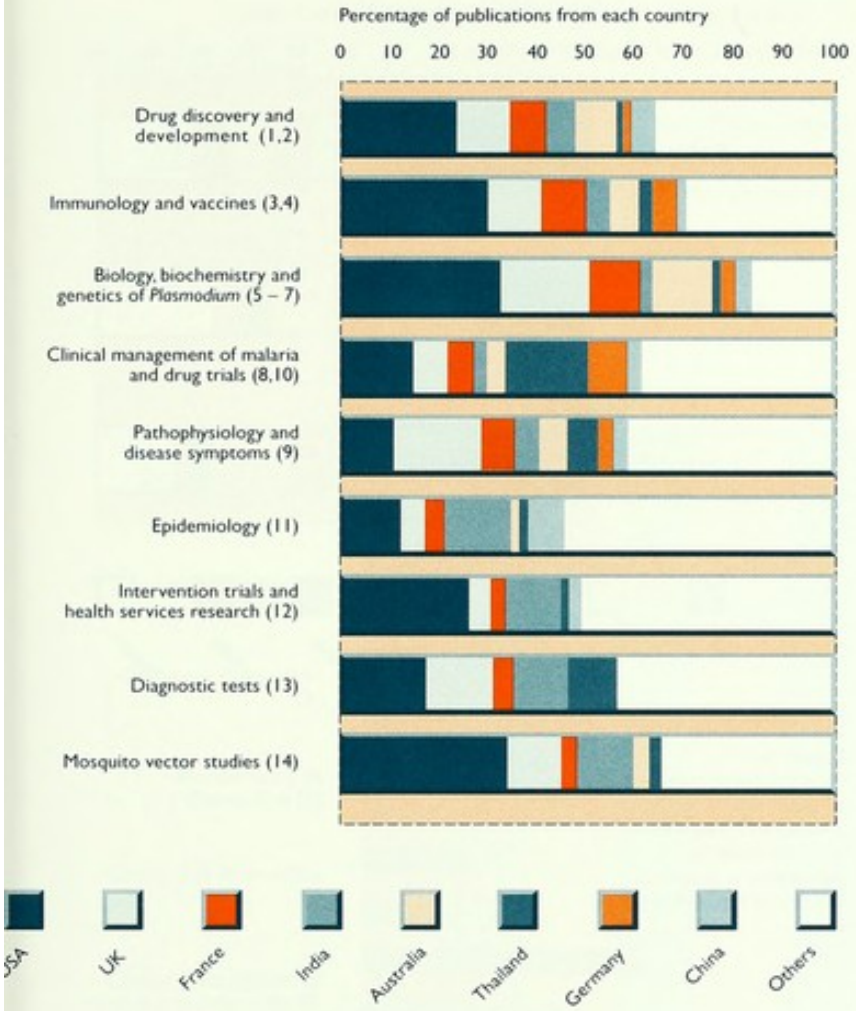


Figure 4.4: Geographical distribution of 1994 malaria publications in different research subfields (based on country of first author only)

strong collaborative link between the two countries. It is worth recalling that, because of the small number of papers published in the different disciplines (the maximum was 244 in basic science studies of *Plasmodium*), output may be strongly influenced by the productivity of individual research teams.

Laboratory-based research was predominantly located in developed countries and had a relatively narrow geographical spread (Figure 4.4). For example, only 13 countries in total contributed to the field of genetics of *Plasmodium* (7). In contrast, the geographical spread of research was much greater for the field-based and clinical disciplines. For example, in 1994 a total of 52 countries published in the subfield epidemiology (11), and 57 per cent of those publications were from countries outside the top eight publishing countries.

The USA dominated all subfields except those relating to clinical medicine and pathophysiology (8,9,10) in which it fell into second place. Thailand was the greatest publisher in the field of clinical management of malaria and drug trials (8), although about one-third of papers with a contact address in Thailand also involved a UK collaborator. The UK was the greatest-publishing country internationally in the subfield concerning pathophysiology and clinical disease symptoms of malaria (9). The UK also published substantially in basic science studies of *Plasmodium* (5, 6, 7). India published the second-greatest number of papers in three subfields: epidemiology (11), intervention trials and health services research (12), and mosquito vector studies (14).

A more detailed analysis of the countries most active in the subfields of biology, biochemistry and genetics of *Plasmodium* is illustrated in Figure 4.5. The USA was again dominant, although the UK was the second-largest publisher in each subfield. Australia and France were also important contributors.

The geographical analysis also indicated the particular research strengths and weaknesses of individual countries (Figure 4.6). The first-author publications from the USA and Australia were biased towards laboratory-based, basic science studies. France and the UK had very similar portfolios, with about 65 per cent of their publications on laboratory-based subfields and the remainder being devoted to clinical and field-based research. As noted above, the UK had a particular strength in the area of pathophysiology and disease symptoms of malaria (9) and 18 per cent of its 1994 publications were relevant to this area. India was the fourth-greatest publisher of malaria research papers (captured by Medline

and SCI). Half of the papers from India were published in Indian or Southeast Asian journals, and just over one-half were concentrated in the areas of mosquito vector studies (14), epidemiology (11), and drug discovery and development (1). Thailand's malaria research efforts were primarily directed towards clinical research, especially clinical management or the pathophysiology of malaria (8, 9). Germany focused on clinical management of malaria (8), basic science studies of *Plasmodium* (5–7) and immunology and vaccine development (3), and in 1994 no first-author papers from Germany were published in the fields of epidemiology (11), health services research and interventions trials (12) or mosquito vector studies (14). China was the eighth-greatest publisher in the field of malaria research in 1994 (Medline and SCI), although three-quarters of its publications were in Chinese journals. One-quarter of China's 1994 malaria outputs focused on epidemiology (11), but other important subfields were drug discovery and development (1) and basic studies of *Plasmodium* (5–7).

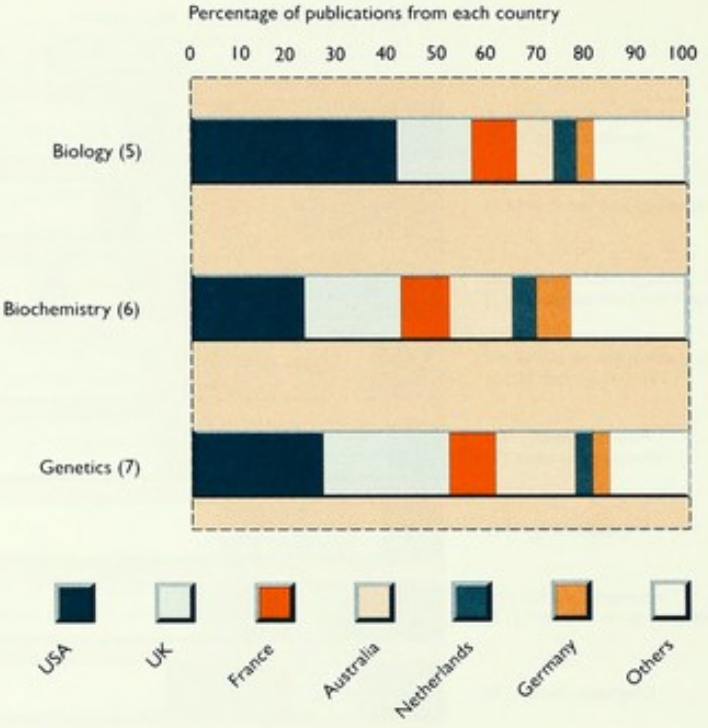


Figure 4.5: Geographical location of basic science studies of *Plasmodium* in 1994 malaria publications (based on country of first author only)

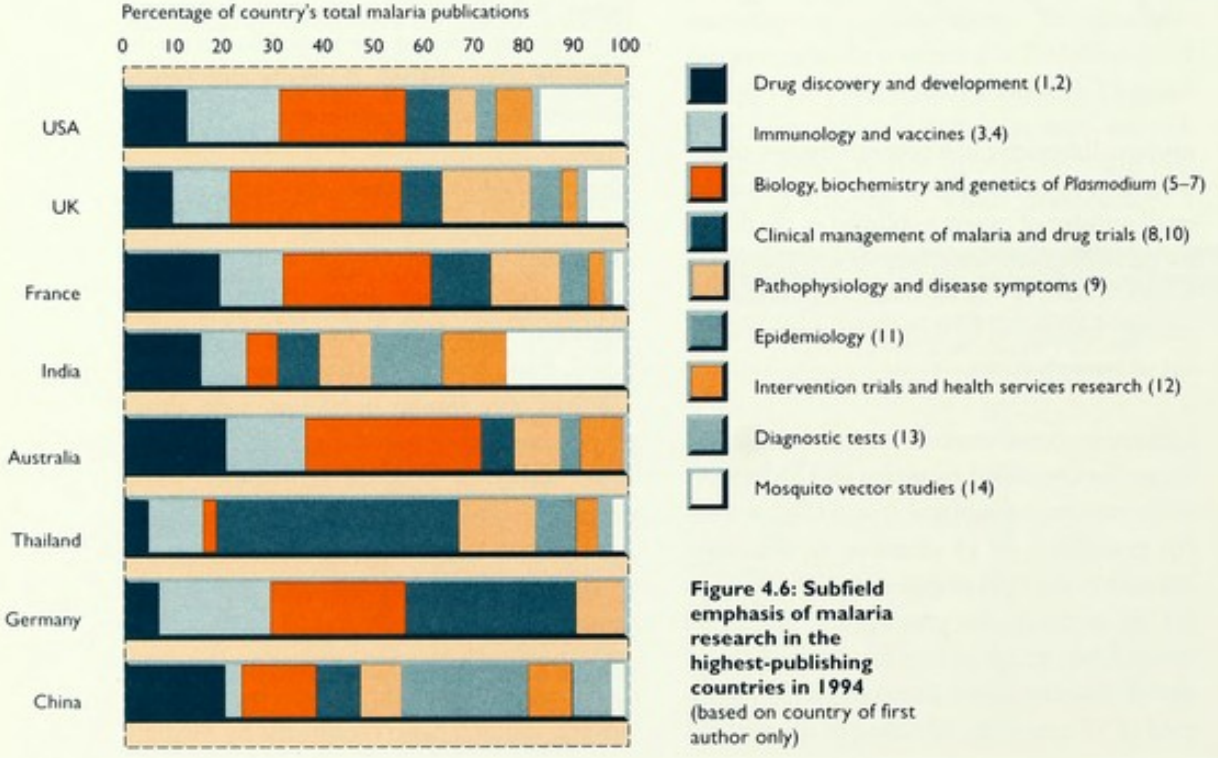
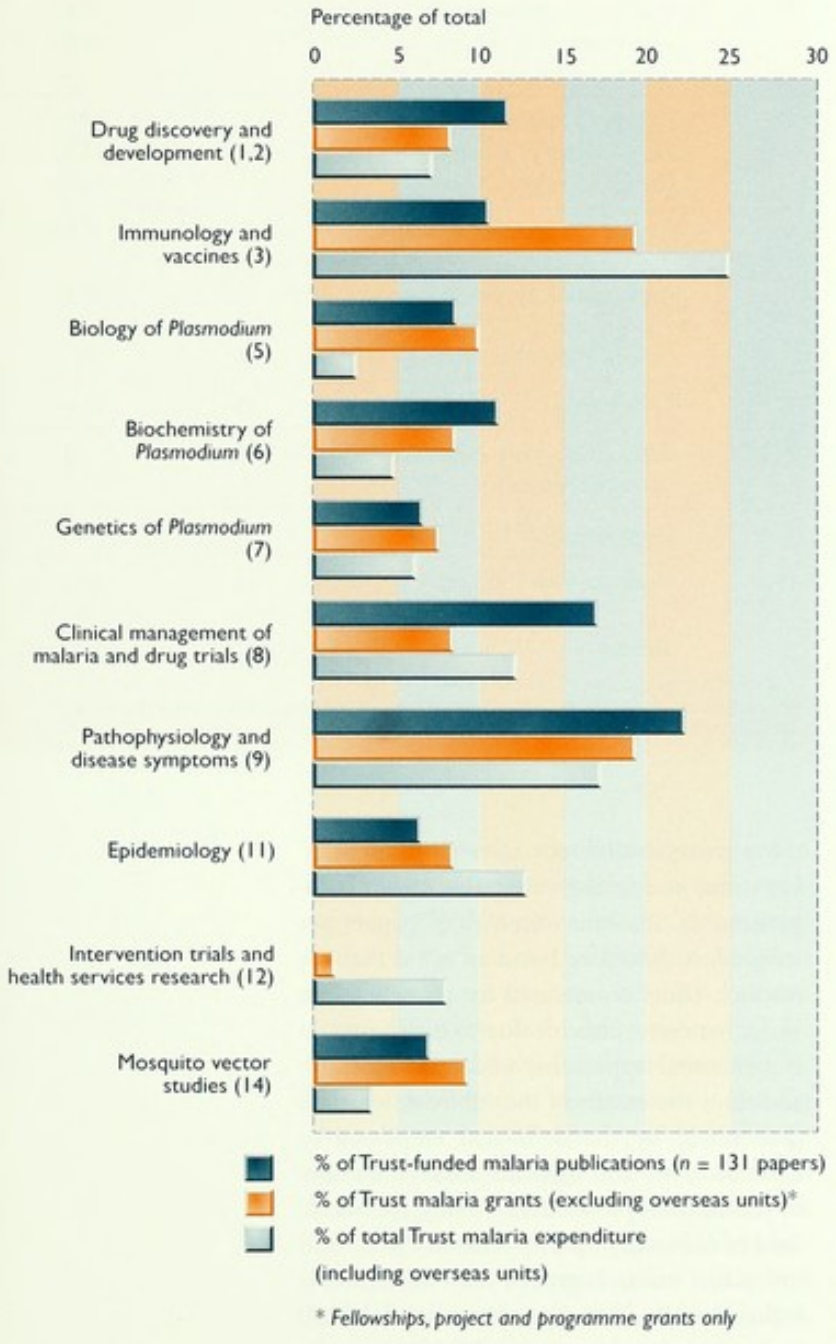


Figure 4.6: Subfield emphasis of malaria research in the highest-publishing countries in 1994 (based on country of first author only)

4.3.3 Wellcome Trust support for different subfields of malaria research

The allocation of Wellcome Trust support across the different subfields of malaria research, according to both the numbers of grants awarded and expenditure, is summarized in Table 4.2 and Figure 4.7.

Figure 4.7: Subfield distribution of Wellcome Trust expenditure on malaria research (1984–1994) and of publications arising from Trust support (1984, 1989 and 1994)



Over the period 1984 to 1994, about one-third of the Trust's total malaria research expenditure was for the support of overseas units in Kenya, Thailand and Vietnam (see Chapter 2). Malaria research at these units had a particular focus on the development of improved methods for the clinical management of malaria, studies of antimalarial drug pharmacokinetics, clinical observations of malarial disease symptoms and pathophysiology (8,9). Research programmes also include epidemiological studies of malaria prevalence and severity and the distribution of mosquito vectors (11), studies of the human immune response to *Plasmodium* (3), and mosquito control intervention trials and health services research (12). As it was not possible to determine accurately the proportions of unit funding that were assigned to the individual subfields of research, expenditure was divided equally between the subfields 3, 8, 9, 11 and 12. It is recognized that this procedure introduced significant approximations into the resulting figures and calculations were therefore carried out both to include and exclude the costs of overseas units. Inclusion of unit expenditure does, however, indicate the significant allocation of funds by the Trust to field-based malaria research.

About one-quarter of Wellcome Trust support for malaria research between 1984 and 1994 was in the area of clinical management and pathophysiology (8, 9) – 28 per cent by number of grants and 24 per cent by amount. When the costs of overseas units were included, support in these two areas accounted for 30 per cent of expenditure.

Just over one-quarter of Trust malaria research grants were for basic science studies of *Plasmodium,* and these grants were awarded almost equally between the three areas of biology, biochemistry and genetics (5,6,7). These subfields of research together accounted for 20 per cent of Trust expenditure on malaria research fellowships, project grants and programme

grants, but only 14 per cent of total expenditure. The area of immunology and vaccine development (3,4) was strongly represented in the portfolio of malaria research funded by the Trust, accounting for 19 per cent of awards, and 25 per cent of the overall expenditure on the field. The high expenditure on this research area reflected a number of major (five-year) awards (fellowships and programme grants).

The research areas of drug discovery and development, and biochemistry of drug action (1,2); mosquito vector studies (14); and epidemiology (11) each accounted for 8–9% of all Trust malaria research awards. A proportion of several fellowship awards to individuals associated with Trust overseas units were for studies in the subfield of intervention trials and health services research (12). No support was assigned to research in the small areas of diagnostic test development (13) or treatment and prophylaxis of malaria in travellers (10).

Figure 4.7 compares the subfield distribution of Trust malaria research grants and total expenditure between 1984 and 1994, with the distribution of SCI papers published in 1984, 1989 and 1994 that acknowledged Trust support. The data clearly demonstrate that the high Trust expenditure on research into the pathophysiology and clinical disease symptoms of malaria (9) and the clinical management of malaria and drug trials (8) was reflected in a high output of papers in these areas. Conversely, the high expenditure on the subfields of immunology and vaccine development (3,4) and on epidemiology (11) was not mirrored by a correspondingly high output of publications.

Table 4.2 Wellcome Trust support for the different categories and subfields

Category	Subfield	No.	No. of grants awarded*
A	Drug discovery and development (*in vitro* and in animal models)	1	5.5
B	Mechanisms of drug action	2	7.5
	Immunology and vaccine development	3	28.4
C	Biology of *Plasmodium*	5	14.2
	Biochemistry of *Plasmodium*	6	13.2
	Genetics of *Plasmodium*	7	10.7
D	Clinical management of malaria and drug trials	8	11.6
	Pathophysiology and disease symptoms	9	28.6
	Malaria in travellers and migrants	10	0
E	Epidemiology	11	12.1
F	Intervention trials and health services research	12	1.3
G	Diagnostic tests for malaria	13	0
H	Mosquito vector studies	14	13.0
	Totals		

*Fellowships, project and programme grants only.
**Total expenditure on overseas units in Thailand, Vietnam and Kenya (1984–1994): $15.4 million on subfields 3, 8, 9, 11, and 12.

4.4 SUMMARY

Malaria research publications were classified into a series of defined subfields. The numbers of papers per subfield gives some measure of the activity in different research disciplines. However, in drawing conclusions from comparisons of absolute numbers of papers per subfield, it should be borne in mind that the research effort represented by a single paper varies between subfields due to differences in experimental approaches and techniques. In addition, the extent of the subfield, which is determined by the definition employed to describe it, will also affect the absolute number of publications per subfield. Finally, the overall field of malaria research is relatively small and individual research groups may substantially influence output in a particular subfield and hence the balance between subfields.

earch (1984–1994)

Expenditure (US$ million, 1992 base year) excluding overseas units**	Expenditure (US$ million, 1992 base year) including overseas units**	Category % of total expenditure including overseas units**
0.5	0.5	
2.6	2.6	6.8
8.6	11.7	25.0
1.3	1.3	
2.3	2.3	
2.8	2.8	13.7
2.4	5.5	
5.1	8.2	
0	0	29.4
3.0	6.1	13.1
0.8	3.9	8.3
0	0	0
1.8	1.8	3.8
31.2	**46.6**	

Most of the major scientific categories within the field of malaria research were well represented by publications in the three years analysed. Each of the following contributed substantially to the total research output: drug discovery and development (1,2); immunology and vaccine development (3,4); basic science studies of *Plasmodium* (5,6,7); clinical medicine and pathophysiology (8,9,10); epidemiology and mathematical modelling (11); and mosquito vector studies (14). One broad area that appeared to be less active was that of intervention trials and health services research (12), although it is possible that information relevant to this subfield is published in the grey literature of the malaria-endemic countries.

The results of the scientific subfield analysis indicated that international malaria research activity was relatively well balanced between 'clinical' studies of malaria in man (42 per cent) and 'non-clinical' studies of malaria in animal or *in vitro* models, and of mosquito vectors of malaria (58 per cent).

Analysis of publishing trends between 1984 and 1994 indicated that the genetics of *Plasmodium* (7) and the clinical management of malaria and antimalarial drug trials (8) gained an increased share of the overall set of malaria research publications at the expense of biology (5) and biochemistry (6) of *Plasmodium* and mosquito vector studies (14). These trends may in part reflect the recent increased application of molecular biology techniques to the field of malaria research and the move away from more traditional methodology. The increased activity in the area of clinical management of malaria and antimalarial drug trials may reflect the recognition of an urgent need to develop new treatments and to optimize use of existing treatments for malaria as a result of the rise in incidence of antimalarial drug resistance.

The USA dominated most of the subfields of malaria research. However, Thailand and the UK were strongest in two subfields – respectively, clinical management and drug trials (8) and pathophysiology and disease symptoms (9). Fundamental, laboratory-based studies of the malarial parasite were predominantly located within Europe, the USA and Australia. Activity in clinical and epidemiological subfields showed a much greater geographical spread and a substantial proportion of papers were from developing countries.

The portfolio of research supported by the Trust had a particular emphasis on the clinical management of malaria and the

pathophysiology and clinical symptoms of malaria (8,9). This expenditure was reflected in a high output of Trust-supported publications, which contributed to the high UK publication standing in this subfield. One-quarter of total Trust malaria research expenditure (1984–1994) was estimated to have been allocated to studies of the immune response of the vertebrate host to malaria and to the development of antimalarial vaccines. However, this high expenditure was not reflected in a similarly high output of publications in this subfield.

A comparison of Trust support for different subfields of malaria research with the output of publications in these subfields can give an indication of the effectiveness of Trust support in individual research areas. However, caution is warranted in drawing conclusions from these data for a number of reasons. Firstly, publications were analysed from three selected years that may not be completely representative of the overall output of papers acknowledging Trust support. Secondly, this comparison does not take into consideration the timing of the awarding of grants relative to the publication years analysed. Thirdly, individual areas of research differ in their productivity as a result of the differing experimental approaches and techniques that are employed.

The classification of research publications into subfields in this chapter has indicated the extent of activity in the different areas of research. However, this approach did not attempt to identify the practical benefits arising from the research, such as new or improved tools for malaria treatment or control. The following chapter presents the results of a study that aimed at characterizing the broader outcomes of research funded by the Wellcome Trust.

WELLCOME TRUST PORTFOLIO ANALYSIS 5

The overall aim of this phase of the study was to review the achievements and outcomes of malaria research supported by the Wellcome Trust. The analysis relied on independent expert opinion, and focused on Trust-funded papers published in three specific years – 1984, 1989 and 1994. The analysis characterized the advances in knowledge which had arisen from Trust-funded research, and identified broader research outcomes such as instances of improving disease prevention or modifying clinical treatment. The exercise permitted a retrospective review of research results in the light of advances made since their publication.

The analysis reviewed the scope of outputs from malaria research funded by the Trust – hereafter referred to as the Trust's 'portfolio' of publications. The distribution of the portfolio across 14 subfields of malaria research (see Chapter 4) was identified. This information can provide an important input both to understanding the consequences of past research funding strategies, and to developing new policies for the future. However, decisions on future funding also require information on the prospective opportunities of research fields and subfields. Consequently, the current analysis sought to identify research topics with high future potential. Although the analysis focused on research supported by the Wellcome Trust, the approach could be used to assess the portfolios of other funding bodies.

However, the following points should be noted. Firstly, the assessment was not comprehensive, as only papers from three selected years were examined. While these papers clearly reflect the type of results arising from Trust-supported research, they may not, however, be completely representative of the overall output. Secondly, the papers analysed in this exercise reflect the lower level of funding provided by the Trust some years ago and not the recent high level of investment. Thirdly, such an assessment exercise was inevitably subjective as it relied on the opinions of a small number of reviewers. Finally, the numbers of papers and of reviewers in each subfield were small, and detailed statistical analysis at the level of the subfield was not possible.

5.1 METHODS

Malaria research papers arising from Trust-funded research and retrieved from SCI were selected for three specific publication years (1984, 1989 and 1994: see Chapter 3) and subjected to a process of expert review. Of the 134 publications acknowledging Trust support, 131 were located and categorized by subfield (see Chapter 4, Box 4.1 and Figure 4.7). Three subfields [malaria prophylaxis and treatment in travellers and migrants (10), intervention trials and health services research (12) and development of diagnostic tests (13)] were not represented by any Trust-supported papers. The different subfield sets of papers contained between eight and 29 papers.

International and independent reviewers were selected on the basis of their scientific expertise in the various subfields of malaria research. Each set of papers was sent for review by either one or two individuals with relevant expertise. Reviewers were asked to complete a questionnaire that concerned the overall set of papers (see Annex 6a). Qualitative written responses on the 13 questionnaires were read and analysed manually.

Reviewers were also asked to complete a questionnaire for each paper (see Annex 6b). The data from these questionnaires were aggregated across subfields and analysed using SPSS. In this quantitative analysis, the variable number of subfield reviewers (n = 1 or 2) was accounted

for prior to summing the data across subfields. The resulting data were expressed in pie charts as the percentage of survey responses supporting a particular opinion.[32] Throughout the text, numbers in brackets refer to the subfield classification system defined in Box 4.1.

5.2 RESULTS

Several subfields were well represented in the Trust's output portfolio of papers published in 1984, 1989 and 1994. These included pathophysiology and disease symptoms (9), clinical management of malaria (8), and the combined subfields of *Plasmodium* biology and biochemistry (5,6). Other areas were moderately well covered: drug discovery and development (1,2) as well as immunology and vaccine development (3,4). Further details are available in Figure 4.7 and Table 5.1.

5.2.1 Past achievements by subfield

The major advances in knowledge described in papers supported by the Wellcome Trust were characterized by subfield.

Antimalarial drug discovery and development (1,2)

In this area the reviewer felt that 50 per cent of the papers (total, $n = 16$) represented a substantial advance in knowledge. The development of a method for the extraction and measurement of the antimalarial drug artemether and its metabolite from plasma, and the description of a new *in vitro* test for the susceptibility of *P. falciparum* to pyrimethamine–sulphadoxine were noted as significant advances in methodology. Six papers were noted as making

[32] One question in the questionnaire concerning individual papers permitted only a single response, or opinion, while the other two permitted multiple responses. For that question which permitted only one response (When do you see the benefits of this research being realized?), the number of responses was equivalent to the number of respondents. However, where multiple responses were possible, each response was attributed an integer count of one (see Chapter 3), and the number of responses was greater than the number of respondents. However, in both instances, the frequency of responses for a particular answer was expressed as a percentage of all responses supporting all possible answers.

Table 5.1 Achievements of malaria research funded by the Wellcome Trus

Subfield	Publication presence of Wellcome Trust-funded research[33] (1984, 1989 and 1994
Antimalarial drug discovery (1,2)	●●
Immunology and vaccine development (3,4)	●●
Plasmodium biology and biochemistry (5,6)	●●●
Plasmodium genetics (7)	●
Clinical management of malaria patients (8)	●●●
Pathophysiology and disease symptoms (9)	●●●
Epidemiology (11)	●
Mosquito vectors (14)	●

[33] Number of papers published in the three-year sample, where ● = 1–10 papers, ●● = 11–20 papers, and ●●● = 21–30 papers. [34] Glucose-6-phosphate dehydrogenase. [35] Tumour necrosis factor.

topics in malaria

Past achievements of Wellcome Trust-funded research (evidence drawn from research published in 1984, 1989 and 1994 only)	Expert views on research topics for the future
Demonstration of synergism of pyrimethamine and sulfadoxine against *P. falciparum*. Identification of genetic alterations associated with parasite resistance to chloroquine, mefloquine and antifolate drugs. Extraction and measurement of artemether and dihydroartemisin in plasma. *In vitro* test for susceptibility of *P. falciparum* to pyrimethamine–sulphadoxine. Effect of fluorine substitution on metabolism and activity of amodiaquine.	Mode of action of antimalarial drugs. Mechanisms of parasite drug resistance. Measurement of artemisin in blood and tissues.
Increased understanding of the role of T cells in protective immunity. Relationship between antibody specificity against regions of merozoite surface protein 1 (MSP-1) and protection from malaria.	Parasite antigenic variation and protective immunity. Significance of fine specificity of immune response in vaccine development. Role of γδ T cells in non-specific immunity.
Characterization of molecular mechanisms of sequestration of parasitized red blood cells (e.g. identification of ICAM-1), and role in malaria pathogenesis. Characterization of merozoite surface proteins (e.g. P190), and recognition of polymorphism and high rates of antigenic switching.	Host–parasite interactions: mechanisms of merozoite invasion; role of adhesion of infected erythrocytes in pathogenesis; mosquito–parasite interactions. Developmental control mechanisms, e.g. gametocyte differentiation with relevance to sequestration and immune evasion.
Cloning of gene for sulfone/sulfonamide resistance (dihydropteroate synthetase). Identification of subtelomeric deletions in plasmodial genomes. Cloning of important parasite genes: ATPases, G-6-PD[14], cell-cycle control proteins. Method for isolation of *P. falciparum* mRNA for use in translation systems and cDNA library construction.	Genetics of drug resistance. Cell-cycle control and developmental switches in *Plasmodium*. Functional studies of genes in pathogenesis, immunity and drug resistance, using parasite transfection methods.
Efficacy of mefloquine prophylaxis in pregnancy. Mefloquine/artesunate for treatment of multidrug-resistant *falciparum* malaria. Use of dichloroacetate for lactic acidosis in severe malaria. Efficacy of quinine, chlorproguanil and Maloprim in treatment or prophylaxis in African countries.	New approaches to disease management. Sodium dichloracetate for lactic acidosis. Mefloquine in pregnancy.
Role of TNF[15] in severe malaria. Link of TNF promoter region to susceptibility to cerebral malaria. Immunohistochemical studies of malaria pathology.	Malaria severity in relation to transmission dynamics. Genetic factors in susceptibility to severe malaria.
Progress in mathematical modelling of malaria transmission dynamics. Variable clinical manifestations of malaria linked to different transmission rates.	Host–parasite infection dynamics. Link between disease manifestation and transmission rates; clinical studies of disease patterns.
Effect of insecticide-impregnated bednets on host-seeking behaviour of mosquitoes. Characterization of glutathione S-transferases in DDT-resistant *Anopheles gambiae*.	Mechanisms and patterns of insecticide resistance. Further studies of insecticide-impregnated bednets.

significant contributions in the following topics: synergism of pyrimethamine and sulphadoxine against *P. falciparum in vitro*; the effect of fluorine substitution on the metabolism and antimalarial activity of amodiaquine; mechanisms involved in parasite resistance to chloroquine, mefloquine and antifolate drugs.

Immunology and vaccine development (3,4)

In this research area both reviewers considered that only 25 per cent or less of the set of papers (total, $n = 14$) represented a substantial advance in our knowledge of malaria. Significant advances identified in the set of papers included progress in understanding the role of T cells in protective immunity, and the relation between the specificity of antibodies against merozoite surface protein 1 (MSP-1) and protection from malaria.

Biology or biochemistry of *Plasmodium* (5,6)

Only 25 per cent or less of the set of papers (total, $n = 27$) relating to the biology or biochemistry of *Plasmodium* (5,6) were considered by each of the two reviewers to represent a substantial advance in the understanding of malaria. Significant advances included increased understanding of host–parasite interactions, in particular the molecular mechanisms of parasite sequestration (e.g. the identification of intercellular adhesion molecule-1) and events leading to malaria pathogenesis. Other important advances were the characterization of merozoite surface proteins, including the recognition of extensive polymorphism in some molecules, the proposed involvement of merozoite surface protein-1 in the process of erythrocyte invasion and the recognition of high rates of antigenic switching in malaria (and its significance in sequestration and immune evasion).

Genetics of *Plasmodium* (7)

In this subfield, one expert estimated that 25 per cent or less of the papers in the set (total, $n = 9$) represented a substantial advance in knowledge or understanding of malaria, whereas the second reviewer indicated a figure between 25 and 50 per cent. Many of the papers presented sequences of malarial parasite genes, reflecting the increased application of molecular biology techniques to malaria research in recent years. Significant advances identified by reviewers included the discovery of the gene for sulfone/sulfonamide resistance, the recognition of subtelomeric deletions in plasmodial genomes, and the identification of *P. falciparum* genes that might lead to significant insights into parasite biology (e.g. genes for ATPases, glucose-6-phosphate dehydrogenase and cell-cycle control proteins). A significant advance in basic methodology was the development of a method for the isolation of *P. falciparum* mRNA for use in *ex vivo* translation systems and in cDNA library construction.

Clinical treatment and management of malaria (8)

In this subfield, one reviewer considered that 25–50 per cent of papers represented a substantial advance in knowledge (total, $n = 19$), whereas the other reviewer indicated a figure of 50–75 per cent. Both reviewers commented that the papers presented results that were of direct relevance and applicability to improving the treatment and prophylaxis of malaria, and that the information should be of interest to clinicians and policy makers in malaria-endemic countries. Results relating to the use of mefloquine in pregnancy and the use of mefloquine/artesunate combinations in the treatment of multidrug-resistant *falciparum* malaria in Thailand were highlighted. Three papers on malaria in Africa advanced knowledge in the use of parenteral quinine in young African children with cerebral malaria, the efficacy of chlorproguanil for malaria prophylaxis in Kenya, and finally, the efficacy of chlorproguanil and Maloprim as chemoprophylactics in Gambian children. Research into the use of dichloroacetate for lactic acidosis in severe malaria was also highlighted for its potential impact on the management of patients with complicated malaria. Both reviewers noted that malaria chemotherapy is a rapidly evolving area and that some of the

results of the earlier papers had now been superseded.

Pathophysiology and clinical disease symptoms of malaria (9)

This set of papers was reviewed by one expert who considered that 25–50 per cent of the papers in the set (total, $n = 29$) represented a substantial advance in knowledge. Most significant were the identification of a link between variations in the tumour necrosis factor promoter region and susceptibility to cerebral malaria; immunohistochemical studies of the pathology of malaria; and the recognition of a possible role for tumour necrosis factor in severe malaria. The last result in particular was noted to have since generated considerable research activity. All of these research findings were considered to be important both because of their contribution in advancing theory and because of their potential therapeutic applications.

Epidemiology of malaria and mathematical modelling (11)

The two reviewers of the papers in this subfield held opposing opinions about the validity and hence value of a particular series of papers; consequently, they disagreed on the proportion of the papers (total, $n = 8$) that represented a substantial advance in knowledge. One reviewer indicated that 75–100 per cent of the papers represented a substantial advance in understanding, and highlighted a series of theoretical studies of the transmission dynamics of malaria as being particularly significant. The other reviewer considered that only 0–25 per cent of the papers represented a substantial advance in understanding. This reviewer highlighted a paper demonstrating that the clinical manifestations of severe malaria differ in regions of differing transmission rates as being extremely important.

Mosquito vectors of malaria (14)

The reviewer for this subfield considered that only 25 per cent or less of the set of papers (total, $n = 9$) represented a substantial advance in knowledge. Two significant contributions to vector control strategies were identified: the effect of insecticide-impregnated bednets on the host-seeking behaviour of mosquitoes; and the characterization of glutathione S-transferases involved in the DDT-resistance phenotype in *Anopheles gambiae*.

5.2.2 Uses and benefits of the research results

Reviewers were asked to identify the uses and benefits of each research paper. Many respondents gave more than one response – the total number was 272. These responses were aggregated to provide an overall view of the uses and benefits of the Wellcome Trust malaria portfolio. The results are expressed as percentages of total responses (not respondents) in Figure 5.1. The main use of the research results was perceived to be in advancing knowledge. However, practical uses and benefits relating to modifying clinical treatment and improving disease prevention or control were also considered likely. A small proportion of the results were perceived as relevant to improving methodology or developing new products.

5.2.3 Realization of the benefits of research

Reviewers were also asked to comment on the timescale for realization of the practical benefits of the research. The total number of responses by reviewers was 191. Results are presented as percentages in Figure 5.2. The

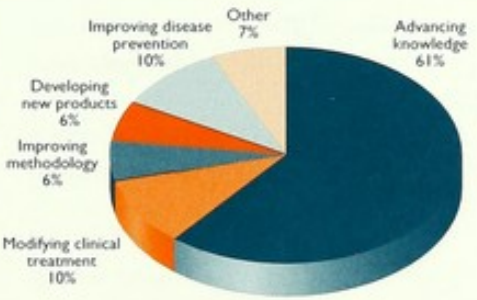


Figure 5.1: Uses of research results
(% of survey responses)

majority view was that benefits were most likely to be realized in the medium term (one to five years). To a lesser degree, benefits were also considered likely to emerge from research either immediately (within 12 months) or in the long term (five to 10 years). Fewer respondents considered that practical benefits would emerge more than 10 years after publication of the research results.

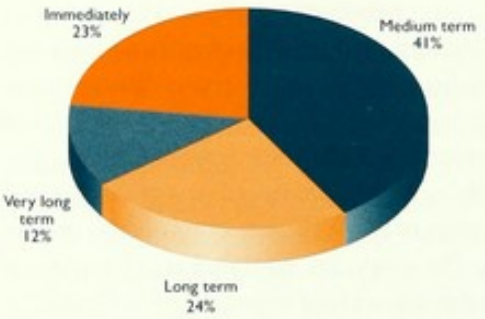


Figure 5.2: The timescale for realization of the benefits of the research
(% of survey responses)

5.2.4 Target audience for the research

Reviewers were asked to identify which professional groups would find the research results of most interest. Responses totalled 378, and the results are shown as percentages in Figure 5.3. Basic researchers were believed to be the group most likely to have an interest in the research findings. However, respondents also indicated that the results would be of interest to non-academic clinicians, policy makers, manufacturers and academic clinicians. The implication here is that material of direct relevance to policy making in the control and treatment of malaria is published in the scientific literature and ought to be accessed by policy makers.

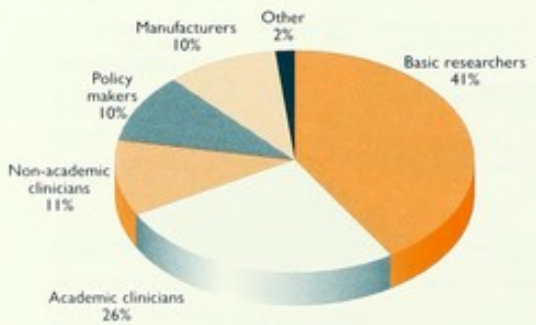


Figure 5.3: The professional groups likely to find the results of most interest
(% of survey responses)

5.2.5 Future hot topics in malaria research

Each reviewer was asked to identify specific research topics in their particular subfield that they considered might lead to important advances in the future.

Drug discovery and development (1,2)

In the research area of drug discovery and development (1,2) topics identified as likely to be of future importance were: studies of the modes of action of antimalarial drugs (chloroquine, quinine, mefloquine, artemisin and antifolates) and the mechanisms of parasite resistance to these drugs; and methods of measuring artemisin and its derivatives in blood and other tissues.

Immunology and vaccine development (3,4)

Topics of importance identified by reviewers in this area were parasite antigenic variation and its relationship to both humoral and cellular protective immunity, studies aimed at understanding the importance of the fine specificity of the immune response in vaccine development, and γδ T cells and their role in non-specific immunity to malaria.

Biology and biochemistry of *Plasmodium* (5,6)

Important developments in the biology and biochemistry (5,6) of *Plasmodium* were expected from research into host–parasite relationships and pathogenesis, and studies of parasite biology in the mosquito vector. Specific topics highlighted were mechanisms of merozoite invasion and host-cell specificity, adhesion of infected erythrocytes in relation to pathogenesis, developmental control mechanisms and in particular gametocyte differentiation, and studies of vector–parasite interactions with a view to identifying vaccine candidate antigens.

Genetics of *Plasmodium* (7)
Topics of importance for the future included studies of cell-cycle control and developmental switches during the life-cycle of *Plasmodium*, the genetics of drug resistance, and the use of parasite transfection techniques, linkage analysis and heterologous expression of functional gene products to carry out functional studies of genes important in pathogenesis, immunity and drug response.

Clinical management of malaria patients (8)
The use of sodium dichloroacetate for acid lactosis in severe malaria, as well as other new approaches to disease management, were specifically identified as topics that should be pursued in the future. Mefloquine prophylaxis in pregnancy was indicated as a research area that required further work.

Pathophysiology and disease symptoms (9)
Important topics in this subfield included epidemiology of malaria morbidity/mortality in relation to transmission intensity, as well as mechanisms, especially genetic, of severe disease.

Epidemiology and mathematical modelling (11)
Future hot topics were identified as the infection dynamics between parasite and host, the relationship between disease patterns and transmission, and clinical investigations of disease patterns.

Mosquito vector studies (14)
Suggestions for future topics in this subfield focused on basic analysis of insecticide resistance to help plan future chemically based control programmes, and further work on the use of insecticide-impregnated bednets.

5.3 SUMMARY

The analysis of Trust-funded papers published in the three-year sample indicated that several subfields were particularly well represented in the outputs portfolio (see Figure 4.7). These included pathophysiology and disease symptoms (9), clinical management of malaria (8), and the combined subfields of *Plasmodium* biology and biochemistry (5, 6). There was moderate coverage of drug discovery and development (1, 2), as well as immunology and vaccine development (3, 4). Three subfields were less well represented: genetics of *Plasmodium* (7); epidemiology and mathematical modelling (11); and studies of mosquito vectors (14). In the three years analysed, the Trust had no publications in three subfields: malaria prophylaxis and treatment in travellers and migrants (10); intervention trials and health services research (12); and development of diagnostic tests (13).

The overall portfolio was balanced in both advancing knowledge as well as the more applied aspects of research, such as those with relevance to clinical treatment, disease prevention, and the development of new products. These results reflect the emphasis that the Trust places on supporting basic research related to medicine as well as clinical aspects of medicine.

The timeframe for the realization of the practical benefits of the overall set of research results was largely considered to be within five years of publication of the results. This suggests that research, generally, has potential for rapid impact on treatment and control of the disease. However, anticipating the time to realization is difficult, and the views of experts in research may be overoptimistic. Previous studies have shown that the difficulties associated with, and hence time required in, transferring scientific research results into practice are often underestimated (see Roberts *et al.*, 1981).

Subfield achievements or outcomes of Trust-funded research were well characterized by the expert reviewers. Future opportunities arising from the published work were also considered by the expert reviewers who identified a large number of hot topics. Achievements and

opportunities included advances both in knowledge and in broader outcomes: clinical management, treatment and prophylaxis of malaria and vector control (Table 5.1).

As indicated in Table 5.1 there was some overlap of views concerning past achievements of Wellcome Trust research and future hot topics in malaria. These matches suggest that although significant advances have been made, opportunities for further advance still remain. In antimalarial drug discovery and development (1,2) overlap was evident in relation to methods for measuring artemether and its metabolite, drug resistance, and the mode of action in antimalarial drugs. In immunology and vaccine development (3,4) overlap was evident in relation to specificity of the immune response and the role of T cells. Studies of merozoite surface proteins and of adhesion mechanisms of infected erythrocytes were common themes in past and future plasmodial studies. Functional studies of parasite genes, and in particular genes concerned with drug resistance, were highlighted in parasite genetics (7). In the subfield clinical management of malaria patients (8), studies on the use of mefloquine and dichloracetate were considered to be both past achievements and future opportunities. Genetic factors influencing disease severity were recommended as an area of future opportunity in the subfield pathophysiology of disease symptoms (9). The relationship between transmission rates and disease manifestation was a topic highlighted as an important achievement and future opportunity in epidemiology (11), and also an important opportunity in pathophysiology (9). Mechanisms of resistance to insecticides were quoted in both past achievements and future prospects for studies on mosquito vectors (14).

A number of areas that cut across subfields were highlighted as offering high future potential. These included studies on genetics, drug resistance, and transmission dynamics in relation to disease severity. Significant opportunities for malaria research would appear to exist in these three broad areas.

This chapter has examined the views of a number of experts on malaria papers supported by the Wellcome Trust and published in three specific years. For a fuller analysis of international achievements in malaria research, as well as future directions for the field, it is necessary to survey the international malaria community including groups who do research, as well as those who use the results of research. The next chapter discusses such a survey. The analyses follow a similar qualitative approach to those introduced in the current chapter, and focus on identifying the broader achievements of malaria research, its potential impact on health care, and the barriers to the implementation of research findings.

OPINION SURVEY 6

The aim of the final phase of the study was to survey opinion among a large and diverse group of researchers and users within the international malaria community on issues relating to the current practice and future direction of malaria research. The community canvassed included researchers, clinicians, health services practitioners and advisers, industrialists, administrators and policy makers. Views were sought on mechanisms for translating research results into practice, measures to strengthen the field of malaria research, and potential future prospects for advancing understanding in malaria research.

The survey offered an opportunity for respondents to express their experiences and opinions on mechanisms of communication and information transfer, and thus suggest how research results may better inform the prevention, control and treatment of malaria in practice. It also encouraged participants to consider opportunities for advancement of the field beyond any current constraints of finances or institutional affiliation. The analysis was complementary to, but broader than, the preceding phase of the study, which concentrated only on the portfolio of the Wellcome Trust.

6.1 METHODS

A questionnaire was designed concerning the current practice and future directions of malaria research. The questionnaire was piloted with the Steering Committee for the study. Following amendments suggested in the pilot study, the questionnaire (see Annex 7) was distributed by post.

The questionnaire was sent to an international group of 224 individuals who work in malaria-related disciplines including research, control or treatment. The group was identified from several sources: membership of the British Society of Parasitology, contact lists of the London School of Tropical Medicine and Hygiene and of the Tropical Medicine Interest Group at the Wellcome Trust, and data generated in the bibliometric stage of the review on prolific authors of malaria publications.

Within six weeks of distribution and following two postal reminders, 51 per cent of the questionnaires had been completed and returned, and the survey was closed. Responses were analysed using the software package SPSS. In some instances, results have been analysed according to two professional groupings, defined as follows for the purposes of this report: the 'researcher group', composed of basic science and clinical researchers, and the 'user group', consisting mainly of health services practitioners/advisers, and administrators/policy makers but also including a few industrialists/manufacturers (Table 6.1). The profile of the entire set of individuals contacted for their opinions was composed of 65 per cent researchers and 35 per cent users.

Where possible, categories of malaria are referred to in the text by letters (A–H), and subfields of malaria by numbers (1–14), describing the classification system defined in Chapter 4.

Table 6.1 Composition of researcher and user groups

Researchers	Users
Basic scientists	Health services practitioners/ advisers
Clinical scientists	Administrators/policy makers Industrialists/manufacturers

6.2 RESULTS

6.2.1 Profile of respondents

The majority of respondents to the survey were researchers (Figure 6.1). Researcher and user groups composed approximately[36] 78 and 22 per cent of the respondent profile, respectively, indicating a higher response rate from researchers than from users (given the professional profile of 65 per cent researchers and 35 per cent users in the entire set of individuals who were sent the questionnaires). A small number of respondents indicated that they were industrialists, and a number of individuals indicated other positions such as malaria ecologist, epidemiologist, or health services researcher. Some individuals indicated a combination of professions.

Roughly one-half of respondents worked in the university environment (Figure 6.2). The government sector was also well represented. A total of only 2 per cent of respondents indicated that they worked in non-governmental organizations (NGOs), although the participation may have been greater if some of the 5 per cent of respondents who worked in funding bodies included those in NGOs. Some respondents (3 per cent) indicated a workplace other than the proffered categories, and quoted international health agency and university field station. A total of 7 per cent of individuals worked in a combination of work environments, and almost three-quarters of respondents indicated that they were involved in fieldwork in a malaria-endemic country.

Just over one-fifth of all respondents specified that their main interest was in immunology and vaccine development (3, 4) (Figure 6.3). A substantial number of respondents indicated a main interest in the biology of *Plasmodium* (5) and in intervention trials and health services research (12). A substantial number also identified a combination of the proffered subfields as their main areas of interest. The subfield concerning the development of diagnostic tests (13) was an area poorly represented by the sample. However, as seen in the subfield analysis (Chapter 4), the subfield is small internationally.

6.2.2 Translating research results into practice

More than two-thirds of respondents indicated experience in projects where research results were taken up and developed further, with a view to improving the treatment or control of

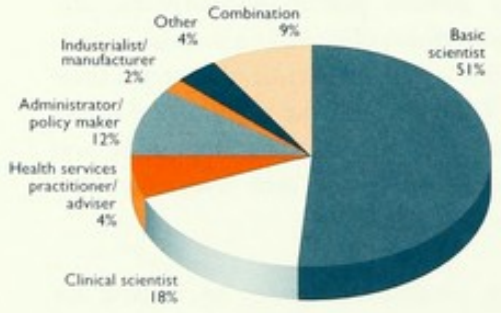


Figure 6.1: How respondents categorized their professional positions
(% of survey respondents)

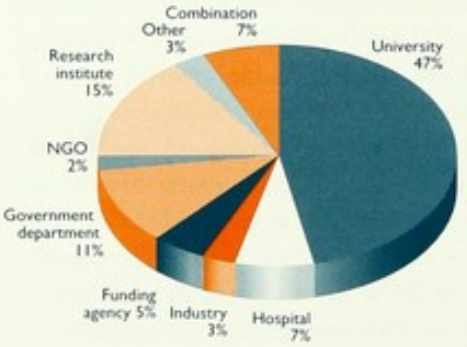


Figure 6.2: How respondents categorized their working environment
(% of survey respondents)

[36] Approximations are due to the inability to categorize certain individuals who indicated a combination of positions.

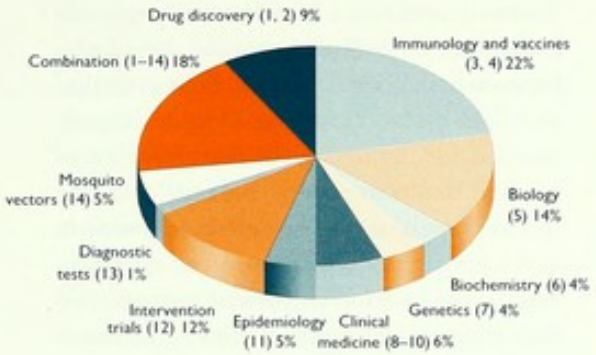


Figure 6.3: Respondents' main areas of interest in malaria research
(% of survey respondents)

malaria. A high percentage (74 per cent) of these respondents were researchers, thus suggesting the existence of active links between research and development. Indeed, those researchers who cited experience in such projects represented a high percentage (64 per cent) of all the researchers in the survey. This finding supported the argument that the field is well represented by clinical research (see Chapter 4).

Analysis of the responses was based on the categories of malaria research (A–H: see Chapter 4), because most responses could not be allocated to specific subfields. Most frequently cited experiences were in two categories: antimalarial drug discovery and development (A) and clinical treatment and pathophysiology (D). Together, these categories accounted for 37 per cent of all responses. These focused on involvement in some stage of the development and testing of antimalarial drugs, in optimization of treatment or prophylaxis drug-dosage regimens, or in improving methods for the management of malaria. Examples included: study of the efficacy of combinations of antimalarial drugs; monitoring the development of resistance to antimalarials, pharmacokinetic and toxicity evaluations; studies of malaria prophylaxis in pregnancy; the development of non-human primate models for testing of antisulphamalarial drugs; and trials of sodium dichloroacetate for the management of lactic acidosis in complicated malaria.

Intervention trials and health services research (F) was cited in 25 per cent of responses. Examples included: field-testing of impregnated bednets and their incorporation into large-scale control programmes; development of standard malaria treatment guidelines based upon local information on parasite drug sensitivity; design of treatment and control programmes; and advising governments and NGOs on the policy implications of research concerning malaria treatment and control.

Immunology, vaccine development and vaccine trials (B) were cited in 18 per cent of responses. Experiences included: characterization of potential vaccine candidate antigens; development of vaccines to induce antimalarial cytotoxic T cell responses; monitoring human immune response to specific antigens; animal and human vaccine trials; and the development of vaccine delivery systems.

Each of the other categories of malaria research were cited much less frequently (<8 per cent of responses).

6.2.3 Untapped potential of research results

Half of the respondents indicated that they were aware of research results which might have influenced the treatment or control of malaria but which had not been developed further. Again, a high percentage (71 per cent) of these respondents were researchers. Those researchers who were aware of research results which had not been developed, despite their potential impact, represented just under half (44 per cent) of all the researchers in the survey. Consequently, over half of all researchers were not aware of any research results which were left unexploited. Users who were aware of research results which had not been developed, despite their perceived potential, represented almost one-third (29 per cent) of all the respondents familiar with examples of unexploited research. Consequently, over one-half (58 per cent) of all users knew of research results which, potentially, could still influence the treatment

or control of malaria. Barriers to the transfer of research results are discussed below.

Many different cases of untapped research results were reported and examples are listed in Annex 8. A substantial number of the cases reported were methods for the management and treatment of malaria. A number of examples were given of potential antimalarial drugs that were awaiting further development, and some respondents also referred to the lack of incentives for commercial investment in the development of antimalarial drugs and vaccines. Several individuals expressed concern that some research results had been selected for further development or implementation without adequate evidence of their effectiveness or value.

6.2.4 Barriers to the transfer of research results into practice

Respondents identified three groups of barriers limiting the transfer of research results into the treatment and control of malaria. These barriers related to: obstacles in the design and organization of research programmes; issues concerning the evaluation of research results and the development of new products; and resources in malaria-endemic countries.

Barriers relating to the design and organization of the research programme

Insufficient orientation to user needs and inadequate standardization of methods

Several issues regarding the organization of research programmes were highlighted. Insufficient orientation of research programmes on identified needs or problems was cited by a number of respondents. A low awareness by basic scientists of the mechanisms and requirements for product development was also cited. Respondents also perceived a need for increased standardization of techniques, reagents and data analysis methods employed in field trials to ensure comparability of research results.

Recommendations to deal with these barriers included strengthening links between malaria control agencies, health workers and researchers, as well as increasing interaction between basic scientists and workers in clinical and field-based disciplines. Measures recommended for improving the dissemination of research results in malaria-endemic countries included: publishing in journals accessible in developing countries, inclusion of a 'recommendations' section in journal formats, and strengthening Internet facilities. Increased investment in operational research was also recommended to optimize implementation of control and treatment methods on a large scale and under non-ideal conditions.

Barriers relating to the evaluation and development of the results of research

Inadequate mechanisms for evaluating findings and for developing results into practice

Respondents cited the need for an effective mechanism for the independent evaluation of research results which have potential for improving malaria treatment and control. They also indicated that the substantial cost involved in fulfilling registration requirements was a major inhibitory factor in the development of new products. The lack of incentives for commercial companies to invest in products to be used in resource-poor countries was highlighted.

Respondents recommended that governments and donors – possibly the WHO – should take a more proactive role in evaluating research results and in developing new products. This could involve establishing consortia of institutes and companies with relevant expertise in product development, providing tax incentives to companies and tailoring the complex regulatory requirements of developed countries to a registration procedure more appropriate to developing countries.

Another problem identified by a number of respondents was the limited facilities available for conducting the preliminary stages of vaccine trials: only one suitable facility exists in Europe, which is shortly to close, and vaccine

developers are primarily dependent upon facilities in the USA and Australia. Respondents recommended that facilities for conducting the preliminary stages of vaccine trials be made more readily available.

Resource limitations in malaria-endemic countries

Resource limitations in malaria-endemic countries cited by respondents included: insufficient research expertise; inadequate local policies for appropriate drug and insecticide usage; inadequate infrastructure for the implementation of local policy relating to health services; and gross underfunding of health services.

Measures to tackle the lack of research expertise included greater funding of collaborations between laboratories in developed countries and malaria-endemic countries, and greater exchange of trainees between these countries. Increased communication between individuals in different malaria-endemic countries was also suggested.

Further recommendations included increasing the funding of local health services, and establishing an adequate infrastructure for the implementation of policy decisions relating to health care. International leadership in the effective management of new and existing tools for malaria treatment or control was also considered very important, for example by ensuring the development of policies for drug usage that aim to prevent the further development of drug resistance. The potential for the WHO to play a more effective role as an independent adviser in coordinating, informing and implementing policy decisions was identified by a number of respondents.

6.2.5 Collaboration, dissemination of results and networks

Communication networks were analysed on the basis of two groupings, researchers and users (see Table 6.1 for definitions). The percentage of researchers reporting regular communication with other researchers (81 per cent) was higher than the percentage of users reporting regular communication with other users (68 per cent) (Table 6.2). However, a higher percentage of users reported regular communication with researchers (74 per cent), than did researchers with users (34 per cent). Overall, these results suggest that the majority of respondents (researchers plus users) engage in regular communication with others working in malaria-related disciplines. The exception was the low percentage of researchers who indicated that they had regular communication with users.

The percentage of users reporting a need for improved communication (Table 6.3) with other users (54 per cent) was higher than the percentage of researchers reporting a need for improved communication with other researchers (26 per cent). However, a higher percentage of researchers recognized a need for improved communication with users (43 per cent), than did users recognize the need for improved communication with researchers (29 per cent). Overall, a need for improved communication with users was viewed by a

Table 6.2 Percentages of researchers or users who view that they have regular current communication within and between groups

The views of ...	current communication with (other) researchers (%)	current communication with (other) users (%)
researchers on their ...	81	34
users on their ...	74	68

higher percentage of all respondents (researchers plus users) than was a need for improved communication with researchers. This result emphasizes the growing recognition of the role of the user in the research process.

Scientific journals and personal communication were considered, by all respondents, to be the most important mechanisms for obtaining information (Figure 6.4a). Researchers and users reported broadly similar preferences for obtaining information, although researchers gave less importance to reports, Internet and informal mechanisms (television, popular press and radio). There was less agreement between researchers and users with reference to the dissemination of information (Figure 6.4b). Whereas researchers rated journals as most important, users rated both personal communication and conferences as most important.

Almost half of the total number of respondents indicated an involvement in research networks. However, other formal collaboration was minimal: only one in 10 respondents indicated an involvement in collaboration to implement/disseminate research results, and only one in 20 said they had access to policy-making arenas.

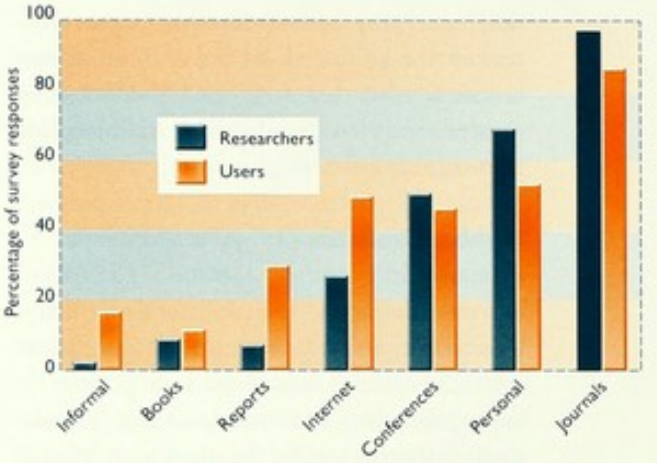


Figure 6.4a: Methods used to obtain information on current malaria research

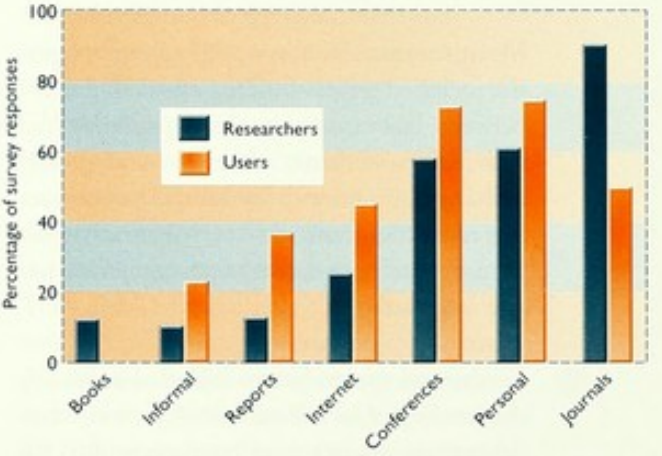


Figure 6.4b: Methods used to disseminate information on current malaria research

6.2.6 Measures to strengthen malaria research

Respondents ranked a multidisciplinary approach to research as the most important measure for strengthening the field of malaria research (Figure 6.5). Researchers and users also ranked two other measures as important: improved consultation with users and improved training in malaria-endemic countries. Both researchers and users viewed improved mobility of researchers as relatively unimportant.

Table 6.3 Percentages of researchers or users who view that they have a need for improved communication within and between groups

The views of ...	need for improved communication with (other) researchers (%)	need for improved communication with (other) users (%)
researchers on their ...	26	43
users on their ...	29	54

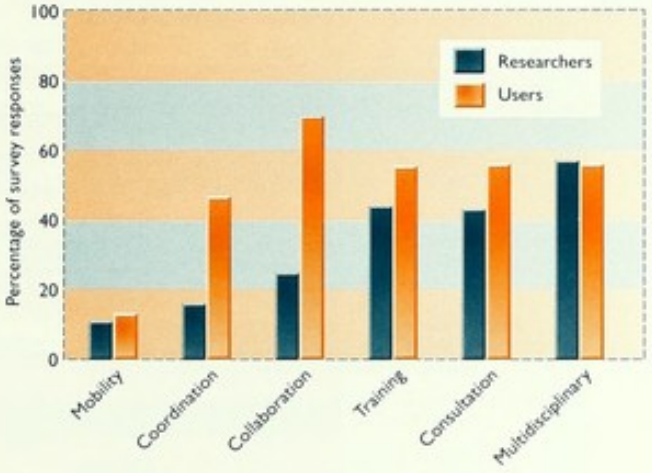


Figure 6.5: Most important measures for strengthening malaria research

6.2.7 Under-resourced subfields

The analysis was again based on the categories of malaria research (A–H: see Chapter 4), because most responses could not be allocated to specific subfields. The category which was cited most frequently as likely to benefit from increased effort in resources was intervention trials and health services research (F). This subfield was cited in 23 per cent of responses. Attention was drawn to the need for promoting research into the implementation of control measures, including consideration of cultural and economic factors.

Several other categories were also perceived as under-resourced. Basic studies of the parasite (C) were cited in 15 per cent of all responses. Respondents suggested that a greater understanding of parasite biochemistry would reveal parasite-specific pathways or processes that could be targeted by chemotherapy. Funding directed towards obtaining a complete map of the genome of *P. falciparum* was also supported, as well as the development of effective transfection systems for *P. falciparum*.

Epidemiology (E) was considered under-resourced in 14 per cent of all responses. Attention was drawn to the need for various studies: on the epidemiology of childhood malaria (from birth to the age of five years); the use of immunological tools in applied epidemiology–entomology studies; and the implementation of improved methods for the collection, handling and analysis of statistical information.

The category immunology, vaccine development and vaccine trials (B) was cited in 12 per cent of responses. Studies of the immunogenicity of vaccine candidates in primates was given as an example of a specific area that might benefit from greater attention. The category antimalarial drug discovery and development (A) was also cited in 12 per cent of responses. Other subfields were less frequently cited as likely to benefit from increased research effort.

6.2.8 Future prospects for advancing understanding

Figure 6.6 presents the views of respondents on the prospects, in each subfield, for substantial advances in understanding over the next five years. Two subfields, genetics of *Plasmodium* (7) and biology of *Plasmodium* (5), received the greatest percentage of votes cast for subfields considered to offer 'very good' prospects for making substantial advances in understanding (43 and 34 per cent of all responses cast in each subfield, respectively). Some respondents also anticipated that the probable sequencing of the malaria genome within the next five years may lead to new challenges and opportunities hitherto unidentified. Three other subfields were also perceived by a large number of respondents as having very good prospects for advancing understanding in the medium term: epidemiology and mathematical modelling (11: 23 per cent of all responses cast in that subfield); intervention trials and health services research (12: 21 per cent of all responses cast in that subfield); and immunology and vaccine development (3: 21 per cent of all responses cast in that subfield).

Prospects in each subfield were also examined from the perspective of those who work in that subfield. This analysis is necessary to detect the extent to which experts were voting for their own subfields. Figure 6.7 presents the percentage

of subfield experts who rated their own field of expertise as having very good prospects for advancing understanding over the next five years. For example, 81 per cent of all those individuals who indicated that their field of main interest was the genetics of *Plasmodium* rated that same subfield as having very good prospects. However, caution in interpreting the analysis is urged because of both the variable number of subfield experts (n = 1–24) and the small number of experts in certain subfields (e.g. diagnostic tests, where n = 1). Nonetheless, the results suggest that in three subfields more than half of the experts rated each of those subfields as having very good prospects for advancing understanding in the medium term: these were the genetics (7), biology (5), and biochemistry (6) of *Plasmodium*. The single expert working in diagnostic tests (13) rated his area highly. This analysis presents an interesting viewpoint given that subfield experts may rate their own subfield highly for two related reasons: familiarity with a subfield and commitment to its future potential; or vested interest in encouraging support for one's own area of research. In this sense, the results from Figure 6.7 provide useful insight for interpreting the results in Figure 6.6.

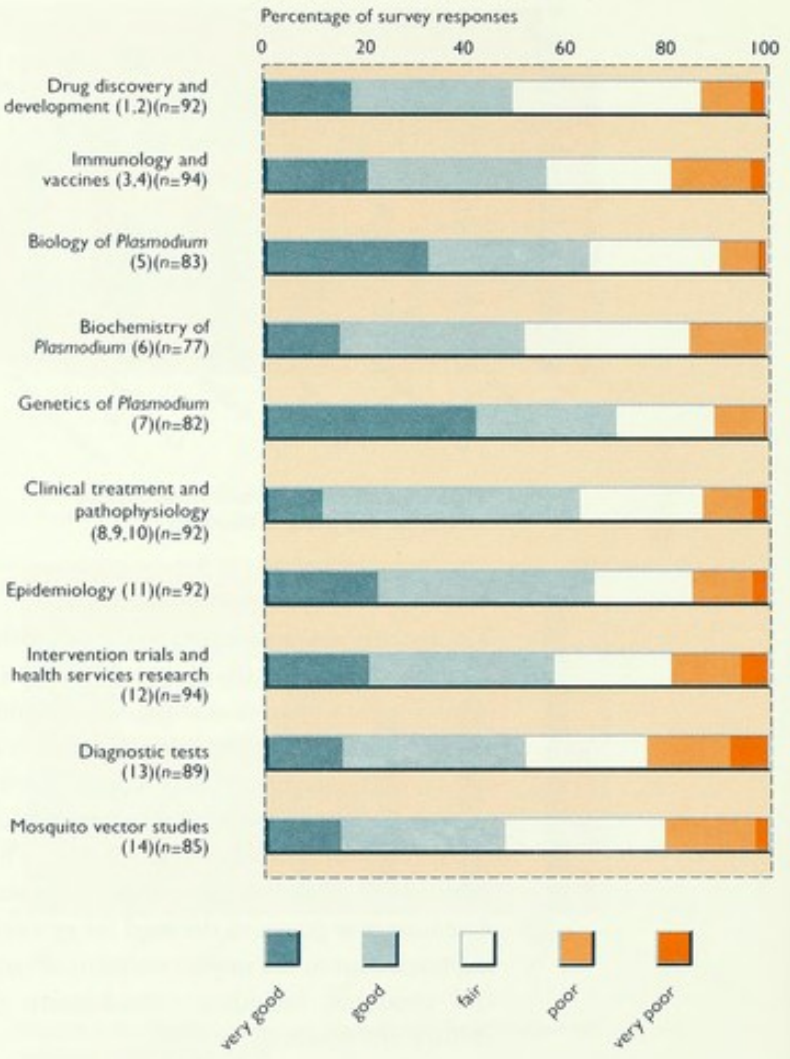


Figure 6.6: Prospects in each subfield for substantial advances in understanding over the next five years
(where n = total number of responses)

6.2.9 Funding malaria

Recommendations for the expenditure of US$ 10 million in malaria covered seven main areas, and each respondent had multiple suggestions for spending the money. About 65 per cent of all respondents suggested funding research. Specific recommendations for the funding of subfields were very similar to the opinions expressed concerning under-resourced subfields reported above.

Approximately 40 per cent of all the respondents recommended investing in human capital, through education and training, career structures and exchange of scientists. About 20 per cent of all respondents argued for the use of funds in each of four areas: (1) treatment and control policy (such as the development/monitoring of drug use/control programmes or the provision of bednets, insecticides etc.); (2) communication, especially via networks and workshops; (3) research management (such as more multidisciplinary studies, research goals targeted at health needs, a balance between short- and long-term projects/aims, and a balanced portfolio of subfields); and (4) infrastructure – both organizational (such as malaria research institutes or development agencies) and local or regional in malaria-endemic areas (such as in laboratories, equipment, information systems, or techniques).

Recommendation was also made for investment in schemes to promote the translation of research results to clinical practice and control programmes (10 per cent of respondents), as well as industrial involvement (7 per cent of respondents).

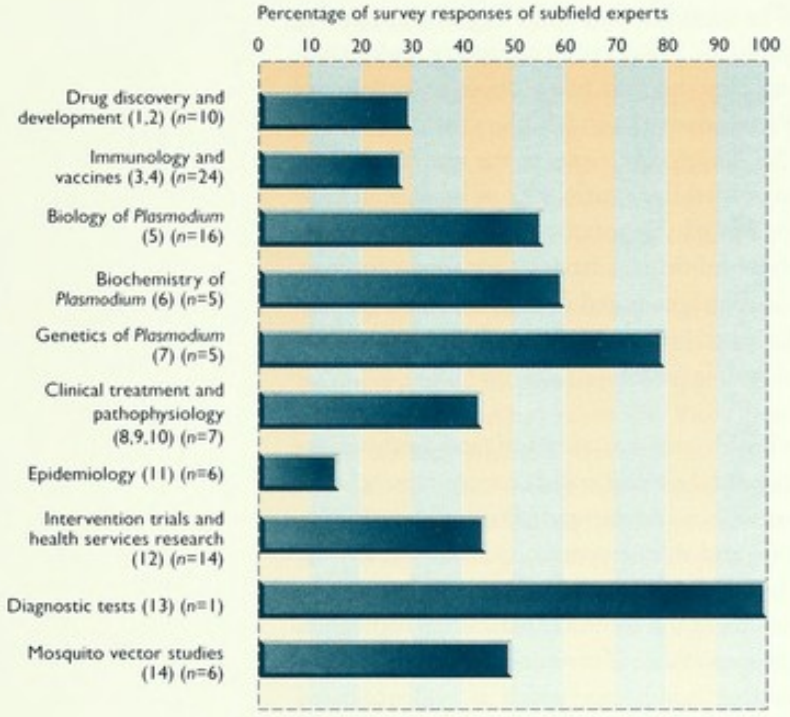


Figure 6.7: Percentage of subfield experts who rated their own interest as having very good prospects for advancing understanding over the next five years
(where n = total number of subfields experts)

6.3 SUMMARY

The survey highlighted a number of key points concerning research and the implementation of research results into practice. More than two-thirds of respondents indicated that they had personal experience of projects where research results were developed for improvements in disease prevention, treatment or control. However, almost half of the respondents were also aware of valuable research results which had not been developed. These findings indicate that research in the field of malaria has the potential for having a direct impact on health care, but that the potential has not been fully exploited.

Three groups of barriers to the transfer of research results into practice were identified. These barriers related to: (1) obstacles in the design and organization of research programmes, (2) issues concerning the evaluation of research results and the development of new products, and (3) resources in malaria-endemic countries. Key obstacles were insufficient orientation of research programmes to practical problems and public needs; inadequate standardization of field techniques; insufficient mechanisms to evaluate research results and to develop products to market; and limitations in human capital, infrastructure, and funding in malaria-endemic countries.

The identification of these obstacles raises a number of issues of relevance to international agencies and funding bodies, as well as to governments in malaria-endemic countries. Firstly, specific problems and user needs could be taken into account in the design and support of research programmes. To achieve this aim, encouragement could be given, and mechanisms supported, to promote active and international communication between groups. In particular, interaction between scientists, administrators and policy makers on the one hand, and health services practitioners and advisers on the other hand, might be encouraged.

Secondly, the need for a mechanism to evaluate research results for their potential uptake into practice offers a unique opportunity for an international organization – perhaps the WHO, an NGO or a funding body – or indeed a collaborative group, to play an influential role in informing, coordinating and implementing policy. Evaluating the effectiveness of health-care interventions using reliable systematic reviews is now widely recognized as useful practice in both planning trials and informing policy. A precedent for such a mechanism is the Cochrane Collaboration, the international network for the systematic review of clinical research results in specific health-care interventions (Bero and Rennie, 1995; Garner *et al.*, 1996).

Thirdly, the need for establishing mechanisms for the development of products offers an opportunity for an NGO or funding body to have a proactive role in an arena which is typically the remit of the private sector or regulatory commissions. Alternatively, a consortium could be established to include groups

with relevant expertise such as industry and government, as well as NGOs and funding agencies.

Finally, the lack of scientific expertise in malaria-endemic countries might be addressed through increased training and collaboration with non-endemic countries. The development of further overseas units, such as those funded by the Wellcome Trust and the UK MRC, might assist in this process. Furthermore, overseas units have a role not only in training, but also in encouraging project design which is relative to needs in malaria-endemic countries, as well as providing a route for applying research results to field conditions.

The survey also identified specific measures to strengthen the field of malaria research, and subfields with particular promise or needs. The most important measure to strengthen the field of malaria research was considered the use of a multidisciplinary approach to research. The category judged to be most likely to benefit from greater research effort, improved training opportunities or an increased input of funding was intervention trials and health services research. Several other categories were perceived as under-resourced: basic studies of the parasite; epidemiology; immunology and vaccine development; and antimalarial drug development. The allocation of funds to research was recommended in these areas.

The subfields cited most frequently as having very good prospects for advancing understanding over the next five years were: genetics of *Plasmodium* (7) and biology of *Plasmodium* (5). A high percentage of the individuals who identified their main area of interest in basic studies of the parasite (5,6,7) also perceived those subfields as having very good prospects. Caution is required in this last interpretation, however, because of the small number of individuals involved.

This chapter has surveyed and analysed the views of the broad malaria community including researchers and the users of research. Both scientific and infrastructural issues have been discussed. The active role of research in the practical treatment and control of malaria has highlighted the importance of investing in research and promoting health care which is evidence-based. However, barriers which limit the transfer of research results into practical application have also been identified. The report has suggested mechanisms to tackle these obstacles, and highlighted the need for international action. It has also indicated which subfields are viewed by the community as being currently under-resourced, and which have the greatest prospects for advancing knowledge over the next five years. These findings should be of interest to all those engaged in the research, treatment or control of malaria, and to those organizations which support scientific studies in malaria.

7 DISCUSSION AND POLICY ISSUES

Malaria is a major killer which threatens 40 per cent of the world's population and causes between 1.5 and 2.7 million deaths per year. Disease prevalence is increasing and geographical boundaries are extending. The main factors influencing this growing burden are decreasing efficacy of both antimalarial drugs and insecticides, major environmental developments such as land clearance for mining or farming, and social disruption such as that caused by war.

The current situation demands informed action in disease prevention, treatment and control. Any practical approach to combat disease must be underpinned by research which is focused on specific public needs and characterized by excellence. The current study has indicated the impact which malaria research has had on practical health care. Indeed, more than two-thirds of respondents in an international survey of the malaria community indicated that they had personal experience in research that was later developed to improve the prevention, treatment and control of malaria.

7.1 POLICY ISSUES FOR MALARIA RESEARCH

Funding trends

Despite the extent and severity of the condition, as well as the proven value of research for practical health gain, global expenditure in malaria research is very low. Total identifi -able worldwide spend was approximately US$84 million in 1993, representing a research investment for each malaria-related death of approximately US$42. This figure compares very poorly with available data indicating that research expenditure per death may be orders of magnitude higher for conditions such as cancer, HIV/AIDS or asthma.

The funding survey revealed that support for malaria research is principally derived from governments in Europe and the USA, and from international bodies. Support from industry was difficult to discern, but is likely to be low. The largest source of funding is currently the USA, although there has been a downward trend in funding from that country over the past 10 years. Meanwhile, the trend is upward in the UK, and especially at the Wellcome Trust where funding effort has increased eightfold in the past decade.

Research outputs

An analysis of worldwide publication activity, identified through scientific papers written in international peer-reviewed journals, indicated that the total number of malaria publications per year is approximately 1000. This figure is very small compared with other biomedical fields such as cardiovascular science which has over 70 000 publications worldwide per year (Anderson *et al.*, 1994). The USA is the single largest contributor to malaria research, although its share of world publications has been decreasing over the past 10 years. Meanwhile, the share of the UK – currently the second-largest contributor worldwide – is increasing. The number of acknowledgements

in research publications largely corresponded with the relative funding levels of different agencies, as determined through direct survey of the funding bodies. Citations to the papers supported by major funding bodies were more numerous than citations to papers acknowledging other organizations. These results indicate the high scientific impact of research funded by the major agencies.

International research in the field of malaria covers a large number of subfields including both clinical and non-clinical areas. The study showed that worldwide research publications are evenly distributed across most subfields. Two categories have had the largest share of outputs: clinical treatment and pathophysiology; and basic science studies of the malarial parasite. However, studies of antimalarial drugs, immunology, epidemiology and mosquito vectors were also well represented by publications. Intervention trials and health services research appeared less active than other subfields. Changes in research emphasis over the decade have slightly favoured research on the genetics of *Plasmodium*, as well as the clinical management of malaria. Meanwhile, emphasis has shifted away from the biology and biochemistry of *Plasmodium*, as well as mosquito vector studies.

Laboratory-based studies have been predominantly located in developed countries, whereas clinical and field-based research has tended to have a broader geographical spread, including many developing countries. The emphasis of research in the UK has been on basic studies of the parasite, as well as pathophysiology and disease symptoms of malaria.

Future opportunities

The need to focus limited financial resources in all fields of biomedical endeavour, as well as the increasing disease prevalence of malaria, demand that funding for malaria research be appropriately directed to subfields which have good prospects for advancing knowledge and/or improving the quality of health.

Expert scientific opinion of the Wellcome Trust portfolio of papers identified specific research topics of high future potential. Also identified were several broader areas that cut across a number of malaria subfields. These included genetics, drug resistance, and transmission dynamics in relation to malaria severity. Members of the international malaria community, including researchers and the users of research, most frequently cited two subfields as having very good prospects for advancing understanding over the next five years. These were the genetics and biology of *Plasmodium*. The under-resourced subfield which was perceived most likely to benefit from increased research effort was intervention trials and health services research. This area was also identified as having a low publication output. The analysis suggested that a focus on one of these subfields may encourage research with a high potential impact to promote either knowledge or practical healthcare gains.

Barriers to the uptake of research results

The success and impact of research depends on effective mechanisms to transfer the results into practical application. Effective mechanisms to transfer knowledge into practice are required to overcome the very real obstacles which limit or prevent the uptake of research. Indeed, almost one-half of the respondents in the international community survey indicated knowledge of research with potential healthcare gains which had not been developed.

Three groups of barriers were identified. The first group focused on obstacles concerning the research itself. Respondents cited insufficient orientation of research on user needs, as well as inadequate standardization of methods used in field trials. The second group of barriers related to issues concerning the evaluation and utilization of the results of research. Respondents cited insufficient independent evaluation of research results, as well as inadequate schemes for the development of research results into products. The third group of bar-

riers concerned resources in malaria-endemic countries. Respondents cited limitations in both human capital and funding.

Tackling the barriers

The identification of these barriers raises a number of issues of relevance to international agencies and funding bodies, as well as to governments in malaria-endemic countries. These include options to direct and manage research funds to best effect, and to evaluate and develop the results of research.

Clearly, specific problems and user needs could be taken more into account in the orientation of research programmes. To achieve this aim, renewed efforts could be made to promote active communication between individuals in malaria-endemic and non-endemic countries. Equally, further efforts to increase communication between professional groups could be recommended, especially between scientists, administrators and policy makers on the one hand, and health services practitioners and advisers on the other. The management of research could be improved by several means: further attempts to introduce standardization of methods in field trials, increased investment in operational research, wider dissemination of research results, and greater research collaboration between countries.

The need for a mechanism to evaluate research results for their potential uptake into practice offers a unique opportunity for an international organization – perhaps the WHO, an NGO, a government, funding body or global collaboration network – to play an influential role in informing and coordinating research findings. There is a precedent in some developed countries which have established academic centres for the systematic review of research results bearing on specific health problems. The Cochrane Collaboration is an international network of individuals organized around centres which prepare, maintain and disseminate systematic reviews of the results of clinical research – usually of different randomized control trials of specific health-care interventions. Techniques such as 'meta-analysis' and 'sensitivity analysis' are being developed in an effort to promote evidence-based medicine. The work of such centres and their international collaborators has helped to guide health-care practice and to plan future research. Developing further initiatives for the systematic review of the results of malaria research, prior to their introduction in practical health-care settings, could be a valuable development.

The need to develop new products based on research findings also offers an opportunity for an NGO or funding body to have a proactive role in an arena which is typically the remit of the private sector or the regulatory commission. Alternately, a consortium could be established to include groups with relevant expertise such as industry and government, as well as NGOs and funding agencies.

In relation to resources, the lack of research expertise in malaria-endemic countries might be addressed through collaborations and exchange of personnel. The development of additional overseas units, such as those funded by the Wellcome Trust and the UK MRC, could further promote the development of local expertise. Indeed, overseas units could play an increasingly important role not only in training, but also in designing projects relative to needs in malaria-endemic countries, as well as providing opportunities for applying research results to field conditions. However, the majority of funding for malaria research is presently invested in research teams based in developed countries. The lack of available funding for health-care services in malaria-endemic countries is a recognized problem, but one which is beyond the scope of this report.

7.2 REFLECTIONS ON METHODS USED IN THIS STUDY

This report has described a number of quantitative and qualitative methods used to produce an evidence-based report on the status and future options in malaria research. In order to guide similar studies which might be conducted in the future, a number of general points should be made concerning the approach and techniques used in this study.

Assessing research inputs and outputs

Firstly, the identification of funding bodies was achieved through two separate means (Chapters 2 and 3). Direct contact with funding agencies identified through literature searches and scientific attachés in London-based embassies was time-consuming. However, this approach provided detailed information on the funding of malaria research, and also allowed for the confirmation of the data with source organizations once it had been collected, analysed and collated. The use of acknowledgements in scientific publications provided an alternative and comprehensive approach to identifying the full range of sources of support for research. That method had the advantage of relative rapidity and simplicity, but did not provide data on the amount of funding support, nor on its allocation either to different areas of research or to geographical regions. Both direct survey of funding bodies, and indirect analysis using funding acknowledgements in papers, are recommended for a full picture of the agencies involved in supporting research.

Publication output analysis (Chapter 3) required the use of commercially available databases which are not designed for bibliometric analysis, nor for an examination of the full extent of outputs from malaria research. Although two appropriate science databases exist, the Science Citation Index (SCI) and Medline, neither covers completely the so-called 'grey literature' of national or regional journals, technical memoranda, conference proceedings, and non-English-language publications. This omission is an important consideration for the field of malaria, which mainly affects developing countries and is of local interest to researchers in those countries.

The subfield analysis was very specific and useful for identifying differences in the output of publications in different subfields (Chapter 4). However, there was an inevitable degree of subjectivity associated with the definitions of the categories and subfields. Furthermore, the partial reliance on the Medline database limited the interpretation of the geographical analysis of national strengths and weaknesses to publication activity based only on the first-author address of a paper. However, it was felt that for the purposes of subfield analysis, the advantages of the Medline database in allowing for a more accurate classification of research by subfield (on the basis of the abstract), and a greater coverage of clinical and epidemiological publications, outweighed the disadvantage of the limited author-address information.

A full analysis of input/output ratios, based on funding and on publications, was not attempted because of a variety of factors. Firstly, the time-lag between the awarding of grants and the publication of research results complicates any such relationship. Secondly, the variability between subfields in research effort required to produce results, and hence publications, meant that a comparison between subfields might be misleading.

Conducting surveys

Lastly, the use of both an expert review of published papers (Chapter 5) and an international, community-wide survey on future directions for scientific endeavour (Chapter 6) proved very valuable in identifying past achievements and future opportunities in malaria research. Analyses indicated the impact that research has had on the broader outcomes of medical investigation, such as the development of products or health-care practices. This approach was complementary to citation analysis which

indicates impact specifically in the research arena. The international survey also identified barriers to the transfer of research results into practice, and recommended schemes to deal with those obstacles.

One useful design feature of the community survey was the inclusion of a large number of professional groups. This breadth limited the likelihood that the findings of the survey would reflect the views of any particular professional group, and provided an opportunity for less vocal groups to be heard. The process also raised the awareness of individual groups to the broader issues of malaria research, and identified opportunities for increased communication and coordinated action between groups.

7.3 THE CHALLENGE

This report has been published in an effort to inform the international malaria community of the current status and future opportunities in the field of malaria research. Although the study was initially intended for the Wellcome Trust alone, it has since become evident that the information may be of value to other organizations which fund, manage or conduct malaria research.

The Wellcome Trust recognizes its growing presence in the field of malaria research. However, the Trust is also conscious of the need for an international, collaborative approach to scientific investigation and evidence-based medicine. The pressing need and growing challenge to combat malaria is clearly evident. The current study has indicated potential directions and effective approaches to address the challenge, and calls for a coordinated response from the international malaria community.

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Garner P, Zaat J, Robb R (1996) Tropical medicine on trial: getting hold of all the evidence. *Parasitology Today* **12:** 211–212.

Katz J S, Hicks D, Sharp M, Martin B R (1995) *The changing shape of British science*. STEEP Report 3. Falmer, Science Policy Research Unit, University of Sussex.

Kerr J (1995) Greenhouse report foresees growing global stress. *Science* **270:** 731.

Lewison G, Seemungal D (1995) *Benchmarking information: research investment and research output*. Companion Paper A to the Office of Science and Technology Health and Life Sciences Report. London, Cabinet Office.

Leydesdorff K (1988) Problems with the measurement of national scientific performance. *Science and Public Policy* **15:** 149–152.

Michaud C, Murray C J L (1996) Resources for health research and development in 1992: a global overview. In *Investing in health research and development*. Ad Hoc Committee on Health Research Relating to Future Intervention Options, World Health Organization, TDR/Gen/96.1. Geneva, WHO.

MRC (1994) MRC Annual Report April 1993–March 1994. London, Medical Research Council.

Murray C J L, Lopez A D (eds) (1994) *Global comparative assessments in the health sector: disease burden, expenditures and intervention packages*. Geneva, WHO.

Narin F (1976) *Evaluative bibliometrics: the use of citation analysis in the evaluation of scientific activity*. New Jersey, Computer Horizons.

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Oaks S C, Mitchell V S, Pearson G W, Carpenter C J (eds) (1991) *Malaria: obstacles and opportunities*. National Academy Press for The Institute of Medicine.

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Rogers L A, Anderson J (1993) A new approach to defining a multidisciplinary field of science: the case of cardiovascular biology. *Scientometrics* **28:** 61–77.

Sancho R (1992) Misjudgements and shortcomings in the measurement of scientific activities in less developed countries. *Scientometrics* **23:** 221–233.

Wadman M (1996) Budget politics jeopardizes US drug credit. *Nature* **379:** 287.

World Health Organization (1993) *A global strategy for malaria control*. Geneva, WHO.

World Health Organization (1995a) *Fact sheet*, no. 94. Geneva, WHO.

World Health Organization (1995b) *Tropical disease research: twelfth programme report of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)*. Geneva, WHO.

World Health Organization (1995c) Unpublished document – The WHO action plan for malaria control, 1995–2000. Division of Control of Tropical Diseases, CTD\MAL\95.2.

World Health Organization (1995d) *The world health report 1995: Bridging the gaps*. Geneva, WHO.

World Health Organization (1996) *Investing in health research and development*. Ad Hoc Committee on Health Research Relating to Future Intervention Options, World Health Organization, TDR/Gen/96.1. Geneva, WHO.

Search strategy to identify malaria papers using the SCI (January 1994–December 1994) (the same strategy was used for Medline)

Set	Records	Field
1	961	Title (ANTIMALARIA* OR MALARI* OR PLASMODIUM OR PLASMODIA*) NOT PHYSARUM
2	273	Title PROGUANIL OR QINGHAOSU OR HALOFANTRINE OR AMINOQUINOLINE OR PRIMAQUINE OR ARTESUNATE OR ARTEETHER OR DARAPRIM OR FANSIDAR OR NAVIQUINE OR FANSIMEF OR CAMOQUINE OR CHLOPROGUANIL OR ARTEMETHER OR ARTEMESIN* OR QUININE OR CHLOROQUINE
3	334	Title MOSQUITOES OR PYRIMETHAMINE OR MEFLOQUINE OR MOSQUITO OR MOSQUITOS OR MOSQUITOCID* OR ANOPHEL*
4	12576	Title AEDES OR SCHISTOSOM* OR ONCHOCERC* OR BRUGIA OR CULEX OR HIV OR LEISHMAN OR TRYPANOSOM* OR WUCHERERIA OR FILARIA* OR ARBOVIRUS* OR DENGUE OR (YELLOW AND FEVER) OR VIRAL OR VIRUS
5	256	Set : Article (2 OR 3) NOT (1 OR 4)
6	43	Set : Note (2 OR 3) NOT (1 OR 4)
7	3	Set : Review (2 OR 3) NOT (1 OR 4)
8	19	Set : Review 1
9	120	Set : Note 1
10	637	Set : Article 1
11	776	Set 8 THRU 10
12	302	Set 5 THRU 7

Unconditional sets: 1; 11.

Conditional sets: 2; 3; 4 (exclusions from the conditional set); 5/6/7 (conditional without automatic exclusions); 12.

ANNEX 2

Acknowledgements by funding body for papers from 1984, 1989 and 1994 (SCI)

Funding body	Papers
Special Programme for Research and Training in Tropical Diseases (TDR)[37]	412
National Institute of Allergy and Infectious Diseases (NIAID)	294
US Department of Defense, The Pentagon, Washington, DC	206
MRC (Medical Research Council, UK), London W1N 4AL	160
US Agency for International Development (USAID), Washington, DC	149
Wellcome Trust, 183 Euston Road, London NW1 2BE	126
Centers for Disease Control (CDC), Atlanta, GA	83
Australian National Health and Medical Research Council, Canberra	85
Institut National de la Santé et de la Recherche Médicale (INSERM)	65
Institut Pasteur, Paris	62
John D and Catherine T MacArthur Foundation, Chicago, IL	60
Unidentified funding bodies	60
Rockefeller Foundation, The, New York	55
EEC (European Economic Community), Brussels	50
Walter and Eliza Hall Medical Institute, Melbourne	49
Centre Nationale de la Recherche Scientifique (CNRS)	44
Hoffmann-La Roche sa, Basel	41
Indian Council of Science and Industrial Research, New Delhi	40
US Department of Agriculture (ARS), Washington, DC	37
Kenya Medical Research Institute (KEMRI)	35
US National Institutes of Health, Bethesda, MD	37
Papua New Guinea Government	33
SmithKline Beecham plc (formerly Smith Kline French), Brentford, Middx TW8 9EP	34
Queensland Institute for Medical Research	30
National Science Foundation (NSF), Washington, DC	29
Health and Family Welfare, Ministry of (India)	29
L'Institut Francais de Recherche Scientifique (ORSTOM)	27
Deutsche Forschungsgemeinschaft	25
National Cancer Institute, US (NIH)	22
National Center for Research Resources (NCRR)	22
Japanese Ministry of Education, Science and Culture	22
Wellcome Foundation / Wellcome plc, Unicorn House, London NW1 2BP	21
Fonds National Suisse de la Recherche Scientifique (FNRS), Bern	21
Medicinska forskningsredet MFR (Swedish Medical Research Council), Stockholm	21
Thai Government	21
National Institute of Arthritis, Diabetes, Digestion and Kidney Research (NIADDK)	20
National Research Council, National Academy of Sciences, Washington, DC	19
National Institute of General Medical Sciences (NIGMS)	17
Pan-American Health Organization	17
Defence, Ministry of (Australia)	16
Swedish Agency for Research Development with Other Countries (SAREC)	16
Brazilian National Research Council	15
Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V, Munich	15
Tanzanian Government	15
British Council, 10 Spring Gardens, London SW1A 2BN	13
Scripps Clinic and Research Foundation, La Jolla, CA	13
Australian Malaria Vaccine Joint Venture	12
National Heart Lung and Blood Institute (NHLBI)	12

[37] The World Bank, the UNDP and the WHO cosponsor the TDR Programme. However, many countries and organizations also make financial contributions (see Chapter 2).

Ten most highly cited malaria papers from 1984 and 1989 (cited over the five-year period following the year of publication: SCI)

A MOST HIGHLY CITED MALARIA PAPERS OF 1984

Dame-JB Diggs-CL Haynes-JD Hockmeyer-WT Maloy-WL Mccutchan-TF Miller-LH Reddy-EP Roberts-D Sanders-GS Schneider-I Weber-JL Williams-JL Wirtz-RA
Structure of the Gene Encoding the Immunodominant Surface-Antigen on the Sporozoite of the Human Malaria Parasite Plasmodium-Falciparum
SCIENCE 1984 Vol 225, Iss 4662, pp 593–599

NIAID, PARASIT DIS LAB, BETHESDA, MD 20205, USA
NCI, DEPT ENTOMOL, BETHESDA, MD 20205, USA
NIAID, IMMUNOGENET LAB, BETHESDA, MD 20205, USA
NCI, CELLULAR & MOLEC BIOL LAB, BETHESDA, MD 20205, USA
WALTER REED ARMY MED CTR, DEPT IMMUNOL, WASHINGTON, DC 20037, USA

Acknowledged sources of support:
US Department of Defense
National Cancer Institute
National Institute of Allergies and Infectious Diseases

Citations (1984–1989) = 236

Enea-V Arnot-DE Asavanich-A Ellis-J Masuda-A Nussenzweig-RS Quakyi-I Zavala-F
DNA Cloning of Plasmodium-Falciparum Circumsporozoite Gene – Amino-Acid-Sequence of Repetitive Epitope
SCIENCE 1984 Vol 225, Iss 4662, pp 628–630

NYU MED CTR, DEPT MICROBIOL, DIV PARASITOL, NEW-YORK, NY 10016, USA
MAHIDOL UNIV, DEPT MED ENTOMOL, BANGKOK 10400, THAILAND
UNIV GHANA, NOGUCHI MEM INST MED RES, IMMUNOL UNIT, LEGON, GHANA

Acknowledged sources of support:
National Institutes of Health
USAID
WHO
Damon Runyan-Walter Winchell Cancer Fund, NYC

Citations (1984–1989) = 121

Hall-R Goman-M Hope-IA Hyde-JE Mackay-M Merkli-B Richle-R Scaife-J Simmons-DL Stocker-J
Major Surface-Antigen Gene of a Human Malaria Parasite Cloned and Expressed in Bacteria
NATURE 1984 Vol 311, Iss 5984, pp 379–382

UNIV EDINBURGH, DEPT MOLEC BIOL, EDINBURGH, MIDLOTHIAN, SCOTLAND, EH9-3JR
HOFFMANN LA ROCHE AG, DIV PHARMACEUT RES, BASEL, SWITZERLAND

Acknowledged sources of support:
Hoffmann-La Roche, Basle
UK MRC

Citations (1984–1989) = 102

Perlmann-H Berzins-K Bjorkman-A Carlsson-J Patarroyo-ME Perlmann-P Wahlgren-M
Antibodies in Malarial Sera to Parasite Antigens in the Membrane of Erythrocytes Infected with Early Asexual Stages of Plasmodium-Falciparum

JOURNAL OF EXPERIMENTAL MEDICINE 1984 Vol 159, Iss 6, pp 1686–1704

UNIV STOCKHOLM, DEPT IMMUNOL, S-10691 STOCKHOLM, SWEDEN
KAROLINSKA INST, ROSLAGSTULL HOSP, DEPT INFECT DIS, S-10401 STOCKHOLM 60, SWEDEN
NATL UNIV COLOMBIA, DEPT IMMUNOBIOL, BOGOTA, COLOMBIA

Acknowledged sources of support:
The Rockefeller Foundation
Swedish Agency for Research Development with other countries
Scottish Medical Research Fund
United Nations Development Fund (UNDP)
World Bank
WHO

Citations (1984–1989) = 98

Coppel-RL Anders-RF Bianco-AE Brown-GV Cowman-AF Kemp-DJ Lingelbach-KR Saint-RB
Immune Sera Recognize on Erythrocytes a Plasmodium-Falciparum Antigen Composed of Repeated Amino-Acid-Sequences
NATURE 1984 Vol 310, Iss 5980, pp 789–792

ROYAL MELBOURNE HOSP, WALTER & ELIZA HALL INST MED RES, PARKVILLE, VIC 3050, AUSTRALIA

Acknowledged sources of support:
Walter & Eliza Hall Institute of Medical Research
Australian National Health and Medical Research Council
Rockefeller Foundation
UNDP
World Bank
WHO

Citations (1984–1989) = 91

Perrin-LH Chizzolini-C Loche-M Merkli-B Richle-R Smart-J
Antimalarial Immunity in Saimiri Monkeys – Immunization with Surface Components of Asexual Blood Stages
JOURNAL OF EXPERIMENTAL MEDICINE 1984 Vol 160, Iss 2, pp 441–451

GENEVA UNIV HOSP, GENEVA BLOOD CTR, WHO UNIT, CH-1211 GENEVA 4, SWITZERLAND
BIOGEN INC, CAMBRIDGE, MA 02142, USA
F HOFFMANN LA ROCHE & CO LTD, DIV PHARMACEUT RES, CH-4002 BASEL, SWITZERLAND

Acknowledged sources of support:
Biogen Inc., Cambridge MA
Fonds National Suisse de la Recherche Scientifique (FNRS)
Biogen sa, Switzerland (Glaxo)
Hoffmann-La Roche, Basle
WHO
UNDP
World Bank

Citations (1984–1989) = 77

Franzen-L Aslund-L Perlmann-H Persson-T Pettersson-U Shabo-R Westin-G Wigzell-H
Analysis of Clinical Specimens by Hybridization with Probe Containing Repetitive DNA from Plasmodium-Falciparum – A Novel-Approach to Malaria Diagnosis
LANCET 1984 Vol 1, Iss 8376, pp 525–528

UNIV UPPSALA, CTR BIOMED, DEPT MED GENET, S-75123 UPPSALA, SWEDEN
UNIV UPPSALA, DEPT IMMUNOL, S-75123 UPPSALA, SWEDEN
UNIV UPPSALA, DEPT MICROBIOL, S-75123 UPPSALA, SWEDEN
KAROLINSKA INST, DEPT IMMUNOL, S-10401 STOCKHOLM 60, SWEDEN
UNIV STOCKHOLM, DEPT IMMUNOL, S-10691 STOCKHOLM, SWEDEN

Acknowledged sources of support:
Rockefeller Foundation
Swedish Agency for Research Development with other countries
Scottish Medical Research Fund
Swedish National Board for Technical Development

Citations (1984–1989) = 73

Watkins-WM Boriga-DA Kariuki-DM Kipingor-T Koech-DK Sixsmith-DG Spencer-HC
Effectiveness of Amodiaquine As Treatment for Chloroquine-Resistant Plasmodium-Falciparum Infections in Kenya
LANCET 1984 Vol 1, Iss 8373, pp 357–359

CTR DIS CONTROL, CTR INFECT DIS, DIV PARASIT DIS, ATLANTA, GA 30333, USA
KENYA GOVT MED RES CTR, CLIN RES CTR, NAIROBI, KENYA
UNIV NAIROBI, DEPT PHARM, NAIROBI, KENYA
KENYA MINIST HLTH, DIV VECTOR BORNE DIS, NAIROBI, KENYA

Acknowledged sources of support:
Centers for Disease Control, USA
Kenyan Government
Ministry of Research, Science and Technology, Kenya
UNDP
World Bank
WHO

Citations (1984–1989) = 72

Holder-AA Freeman-RR
The 3 Major Antigens on the Surface of Plasmodium-Falciparum Merozoites Are Derived from a Single High Molecular-Weight Precursor
JOURNAL OF EXPERIMENTAL MEDICINE 1984 Vol 160, Iss 2, pp 624–629

WELLCOME RES LABS, DEPT MOLEC BIOL, LANGLEY COURT, BECKENHAM, KENT, ENGLAND, BR3-3BS

Acknowledged sources of support:
The Wellcome Foundation

Citations (1984–1989) = 68

Leech-JH Barnwell-JW Howard-RJ Miller-LH
Identification of a Strain-Specific Malarial Antigen Exposed on the Surface of Plasmodium-Falciparum Infected Erythrocytes
JOURNAL OF EXPERIMENTAL MEDICINE 1984 Vol 159, Iss 6, pp 1567–1575

NIAID, PARASIT DIS LAB, BETHESDA, MD 20205, USA

Acknowledged sources of support:
National Institute for Allergies and Infectious Diseases

Citations (1984–1989) = 65

B MOST HIGHLY CITED MALARIA PAPERS OF 1989

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CTR MED UNIV GENEVA 4, DEPT PATHOL, WHO, CTR IMMUNOL RES & TRAINING, GENEVA, SWITZERLAND
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World Bank
WHO
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Acknowledged sources of support:
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Acknowledged sources of support:
Imperial Cancer Research Fund (ICRF)
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Citations (1989–1993) = 80

Category and subfield classification of international malaria researchpublications retrieved from SCI/Medline combined databases for 1984, 1989 and 1994

	Subfield		% of total malaria papers (absolute numbers)				
			1984	1989	1994	Total	Category total (%)
A	Drug discovery & development (*in vitro* and animal models)	1	12.1 (111.0)	10.5 (123.0)	11.6 (150.5)	11.4 (384.5)	
	Mechanisms of drug action	2	4.4 (40.0)	4.5 (52.5)	3.5 (45.0)	4.1 (137.5)	15.5
B	Immunology and vaccine development	3	9.1 (84.0)	11.0 (130.0)	10.0 (130.5)	10.2 (344.5)	
	Human vaccine trials and vaccine reviews	4	0.8 (7.0)	1.9 (22.5)	2.0 (26.5)	1.7 (56.0)	11.9
C	Biology of *Plasmodium*	5	9.1 (82.5)	8.4 (97.8)	7.03 (91.5)	8.1 (271.8)	
	Biochemistry of *Plasmodium*	6	8.4 (77.5)	5.2 (61.3)	5.6 (73.0)	6.3 (211.8)	
	Genetics of *Plasmodium*	7	3.1 (28.0)	3.8 (44.8)	6.1 (79.5)	4.5 (152.3)	18.9
D	Clinical management of malaria and drug trials	8	7.0 (64.0)	9.9 (115.0)	10.4 (135.5)	9.3 (315.0)	
	Pathophysiology and disease symptoms	9	9.7 (89.0)	9.4 (110.0)	10.7 (139.0)	10.0 (338.0)	
	Malaria in travellers and migrants	10	4.0 (37.0)	4.1 (48.0)	2.7 (35.0)	3.6 (120.0)	22.9
E	Epidemiology and mathematical modelling	11	10.8 (99.0)	12.2 (143.0)	11.9 (155.0)	11.8 (397.0)	11.8
F	Intervention trials and health services research	12	6.1 (56.0)	5.1 (59.5)	6.2 (81.0)	5.8 (196.5)	5.8
G	Diagnostic tests for malaria	13	0.5 (5.0)	1.5 (17.0)	1.8 (24.0)	1.4 (46.0)	1.4
H	Mosquito vector studies	14	13.9 (128.0)	12.5 (146)	10.1 (132.0)	12.0 (406.0)	12.0
	General Reviews		**0.3 (10)**	**0.09 (3)**	**0.12 (4)**	**0.5 (17)**	
	TOTAL		**27 (918)**	**34.6 (1174)**	**38.4 (1302)**	**100 (3394)**	

Top publishing countries (SCI and Medline)

Country	Rank according to analysis of first-author address: SCI/Medline combined (1994) (see Chapter 4)	Number of first-author papers from that country: SCI/Medline combined (1994)	% of total malaria papers: SCI/ Medline combined (1994)	Rank according to analysis of all author addresses: SCI (1984, 1989 and 1994) (see Chapter 3)
USA	1	307	23.6	1
UK	2	149	11.4	2
France	3	87	6.7	3
India	4	85	6.5	5
Australia	5	72	5.5	4
Thailand	6	56	4.3	6
Germany	7	39	3.0	7
China	8	35	2.7	19
Switzerland	9	28	2.2	8
Italy	10	26	2.0	14
The Netherlands	11	25	1.9	9
Sweden	11	25	1.9	11
Japan	12	24	1.8	13
Kenya	13	23	1.8	10
Brazil	14	18	1.4	18
Canada	15	15	1.2	18
Israel	16	14	1.1	12
South Africa	16	14	1.1	20
Denmark	17	13	1.0	20
Mexico	17	13	1.0	21
Nigeria	18	12	1.0	17
Tanzania	18	12	1.0	19
Belgium	19	11	0.8	22
Russia	19	11	0.8	25
Sri Lanka	20	10	0.8	24
The Gambia	21	8	0.6	15
Zimbabwe	21	8	0.6	31
Papua New Guinea	22	7	0.5	16
Senegal	22	7	0.5	31
Austria	23	6	0.5	20
Spain	23	6	0.5	23
Burkina Faso	23	6	0.5	27
Venezuela	24	5	0.4	22
Pakistan	24	5	0.4	28
Cameroon	24	5	0.4	31
Sudan	25	4	0.3	25
Gabon	25	4	0.3	31
Vietnam	25	4	0.3	32
Saudi Arabia	25	4	0.3	35
Sierra Leone	25	4	0.3	35
Norway	25	4	0.3	36
Trinidad	25	4	0.3	36

Questionnaires for the expert review of Wellcome Trust-supported malaria research for (a) a set of papers grouped by subfield, and (b) individual papers

(a)

1. In this set of research papers, what are the most significant advances (for example in theory, methodologies, techniques, new knowledge)?

2. What proportion of this set of papers represents a substantial advance in knowledge/ understanding of malaria/vectors of malaria?

0–25%	25–50%	50–75%	75–100%
☐	☐	☐	☐

3. Of the topic areas addressed in this subset of malaria research papers which, if any, would you encourage bright young learners to pursue and why?

4. In reviewing these papers in terms of quality, what features/issues did you consider? Please list.

(b)

1. How do you see the results of this paper being best used? (tick as appropriate)

- advancing knowledge/theory ☐
- modifying clinical treatment ☐
- improved methodology/experimental technique ☐
- developing new products ☐
- improving disease prevention or control measures ☐
- other (please specify) ☐

2. When do you see the benefits (as outlined above) of this research being realized? (tick as appropriate)

- immediately (within 12 months) ☐
- medium term (1–5 years) ☐
- long term (5–10 years) ☐
- very long term (>10 years) ☐

3. Which specific professional group(s) working in this field/subfield are likely to find these results of most interest? (select all that apply)

- basic researchers ☐
- academic clinicians ☐
- non-academic clinicians ☐
- policy makers ☐
- manufacturers/industrialists ☐
- others (please specify) ☐

Questionnaire for the opinion survey of malaria research: current practice and future directions

A Personal details

1. Which of these categories best describes your current position?
   - Basic science researcher ☐
   - Clinical science researcher ☐
   - Health services practitioner/adviser ☐
   - Administrator/policy maker ☐
   - Other (e.g. industrialist) (please specify)

2. Which of these best describes your work environment?
   - University ☐
   - Hospital ☐
   - Industry ☐
   - Funding agency ☐
   - Government department ☐
   - Non-governmental organization (NGO) ☐
   - Non-university research institute (e.g. Medical Research Council units) ☐
   - Other (please specify)

3. Are you involved in fieldwork in a malaria-endemic country?
   - Yes ☐
   - No ☐

B Future developments in malaria research

4. Please tick one box in column A to indicate your main area of interest in malaria research (see attached appendix of research subfield definitions). In your opinion, what are the prospects for making significant advances in our understanding of these major subfields (A–H) over the next 5 years – please use column B to rate each subfield from 1 to 5 (where 1 is very good and 5 is very poor). If you feel unable to comment on any of the subfields, please leave the box blank.

		A	B
A	Antimalarial drug discovery and development	☐	☐
B	Immunology and vaccine development	☐	☐
C	(I) Biology of *Plasmodium*	☐	☐
	(II) Biochemistry of *Plasmodium*	☐	☐
	(III) Genetics of *Plasmodium*	☐	☐
D	Clinical treatment, prophylaxis and pathophysiology of malaria	☐	☐
E	Epidemiology and mathematical modelling	☐	☐
F	Intervention trials and health services research	☐	☐
G	Development of diagnostic tests for malaria	☐	☐
H	Studies of mosquito vectors of malaria	☐	☐
	Other (please specify)		

5. In your opinion, are there any subfields in malaria research which would benefit from greater research effort, improved training opportunities or an increased input of funding? Please specify.

C Measures to strengthen the field of malaria research

6. In your opinion, which of the following measures are most needed to strengthen the field of malaria research? Please rank the top three measures from 1 to 3 (where 1 is most needed and 3 is least needed; equally necessary measures may be assigned the same number).
   - improved training of researchers in countries where malaria is endemic ☐
   - improved mobility for researchers ☐
   - more collaboration between research groups ☐
   - more multidisciplinary approach to malaria research ☐

- improved coordination and dissemination of research findings ☐
- improved consultation with users of research ☐
- other (please specify)

D Collaboration, dissemination of results, networks

7. With which professional group(s) do you communicate on a regular basis? – please tick a box(es) in column A. Is there a need for improved communication with them or any other of the following groups? – please tick a box(es) in column B.

	A	B
Basic science researchers	☐	☐
Clinical science researchers	☐	☐
Health services practitioners/advisers	☐	☐
Government officials	☐	☐
Workers in non-governmental organizations	☐	☐
Industrialists	☐	☐
Other (please specify)		

8. Which of the following methods do you use to obtain and/or disseminate information on current malaria research? Please indicate the importance of these methods in both obtaining information (column A) and in disseminating information (column B), where 1 is very important and 3 is less important.

	A	B
■ scientific journals	☐	☐
■ pamphlets or reports	☐	☐
■ conferences	☐	☐
■ books	☐	☐
■ Internet/other electronic networks	☐	☐
■ personal communication	☐	☐
■ TV	☐	☐
■ popular press (newspapers, magazines etc.)	☐	☐
■ radio	☐	☐
■ other (please specify)		

9a. Are you involved in formal collaboration in any of the following areas? Please tick those that apply.

- research networks ☐
- policy-making ☐
- implementation/dissemination of research findings ☐
- other (please specify)

9b. How does it/they operate?

E Translating research results into practice

10. Have you had any personal involvement in projects where research results were taken up and developed further with a view to improving the treatment or control of malaria? If so, please give examples.

11. Are you aware of research findings that might have influenced the treatment or control of malaria but that have not been developed further? If so, please give examples.

12. Are there any obstacles that you can identify which are limiting to the transfer of research results into the treatment and control of malaria? If so, what positive measures could be taken to overcome these obstacles?

13. If you had US$10 million to invest in malaria research annually, how would you spend it? Please feel free to express your thoughts on any aspect of policy, research, implementation and dissemination.

Examples of research that might have influenced the treatment or control of malaria but has not been developed further

Clinical management and prophylaxis of malaria

- case management approaches need field-testing
- use of suppositories of artemisin at primary health care level
- rectal administration of antimalarial drugs for very rapid diffusion of the drug in children without the risks of intramuscular or intravenous administration
- use of hyperbaric oxygen in the treatment of severe malaria
- fluid replacement in severe malaria
- no trial to date of allopurinol to test its effectiveness as an adjunctive treatment for high urate levels in severe malaria (as an antioxidant)
- possible role of mannitol in treatment of cerebral malaria
- partial exchange transfusions in severe malaria have not been tested formally
- synthetic cell-free haemoglobin substitutes in severe and cerebral malaria have not been tested formally
- pentoxifylline in cerebral malaria
- although some research findings are quite useful for control activities, e.g. lactic acid level determination for prognosis of cerebral malaria cases, it is not feasible to be applied in developing countries
- maloprim chemoprophylaxis in young African children
- the peptide sequence HPLQKTY, which might be an antisequestering agent and could be a therapeutic tool for cerebral malaria
- identification of putative malarial toxins that have therapeutic implications

Drug and vaccine development

- potential vaccines and drugs await further development or evaluation because of financial restraints and the lack of incentives for commercial involvement
- groups of low-cost, natural/plant products with antimalarial activity have been identified
- research in animals on combinations of drugs to delay the emergence of parasite resistance to drugs has never been tested in practice on *P. falciparum* in man in the field
- low-molecular-weight heparin has been shown to inhibit *P. falciparum* growth *in vitro* and inhibit rosetting, but it lacks anticoagulant activity
- clindomycin as a potential antimalarial agent
- work with diamidines (e.g. pentamidine) indicated that they were effective antimalarials *in vitro*, with activities independent of levels of acute-phase proteins. Pentamidine currently used clinically to treat pneumocystis was deemed too toxic
- pro-oxidants
- testing (in animal models) of compounds that block the new permeability pathways induced by parasites in host cell membranes
- Gambian children with severe malaria have been shown to have increased carriage of hepatitis B surface antigen – the potential value of hepatitis B vaccine in reducing severe malaria has not been tested
- inappropriate evaluation of some vaccine candidates

Vector control

- decades-old information on vector control has not been implemented
- biological methods of vector control have not been integrated into national malaria control programmes
- use of impregnated curtains in China not developed further
- slow-release formulation for residual spraying not implemented
- discovery of housing construction and malaria risk has not led to actions to limit malaria risk through changes in house construction
- inappropriate implementation of impregnated bednets before sufficient research has been carried out into their effectiveness
- research into the molecular biology of vectors is a poorly funded area in which there is a lack of commercial interest
- genetically manipulated strains of mosquitoes refractory to malaria transmission require further development
- development is needed of potential transgenic carriers in mosquitoes, for instance spiroplasms and related agents

Delivery of health care and health services research

- monitoring of drug resistance – poor coordination has resulted in delayed introduction of new treatment regimens
- data rarely cross national borders
- health systems research has not been carried out
- information on socioeconomic environment of malaria has not been utilized in treatment and control programmes
- too many political/economic factors may prevent implementation of control measures
- several diagnostic tools have been developed in laboratories but have not yet reached health facilities in rural Africa

General issue

- many areas of basic biology and biochemistry remain unexplored as funding over the past 10–15 years has been directed towards vaccine development

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