Portfolio Review

Malaria 1990–2009

April 2012

wellcome trust

Acknowledgements

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The views expressed in this report are those of the Wellcome Trust project team – drawing on the evidence compiled during the review. We are indebted to the independent Expert Group, who were pivotal in providing the assessments of the Wellcome Trust's role in supporting malaria and have informed 'our' speculations for the future. Finally, we would like to thank Professor Tony Holder and Professor Terrie Taylor, who reviewed and provided valuable input on this report.

Contents

Key abbreviations used in the report			
ACT	Artemisinin-based combination therapy	MIM	Multilateral Initiative on Malaria
CCGH	MRC Centre for Genomics and Global Health	MMV	Medicines for Malaria Venture
CDC	US Centres for Disease Control and Prevention	MOPS	Major Overseas Programmes
DDT	Dichlorodiphenyltrichloroethane	MVI	The PATH Malaria Vaccine Initiative
DFID	UK Department for International Development	MRC	Medical Research Council
EVIMalaR	European Virtual Institute of Malaria Research	NIH	US National Institutes of Health
FP7	Seventh Framework Programme	NITD	Novartis Institute for Tropical Diseases
G-FINDER	Global Funding of Innovation for Neglected Diseases	PATH	Programme for Appropriate Technology in Health
The Global Fund	The Global Fund to fight AIDS, Tuberculosis and Malaria	PDP	Product development partnership
HRCSI	Health Research Capacity Strengthening Initiative	RBM	Roll Back Malaria Partnership
IHME	Institute for Health Metrics and Evaluation	R&D	Research and development
INSERM	French National Institute of Health and Medical Research	RDT	Rapid diagnostic test
IVCC	Innovative Vector Control Consortium	TDR	WHO-based Special Programme for Research and Training in Tropical Diseases
KEMRI	Kenya Medical Research Institute		
LSHTM	London School of Hygiene and Tropical Medicine	USAID	US Agency for International Development
malERA	Malaria Eradication Research Agenda	WHO	World Health Organization
MalariaGEN	Malaria Genomic Epidemiology Network	WTCMP	Wellcome Trust Centre for Molecular Parasitology
MDG	Millennium Development Goal	WTSI	Wellcome Trust Sanger Institute

The real challenge for the upstream research funders is to try and retain the diversity in thinking, which I think is the most fundamental thing we risk.
Wellcome Trust Expert Group on malaria, April 2010

1. Throughout its 75-year history, the Wellcome Trust has supported a broad spectrum of research focusing on malaria. The research has encompassed: the biology of the parasites and vector; new vaccines and drugs; clinical research to improve treatment and to understand the pathology of the disease; disease transmission and epidemiology; health services research; health policy research; medical humanities; and, recently, through the Wellcome Trust Sanger Institute (WTSI), pathogen and genome sequencing.[1]

2. Over the past 20 years, across its research programmes and funding divisions, the Wellcome Trust has awarded 515 grants to malaria-focused research. These grants account for £189 million,[2] representing just over 3 per cent of the Trust's total funding commitment over this time. Funding has been provided through project-based grants and to support researchers across their career stages, from junior fellows to principal researchers. Wellcome Trust investments have been made both within the UK and outside the UK, particularly in malaria-endemic countries. During this time, an additional £120m (52 grants) was allocated for core support and infrastructure at Wellcome Trust Centres and the Trust's Major Overseas Programmes (MOPs); much of the work undertaken in these Centres and MOPs has played a part in facilitating malaria-focused research and providing training and research capacity development. In addition, the WTSI spend on malaria-focused research during this time period was £8.8m.

3. This review, conducted in late 2009 and 2010, aims to identify the key breakthroughs in malaria R&D over the past 20 years and the Wellcome Trust's role within this. As in any review of the outcomes of research, an intrinsic challenge for a funder is to understand the part it has played among the range of influences and actors that are involved in shaping and delivering research. Indeed, to attempt to attribute breakthroughs in a field solely to an event, researcher and/or funder is to take an improbable view of the way in which science and knowledge progress. To counter this, with the support of a group of independent subject experts, we have attempted to identify where the Wellcome Trust is thought to have played a significant part in the field.

1 This report focuses on human malaria infection research, encompassing parasite and vector biology, host response and pathogenesis, resources and infrastructure, drug development, diagnostics, evaluation and resistance, epidemiology (surveillance and distribution), vaccinology, health services, ethics and policy research, prevention and control (including vector control), research design, technology and methodology, and the history of malaria.

2 Wellcome Trust funding commitment between the financial years 1989/1990 and 2007/2008.

4. We also wanted to use this review in a formative way, to inform future funding strategy; therefore, we bring expert reflections on past developments and crucial breakthroughs together with views on current challenges and future opportunities for research in malaria – both for the Wellcome Trust and for all those involved in supporting research into malaria.

5. Over the past two decades, Wellcome Trust funding has contributed to some of the most important advances and discoveries in malaria research (see Landmarks in Malaria Timeline). In particular, there are four areas where the Wellcome Trust is thought to have had a significant impact on the field:

- the sustained provision of project- and people-based funding for malaria-focused research leaders and young researchers in the field – who, in turn, have delivered a range of breakthroughs in our knowledge of malaria and approaches to tackling the disease
- the support for genomic science, primarily at the WTSI, which is helping to enhance our understanding of the basic biology of malaria
- the support for research capacity building and infrastructure in malaria-endemic regions (particularly through MOPs), which have helped to deliver important clinical investigation studies and tangible impacts on the human malaria burden
- the involvement of and support for multi-agency, cross-sector partnerships and collaborations, which have been important in targeting malaria from several angles.

6. Despite the breakthroughs in our understanding of malaria and evidence of global reductions in the burden of the disease over the past two decades, malaria remains difficult to treat and endemic in many parts of the world and there is no licensed vaccine approved for human use. Although basic research remains key to improving our understanding of human malaria, the majority of the reduction in the global burden of malaria thus far is thought to be the result of investments in clinical investigation and preventative research, associated campaigns and the delivery of interventions. More work needs to be done to translate the improvements in our knowledge of malaria into strategies that have a tangible impact upon health. While this is being done, we should maintain a focus on the clinical and preventative research where current advances are being made in the fight against malaria. To this end, to ensure continued progress towards malaria elimination and eradication, a diversity of sustainable funding for malaria research is needed.

7. International and multi-lateral initiatives and networking have proved to be significant cohesive factors in advancing malaria research; engagement in, and support of, such initiatives can only help increase the effectiveness of investments into malaria research in the future.

8. In summary, we – with the help of our experts – have identified several ongoing and emerging challenges and priorities for the future of malaria research.

Ensure continued support for research into basic immune and biological mechanisms
Improvements in our understanding of several basic research areas (including the biology, biochemistry, immunology and pathobiology of malaria) are needed, specifically:

- the basic biology of all species of the *Plasmodium* parasite, but particularly *P. vivax*
- the basic metabolic functions of the *Plasmodium* species, including metabolomics, lipidomics and glycomics
- the complex mechanisms underlying the immunobiology of malaria.

There is also a need for robust model systems to support human immunological research.

The importance of clinical research and clinical investigation
The Expert Group were in agreement that support for clinical research is crucial if we are to continue to deliver improvements in human health, to complement the ongoing basic research effort. More focus should be given to understanding the pathology and physiology of the disease. In terms of severe malaria, in particular, continued support for clinical research into the pathophysiology of acidosis, anaemia, renal failure and pulmonary oedema is needed.

Ensure a pipeline of antimalarial drugs
The Expert Group discussed the implications of emerging and increasing drug resistance in malaria and emphasised the need for the development of a sustained pipeline of antimalarial drugs. It was agreed that the least expensive and most effective research investment at present would be to optimise the dose regimens for currently available antimalarial drugs. Several priorities for malaria drug development and improvement were highlighted:

- the need to optimise dose regimens for currently available antimalarial drugs

- the need for novel drugs to tackle other malaria parasites, particularly *P. vivax*, which will necessitate a clearer understanding of their resistance mechanisms
- the need for significant investment in building malaria-focused pharmacology and pharmacokinetic research capacity
- the implementation of novel management systems to monitor the use of compounds in the field to protect the drug supply pipeline.

A need to expand the armoury of, and access to, quality-assured diagnostic testing
Investment in antimalarial drug development should be accompanied by commitments to improve diagnostic tools and their availability to ensure appropriate drug treatment and to prevent presumptive treatment of malaria. Achieving high-quality diagnosis in remote and low-resource areas remains a huge challenge because of methodological variability, the lack of reproducibility and the lack of quality control programmes in the field setting. There are important opportunities for funders such as the Wellcome Trust to support research to enhance rapid diagnostic tests (RDTs), including novel low-cost diagnostics that can detect very low levels of malaria parasites in asymptomatic individuals, and to support their availability in low-resource settings.

A need for improved and novel vector control tools
The Expert Group discussed potential approaches to meet the challenges of malaria vector control and proposed directions for future work, including research into:

- vector biology, to support the discovery of alternatives to pyrethroids and new vector control tools
- how community health services can be best mobilised to implement measures such as insecticide-treated bednets and long-lasting insecticide-treated mosquito nets
- the optimum use of existing vector control methods, such as the use of indoor residual spraying alone or in combination with insecticide-treated bednets
- scaling up and improving the maintenance of existing vector control measures and ensuring their regular and proper use is essential
- supporting capacity building and training strategies to address the relative lack of senior entomologists working in the field and assure the pipeline of trained junior researchers entering the field.

Enhanced information systems, surveillance tools and technologies
Without adequate, high-quality surveillance data, monitoring the progress and efforts of malaria control programmes is impossible. Major limiting factors to improving malaria surveillance in resource-poor settings include the weak information infrastructures and lack of adequately trained staff to capture, interpret and analyse the incidence and mapping data – particularly in malaria-endemic regions. Enhanced surveillance tools are required, and they need to be complemented by improvements in health information systems and training to ensure their use in the field. Encouraging collaboration between researchers, information technology providers and industry could have also have a major impact.

Integrated databases to enable data sharing
The Expert Group emphasised the need for funders to support the development of shared, publicly accessible integrated databases that bring together diverse datasets from the host, parasite and vector research communities. Such databases are likely to:

- enable the exchange of robust information (positive and negative) between the host, pathogen and vector communities
- facilitate data sharing between basic and clinical scientists
- enable the malaria research community to share clinical trial data
- enable the efficient exchange of immunology data
- help facilitate a systems biology approach to malaria research
- provide a deeper understanding of the complex host–pathogen system
- increase the speed at which new drugs are developed.

A need to strengthen research capacity and support training
One thread running through this review was the importance of building and sustaining researcher capacity across all the relevant disciplines that contribute to malaria research. To enable this, it was agreed that a focus on short-term and long-term capacity development – both human and infrastructure and systems capacity – is needed. In addition, the Expert Group emphasised the need for improved coordination between researchers working in the field in endemic countries and their international counterparts to ensure that research findings and expertise are shared.

A recognition of the importance of international, multi-sector collaborations to tackle malaria
International collaborations, public–private partnerships and product development partnerships (PDPs), bringing together appropriate expertise to address the complexities of malaria treatment and prevention, have been very important in the fight against malaria to date. Despite the increased funding for malaria research since the early 1990s (from $121m in 1993 to $612m in 2009), malaria funding remains unevenly distributed across regions and product areas.[3] It was agreed that public, private and philanthropic funders should continue to seek out opportunities to work together to minimise the risk of over-reliance on one funder or sector and to ensure a well-balanced, responsive and flexible portfolio of malaria-related research funding across the globe.

To ensure consideration of the social, political and ethical implications of malaria-related research
Looking ahead, it remains crucial that we, as funders, work together with the research community and other funders to engage in key policy issues that surround the conduct of malaria-related research and its application to improve the prevention, control and treatment of the disease globally. Key issues include access to medicines, ethical issues that surround the conduct of clinical research in low- and middle-income countries, and the uptake of research evidence to policy.

To support dialogue with relevant policy and public stakeholders
The Expert Group emphasised the importance and value of raising public awareness of the problems of malaria and the continued need to develop and deliver public awareness campaigns. Public consultation and participation in open dialogue, upstream in the research process, ensure the development of appropriate, culturally relevant technologies. Engagement activities and cultural and social research can help determine the most appropriate way to engage with particular communities, to conduct research and to design health promotion strategies.

3 PATH. Staying the Course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

Landmarks in malaria

Key
- Scientific advance and knowledge
- Funding development
- Policy development

2700 BCE Oldest reference to malaria

1500 BCE High prevalence in ancient Egypt

400 BCE Hippocrates describes malaria

100 BCE Romans drain marshes

340 CE Antimalarial properties of qinghao

3000 2000 1000 CE 1000 2000

1600s Cinchona bark brought to Europe

1712 Torti distinguishes chinchona-treatable fevers

1850s Large-scale use of quinine

1891 Guttman and Ehrlich: methylene blue

1898 Malaria transmission by mosquitoes proven

1500 1600 1700 1800 1900 2000

1630s *Schedula Romana*

1820 Quinine extracted from cinchona

1880 Parasites observed in erythrocytes of malaria sufferers

Quinine affordable

1890 Marchiafava and Bignami describe pathology of malaria and action of quinine

1901 Pyrethrum first used

1921–1924 Kortweg, van Thiel, Swellengrebel and de Buck prove long latency in *Plasmodium vivax* and explain anophelism without malaria

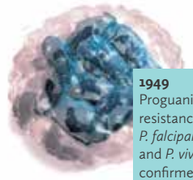
1922 Mott Clinic

1930s Organo-phosphates experimented with as insecticides

1932–1934 Mepacrine introduced

1941 First evidence that irradiated sporozoites can prime the immune system, preventing erythrocyte infection

1944–1948 Therapeutics studies established to dose the cinchona alkaloids and the amino-quinolines based on pharma-cokinetics and pharma-codynamics. Brodie and Udenfriend develop drug assays



1947 First Expert Committee on Malaria

1949 Proguanil resistance in *P. falciparum* and *P. vivax* confirmed in Malaysia

USA malaria-free

Wellcome Trust Research Laboratories (WTRL)

1954 Protectiveness of sickle cell trait in heterozygotes identified

1961 The role of antibodies in acquired immunity to malaria

1962 Pesticides linked to negative ecological effects

1971 Artesunate isolated

1972 DDT banned

1976 First lab-grown malaria parasite

1977 Great Neglected Diseases of Mankind programme

1979 Clinical trials of artemisinin published

Wellcome Trust–Mahidol University –Oxford Tropical Medicine Research Programme

1982 Hypnozoite discovered

1984 Mefloquine SP

WHO advises against the use of parenteral chloroquine

1987 Spf66 field trials

1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010

1904 Larvivorous fish used for the control of malaria vectors

1920s Paris Green

Development of an animal model for drug screening leads to pamaquine

1923 Isolation of the Madagascar strain (*P. vivax*)

1925 Differences between sexual and asexual antimalarial activity in *P. falciparum*

1933 Malaria Commission (League of Nations) limits quinine

1939 Insecticidal action of DDT (dichloro-diphenyltri-chloroethane) discovered

1942–1944 DDT used as an anti-mosquito spray

1944 First antifol antimalarial, proguanil (chlorguanide), discovered

1945 Cyclodiene compounds introduced

1946 Chloroquine introduced

US CDC

DDT resistance reported

1948 Identification of the liver as the site of the erythrocytic development in primate malaria

1950 Malathion, an OP (organo-phosphate), introduced

Carbamates introduced

1951 Pyrimethanine

1955 Global Malaria Eradication Campaign

1959 DDT-resistant mosquitoes detected

Chloroquine resistance

1967 Pyrethroids, synthetic pyrethrum, discovered

1969 WHO revises global malaria eradication strategy

1973 First vaccine trial in man with irradiated sporozoites

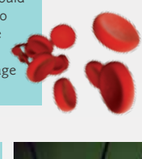
Synthesis of the first photostable synthetic pyrethroid, permethrin

1978 37 countries malaria-free

Africa: first evidence of chloroquine resistance

1980 Identification of the circums-porozoite protein (CSP) as a protective antigen

1981 Demonstration that a single protein could be used to vaccinate against blood-stage malaria



1983 Quinine loading dose treatment of severe malaria

Severe hypoglycaemia in falciparum malaria demonstrated

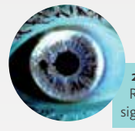
1985 First large-scale trials of ITNs

1986 Severe falciparum malaria – WHO management guidelines

Shoklo Malaria Research Unit

1989 KEMRI–Wellcome Trust Research Programme

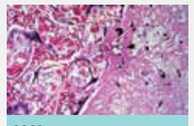
Blantyre Coma Score described



2000 UN: 2001–10 the 'Decade to Roll Back Malaria'

Abuja Declaration

Millennium Development Goals



2003 Placental malaria infection link to HIV

WHO recommendation on intermittent prevention of malaria in pregnancy

1998 Roll Back Malaria Partnership

European Malaria Vaccine Initiative

2005 Largest randomised trial in severe malaria, SEAQUAMAT, shows artesunate reduces mortality substantially

2006 Retinopathy: diagnostic sign for cerebral malaria

Translational repression in gametocytes

ACTs recommended everywhere as first-line treatment for malaria

2008 *P. knowlesi* recognised as fifth malaria species infecting humans; decoded genome reveals extended host range

Efficacy of childhood rectal artesunate

ACTs adopted as first-line treatment for *P. falciparum*

2009 Identification of a specific sign of cerebral malaria

DHA-piperaquine introduced

Coartem® Dispersible launched

2010 Use of advanced genetics to create strains of sterile mosquitoes

malERA Zenith Week

2011 Demonstration that albumin infusion is harmful in children

First results from phase III trial show RTS, S/ASO1 reduces the risk of malaria by half in African children aged 5 to 17 months

1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

1991 ITNs shown to reduce child mortality in the Gambia

Mefloquine resistance reported

1992 WHO Global Malaria Control Strategy

RTS,S vaccine enters clinical trials

1994 First large-scale deployment of an artemisinin combination therapy

1995 Rapid diagnostics tests: Malarone introduced

Identification of the *var* gene family encoding PfEMP1 in *P. falciparum*

Malawi-Liverpool-Wellcome Trust Clinical Research Programme in Blantyre, Malawi

1996 *P. falciparum* isolates bind to chondroitin sulphate A (CSA)

1997 PCR parasite genotyping allows clinical trials to be conducted and interpreted correctly

MIM Pan-African Conference on Malaria

Multilateral Initiative on Malaria

1999 Medicines for Malaria Venture

PATH Malaria Vaccine Initiative

Wellcome Trust Nairobi and Kilifi merger

2000s: Vector defence systems described

2002 GM mosquito incapable of transmitting malaria to humans created

Molecular basis of chloroquine resistance (PfCRT) discovered

Global Fund to Fight AIDS, TB and Malaria

Genome sequences of *P. falciparum* and *A. gambiae*

2004 RTS,S efficacious in children

Demonstration that 25% of the patients who satisfy the standard clinical case definition of cerebral malaria die for reasons unrelated to malaria

DHA-piperaquine introduced

UK All Party Parliamentary Group on Malaria and Neglected Tropical Diseases

2005 President's Malaria Initiative

WHA adopts ITN target

World Bank's Malaria Booster Program

Study of malaria prevalence in African children

MalariaGEN

2007 Gates Malaria Forum

Malaria Elimination Group

World Malaria Day

Guidelines on insecticide-treated mosquito nets – WHO

£10 million pledged to the Novartis Institute for Tropical Diseases

2008 Dynamic alterations in micro-circulatory flow and visualisation of microvascular obstruction demonstrated in buccal and rectal mucosa

RTS,S – phase II trials

Fake ACT in southern China

Affordable Medicines Facility

Wellcome Trust–Mahosot Hospital–Oxford Tropical Medicine Research Collaboration

Elimination main goal for most organisations

2009 Children aged 5–19 least protected

var gene expression modified by host immunity

Global map of *P. falciparum* endemicity published

Cambodia: artemisinin resistance

African Leaders Malaria Alliance

Trust-funded malaria researchers most cited

2010 GSK 'Open Innovation' strategy

WHO revises malaria guidelines

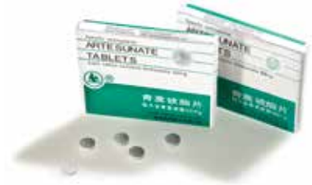
Largest ever study in severe malaria shows that artesunate reduces the mortality of severe malaria in African children by 22% compared with quinine and is highly cost-effective

2011 Atlas of Malaria-Eliminating Countries

Identification of the basigin receptor

Eurartesim® approved

Global map of *P. falciparum* malaria



Images: 1630s: Thomas Sydenham. *Wellcome Library, London.* **1820:** Powdered cinchona. *Science Museum, London/ Wellcome Images.* **1901:** William C Gorgas. *Wellcome Library, London.* **1923:** *Plasmodium vivax. JR Baker/Wellcome Images.* **1941:** A *Plasmodium* sporozoite. *Wellcome Library, London.* **1948:** A pre-erythrocytic schizont stage of *Plasmodium ovale. Wellcome Library, London.* **1949:** *Plasmodium falciparum. Benedict Campbell/Wellcome Images.* **1954:** A normal red blood cell and a red blood cell affected by sickle-cell anaemia. *EM Unit, UCL Medical School, Royal Free Campus/Wellcome Images.* **1976:** William Trager. *Wellcome Library, London.* **1981:** Red blood cells. *Maurizio De Angelis/Wellcome Images.* **1982:** A *Plasmodium* hypnozoite. *Wellcome Library, London.* **1987:** Syringes and needles. *Paul Griggs/Wellcome Images.* **1989:** The Kenya Medical Research Institute in Kilifi, Kenya. *Wellcome Library, London.* **1991:** A bednet in use. *Wellcome Images.* **1995:** The Wellcome Trust Research Laboratories in Blantyre, Malawi. *Wellcome Library, London.* **2000s:** A mosquito biting a human. *Wellcome Library, London.* **2002:** A map of the malaria genome. *Wellcome Library, London.* **2003:** Placental malaria. *Wellcome Images.* **2005:** A MalariaGEN meeting. *Wellcome Library, London.* **2006:** Human eye. *Kate Whitley/Wellcome Images.* **2007:** Insecticide-treated mosquito nets. *Wellcome Images.* **2009:** Human brain. *Heidi Cartwright/Wellcome Images.* **2010:** Transgenic mosquito heads expressing green fluorescent protein in their eyes. *Derric Nimmo and Paul Eggleston/Wellcome Images.* **2010:** Artesunate tablets. *Wellcome Library, London.*

1. Introduction and background

1. Malaria is a parasitic disease in humans and other animals that is transmitted through the bite of an infected mosquito. This report focuses on human malaria infection and is limited to the six species of malaria parasite that can infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*,[4] *Plasmodium malariae* and *Plasmodium knowlesi*.

2. Malaria is one of the world's chief public health concerns. An estimated 216 million cases of malaria, and an estimated 655 000 malaria deaths were reported by the WHO in 2010 – around 86 per cent of whom were children under the age of five.[5] The WHO estimates that there are currently 106 countries where malaria is endemic, with approximately 3.3 billion people 'at risk' of the disease (approximately half of the world's population). A recent study led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle does, however, question the WHO estimates. The IHME study estimated that there were 1.24 million malaria deaths worldwide in 2010 – almost double the WHO estimate of 655 000 malaria deaths for 2010. More than 40 per cent (524 000 individuals) of the victims were older children and adults, challenging the belief that the vast majority of deaths occur among the under-fives. If confirmed, this picture of malaria morbidity and mortality has huge implications for malaria control programmes.

3. Nevertheless, there are signs that the burden of malaria in endemic countries is decreasing; this is thought to be largely due to the recent scale-up in access to antimalaria interventions, such as artemisinin-based drugs, insecticide-treated bednets and indoor residual spraying.[6,7] However, funding support for malaria needs to be sustained if international targets for malaria elimination and eradication are to be achieved.

4. The direct and indirect costs of the disease are significant, affecting not only the quality of life of individuals and the ability of healthcare infrastructures to cope with the burden of disease but also the productivity and economic prosperity of endemic nations. It is estimated that in Africa alone, these 'costs' of malaria amount to $12bn per year.[8] The Copenhagen Consensus[9] ranked malaria prevention and treatment as its 12th most cost-effective intervention in their list of 2008[10] (malaria was ranked fourth in the 2004 Copenhagen Consensus[11]), and it remains very high on the international agenda and third in the Copenhagen Consensus list of disease states needing attention and/or investment.

5. The two most common variants of human malaria are caused by *Plasmodium falciparum* and *Plasmodium vivax*; *P. falciparum* is responsible for the majority (98 per cent) of malaria cases in sub-Saharan Africa, whereas *P. vivax* accounts for an estimated 25–40 per cent of the global malaria burden and is particularly common in Asia and South America.

6. The Wellcome Trust has a long history of funding malaria research and was a pioneer in the development of defined programmes of research into tropical diseases, particularly malaria. Henry Foy became the Trust's first medical research programme director – at the Malaria Research Laboratory, in Thessaloniki, Greece – in 1938. In 1949, Dr Foy and his long-standing colleague Dr Athena Kondi moved to establish the Wellcome Trust Laboratories at the Kenyatta Hospital in Nairobi; the laboratory in Kenya still remains. Now in partnership with the Kenya Medical Research Institute (KEMRI), it is one of the Wellcome Trust's MOPs. From the second half of the 20th century, the Wellcome Trust has continued to fund malaria-related research across the world, and 'combating infectious disease' remains a key part of the Wellcome Trust's funding strategy today.

7. Conducted during the second half of 2009 and early 2010, this review aims to identify the key breakthroughs in human malaria-related research over the past 20 years and attempts to identify the role of the Wellcome Trust within this landscape. This review is the third in a series aimed to help us to assess the impact of the Trust's funding at a macro, subject portfolio level. The first two portfolio reviews focused on human genetics and human functional brain imaging from 1990 to 2009.

8. The review is both reflective and prospective, with three specific aims:

   - to identify the key landmarks and influences on the malaria research landscape over the past two decades (1990–2009);
   - to consider what have been the key features of the Wellcome Trust's impact on this malaria research landscape;
   - to consider the current and future challenges for malaria research and where there may be opportunities for Wellcome Trust strategy and funding.

9. To deliver on these aims, we undertook three specific streams of work (see Annex B for detail):

   - funding, policy and bibliometric landscape analysis
   - narrative case studies
   - an Expert Group, convened to provide an independent view of key landmarks in the development of malaria and the role of the Wellcome Trust, and to speculate on the future.

10. Deciphering the funding investments made into malaria prevention, treatment and diagnosis is complex because of the plethora of agencies involved across the globe and the different ways in which information is recorded. Similarly, data on how much R&D funding has been invested to combat malaria and understand its aetiology, pathogens and transmission mechanisms are difficult to derive precisely. Notable progress has been made, however, after the introduction of the Global Funding of Innovation for Neglected Diseases (G-FINDER) annual survey in 2008. The G-FINDER survey has proved a valuable resource for our landscape analysis.[12]

11. We intend to use this review to learn from our support of malaria research to date and to inform potential future directions. In addition, we hope that this review is of value to other stakeholders – including funders – involved in supporting malaria research, both by highlighting areas where new and continued research is required and in guiding the selection of mechanisms and, potentially, policies to support research.

4 *Plasmodium ovale* has been shown by genetic methods to consist of two separate species, *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri*. See Sutherland CJ et al. Two nonrecombining sympatric forms of the human malaria parasite Plasmodium ovale occur globally. J Infect Dis 2010;201:1544–50.

5 World Health Organization. 2011. World Malaria Report. **www.who.int/malaria/world_malaria_report_2011/en/**

6 World Health Organization. 2011. World Malaria Report. **www.who.int/malaria/world_malaria_report_2011/en/**

7 Murray CJL et al. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2011;379(9814):413–431.

8 Greenwood BM et al. Malaria. Lancet 2005;365(9469):1487–98.

9 The goal of Copenhagen Consensus 2008 was to set priorities among a series of proposals for confronting ten global challenges: air pollution, conflicts, diseases, education, global warming, malnutrition and hunger, sanitation and water, subsidies and trade barriers, terrorism, and women and development. A panel of world economists rank the proposals predominantly by consideration of economic costs and benefits.

10 **www.copenhagenconsensus.com/Home.aspx**

11 **www.copenhagenconsensus.com/Default.aspx?ID=158**

12 The G-FINDER survey, now in its fourth year, provides comprehensive data on public and private funding into R&D for neglected diseases, including malaria. The G-FINDER survey is conducted by the independent research group Policy Cures and funded by the Bill and Melinda Gates Foundation.

2. Malaria research: the global research landscape

12. Over the past few decades, there has been a series of coordinated international efforts to control, eliminate and eradicate malaria (see Timeline). During the 1950s and 1960s, a string of eradication campaigns – including the WHO Global Malaria Eradication Programme (1955–1972), which succeeded in helping to eliminate malaria in 16 countries and territories – were curtailed because of the emergence of drug and insecticide resistance, together with problems in the feasibility and sustainability of malaria control in areas with weak infrastructure and high transmission.

13. During the 1990s, malaria control was re-established as a global health priority by the WHO Global Malaria Strategy (1992), the formation of the Multilateral Initiative on Malaria (MIM, 1997) and the launch of the Roll Back Malaria Partnership (RBM, 1998). In 2000, the United Nations declared 2001–2010 the 'Decade to Roll Back Malaria' in low-income countries, the objectives of which have been built into the internationally agreed Millennium Development Goals (MDGs) – eight goals adopted by the 189 member nations of the UN in 2000 to provide a framework for the international community to combat poverty. There are eight MDGs, 18 targets and 44 indicators to be achieved by 2015.[13] The specific MDGs linked to malaria[14] are:

- MDG 4: to have [by 2015] halted, and begun to reverse, the incidence of malaria
- MDG 6: reduce [by 2015] by two-thirds the mortality rate among children under five.

14. These global strategies together with the Global Fund for AIDs, Tuberculosis and Malaria, since its inception in 2002, have made some significant inroads; for example, the WHO reported that malaria mortality rates have declined by about 26 per cent since 2000.[15] More recently, a study by the IHME published in the *Lancet* described a similar, significant 32 per cent decline in malaria deaths since 2004.[16]

15. In 2011, the RBM revealed that nearly one-third of the 106 malaria-endemic countries are on course to eradicate the disease within ten years, with three countries already certified as malaria free by the WHO since 2007 (Morocco, Turkmenistan and Armenia).[17]

16. Although much progress has been made, with some countries reaching the 2010 universal coverage targets[18] for at least one malaria control intervention, continued progress and funding support is needed from other countries and donors to enable the World Health Assembly and the RBM goals for malaria to be realised and to meet the MDGs in 2015.

17. Up until 2010, international investment in malaria R&D continued to rise, driven largely by the MDGs. In 2002, the estimated global investment in malaria R&D was $200m; by 2009, it had risen to approximately $593.8m (see Table 1). In 2010, global funding for malaria R&D decreased by $45.5m (7.8 per cent) compared to 2009, although this reduction is thought to reflect the near-completion of the malaria vaccine candidate RTS,S development programme (see Table 1).

18. Malaria R&D funding remains highly concentrated, with 12 funders accountable for 92.5 per cent of funding ($547m in 2010). The G-FINDER reports that financial investment in malaria R&D showed a significant decrease in funding from the USA in 2010. The Bill and Melinda Gates Foundation, the largest funder of malaria R&D in 2009, reduced its funding by $95.2m (52.2 per cent) and the US Department of Defence by $14.9m, a 39.7 per cent decrease (see Table 1). These reductions are partly offset by a $20.2m (563 per cent) increase in funding from the UK Department for International Development (DFID) and a $16.9m (14.5 per cent) increase from the US Government's National Institutes of Health (NIH) in 2010.

Table 1 Top 12 malaria R&D funders 2010[19]

Funder	2007 (US$)	2008 (US$)^	2009 (US$)^	2010 (US$)^	2007%	2008%	2009%	2010%
US NIH	84,422,644	104,810,620	116,013,245	132,882,335	18.0	19.3	19.5	24.3
Aggregate industry respondents[AB]	90,793,583	90,611,134	99,303,179	125,621,275	19.4	16.7	16.7	23.0
Gates Foundation	124,464,185	173,722,323	182,444,291	87,251,307	26.6	32.1	30.7	15.9
Wellcome Trust	28,255,207	26,732,141	27,204,542	34,020,635	6.0	4.9	4.6	6.2
European Commission	21,673,026	25,296,589	24,949,051	25,156,063	4.6	4.7	4.2	4.6
UK DFID	4,003,611	3,733,433	3,588,731	23,796,135	0.9	0.7	0.6	4.3
US DOD	33,126,578	30,518,142	37,585,617	22,666,297	7.1	5.6	6.3	4.1
UK MRC[B]	18,594,597	18,985,044	20,012,611	22,432,699	4.0	3.5	3.4	4.1
Australian NHMRC	7,692,288	9,012,351	10,201,615	9,623,199	1.6	1.7	1.7	1.8
Institut Pasteur	13,142,888	7,739,784	7,067,036	9,060,676	2.8	1.4	1.2	1.7
USAID	9,249,900	8,164,740	8,166,618	8,758,051	2.0	1.5	1.4	1.6
Inserm	472,615	459,077	3,541,558	4,560,058	0.1	0.1	0.6	0.8
Subtotal top 12 malaria R&D funders[B*]	442,390,786	507,870,081	544,613,555	505,828,729	94.4	93.7	91.7	92.5
Disease Total[B]	468,449,438	541,746,356	593,860,744	547,042,394	100.0	100.0	100.0	100.0

^ Figures are adjusted for inflation and reported in 2007 US dollars
[A] Includes new survey respondents in 2010
[B] Figures for 2009 have been updated and therefore differ from previously published figures
* Subtotals for 2007, 2008 and 2009 top 12 reflect the top funders for those years, not the top 12 for 2010

19. Malaria is currently a key focus area for the Gates Foundation's Global Health Programme. It has a five-point strategy for the assault on malaria: develop malaria vaccines, develop more effective and affordable drugs and diagnostics, develop new tools to control mosquitoes, research the effectiveness of malaria interventions, and advocate for policies and financing.[20] In 2012, the Bill and Melinda Gates Foundation committed $750m to help sustain the Global Fund. The new commitment is in addition to the $650m already contributed by the foundation to the Global Fund since it was launched in 2002.

20. The NIH supports research through the US National Institute of Allergy and Infectious Diseases and the Fogarty International Centre. The US Department of Defence and US Agency for International Development (USAID) also feature among the top international active funders of malaria R&D in 2010.

21. Funding from Europe – outside the UK – flows primarily through the European Commission Seventh Framework Programme (FP7) for 2007–2013.[21] The development process of the next Framework Programme (to be referred to as Horizon 2020), which will replace FP7 in 2014, is underway, but it is not clear whether Horizon 2020 will involve less funding for malaria research. Malaria is identified as a target area for research support with funding primarily targeted at basic research and vector control. Other major funders in Europe include the Institut Pasteur in France ($9m in 2010), which is also a prominent institute for malaria research, and the French National Institute of Health and Medical Research ($4.5m in 2010).

13 The eight MDGs are to: eradicate extreme poverty and hunger; achieve universal primary education; promote gender equality and empower women; reduce child mortality; improve maternal health; combat HIV/AIDS, malaria and other diseases; ensure environmental sustainability; and develop a global partnership for development.

14 **undp.org/mdg/basics.shtml**

15 World Health Organization. 2011. World Malaria Report. **www.who.int/malaria/world_malaria_report_2011/en/**

16 Murray CJL et al. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2011;379(9814):413–431.

17 Roll Back Malaria Partnership. 2011. Eliminating Malaria: Learning from the past, looking ahead. **www.rbm.who.int/ProgressImpactSeries/docs/report9-en.pdf**

18 **rbm.who.int/rbmroadmaps.html**

19 Source: Moran M et al. Neglected Disease Research and Development: Is innovation under threat? Policy Cures; 2011. G-FINDER grant data includes disbursements made only for active primary grants and does not include 'committed' or grant funding for infrastructure at the Wellcome Trust Centres/MOPs/JRIFs/SRIFs. The Wellcome Trust funding analysis in this portfolio review includes all 'active' and 'completed' grants between the financial years 1989/1990 and 2007/2008, including grant funding for infrastructure at the Wellcome Trust Centres and MOPs.

20 See **www.gatesfoundation.org/topics/Pages/malaria.aspx#**.

21 **ec.europa.eu/**

22. Within the UK, the Wellcome Trust and UK Medical Research Council (MRC) are significant funders, reporting $34m and $22.4m of active malaria-focused research grants, respectively, in 2010. Much of the MRC's malaria work is conducted at its Unit in The Gambia, which focuses on infectious diseases prevalent in The Gambia, and the MRC National Institute for Medical Research. The Wellcome Trust has been in the top five in the list of agencies contributing the most funds to malaria for the four years of the G-FINDER study – disbursing an estimated $28m, $27m, $27m and $34m in R&D during 2007, 2008, 2009 and 2010, respectively (see Table 1).[22]

23. In 1992, with initial contributions from the MRC,[23] the WTSI was established as an advanced facility for mapping, sequencing and decoding the human genome and the genomes of other organisms. One of the earliest genomes to be sequenced through a collaborative project at the Institute was the malaria parasite *Plasmodium falciparum*. Today at the WTSI, the malaria programme uses genomic approaches to study malaria (see Dominic Kwiatkowski case study).

24. Other significant funders outside of Europe include Australia. The Australian National Health and Medical Research Council spent $9.6m on malaria R&D in 2010 (see Table 1). The Australian Government is a major supporter of the Walter and Eliza Hall Institute of Medical Research, which has malaria as a research focus area.

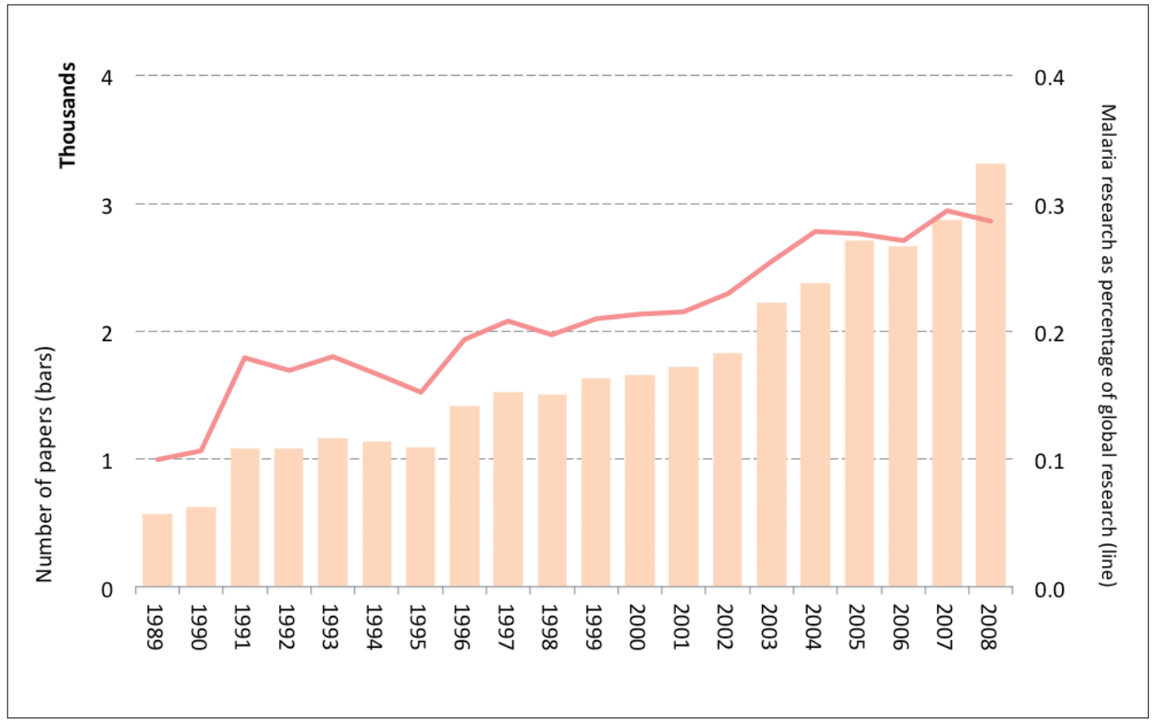
25. Several multilateral and multi-agency initiatives have been established over the past two decades to tackle malaria, and these have involved large research components. Product development specifically has received a significant boost in funding over the past decade thanks to the establishment of malaria-related PDPs – such as the Medicines for Malaria Venture (MMV),[24] the PATH Malaria Vaccine Initiative (MVI) and the Drugs for Neglected Disease Initiative.[25] PDPs address the lack of profit-making incentive to develop pharmaceutical products in low-income countries by bringing together dedicated sources of funding from government, philanthropic and corporate donors.

2.1 Malaria publication output: 1989–2008

26. The increase in funding for malaria-related research over the past two decades is reflected in the associated peer-review publication output. The absolute volume of publications related to malaria research has grown steadily over the past 20 years. Since 1991, there has been a three-fold increase in the numbers of papers, from just over 1000 in 1991 to more than 3000 in 2008. In 1989, malaria research represented 0.1 per cent of all global research publications; by 2008, this proportion had increased to 0.3 per cent of global research output (Figure 1).

27. Over the past two decades, malaria research has been produced by a core set of countries. The relative position of these countries in terms of volume of output to which they are linked is shown in Figure 2.[26] Over the 20-year time period, the proportion of papers linked to the UK has grown, from 16 per cent of the world total between 1989 and 1993 to 19.1 per cent between 2004 and 2008 (725 and 2657, respectively) – see Figure 2, Figure 3 and Table 1, Annex D.

Figure 1 Number of malaria papers and as percentage of all research papers, 1989–2008



28. Overall, throughout this period the UK has retained its 'second place' behind the USA in terms of malaria research publication output (Figure 2). The USA has maintained its leading position in share of global output, producing approximately one-third of the total output, and remains the single biggest producer of malaria research publications (Figure 2 and Table 1, Annex D).

29. The relative position of most of the countries in the top ten ranked by volume of malaria research output has not changed over the past two decades. The exception is Germany, whose relative output increased during the mid- to late 1990s and early 2000s, although its output is now stable (see Figure 3).

30. Outside Europe, countries showing a steady increase in both absolute numbers of papers and relative proportion of papers in this field since the late 1980s include India and Kenya (see Figure 2, Figure 3 and Table 1, Annex D). In terms of world total publication outputs in the field, the number of papers associated with institutions in India has risen from 4.1 per cent in 1989 to 6.1 per cent in 2008 and in Kenya from 2.8 per cent of the world total in 1989 to 4.8 per cent in 2008 (see Figure 3). Elsewhere, countries showing notable growth in terms of malaria research publication production include Belgium, South Africa, Tanzania, Malawi and Japan (see Table 1 and Table 2, Annex D).

22 The Wellcome Trust spend reported in G-FINDER is based on only active, malaria-specific R&D projects and hence does not correlate with our funding analysis, which includes commitments made and funding for infrastructure at Wellcome Trust Centres and MOPs to support and facilitate malaria-related research (see Figure 1, Tables 3 and 3a, Annex C).

23 The MRC contributed approximately £24m to the WTSI for the period up to the end of 2002. Source: WTSI.

24 Medicines for Malaria Venture (MMV) is a product development public–private partnership, which was established in 1999 and is dedicated to discovering, developing and delivering new affordable antimalarial drugs in malaria-endemic countries (**www.mmv.org**).

25 The Drugs for Neglected Diseases Initiative (DNDi), which was established in 2003, is a collaborative, patient-needs-driven, non-profit drug R&D organisation that is developing new treatments for malaria, visceral leishmaniasis, sleeping sickness (human African trypanosomiasis) and Chagas' disease (**www.dndi.org**).

26 The top ten countries have been modified to include Malawi (ranked 32nd), because the Trust is interested in outputs linked to the Wellcome Trust Research Programme in Malawi, and exclude Japan, which was ranked in tenth position.

Figure 2 Malaria papers linked with 'top ten most productive' countries, 1989–2008 (by volume)[27,28,29]

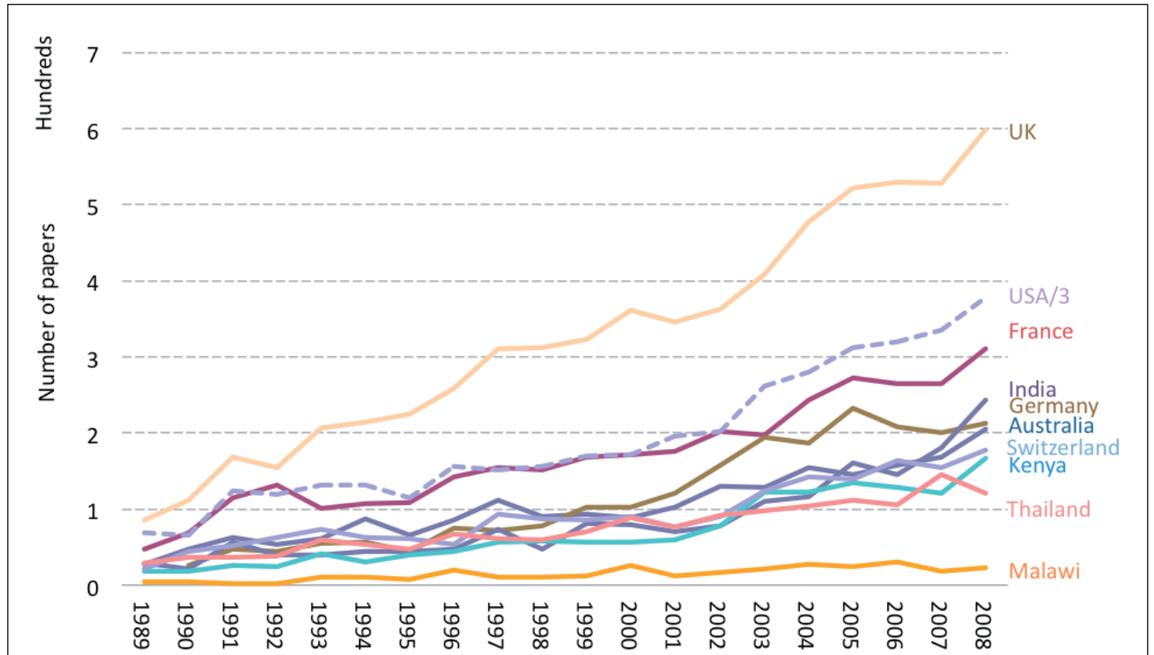
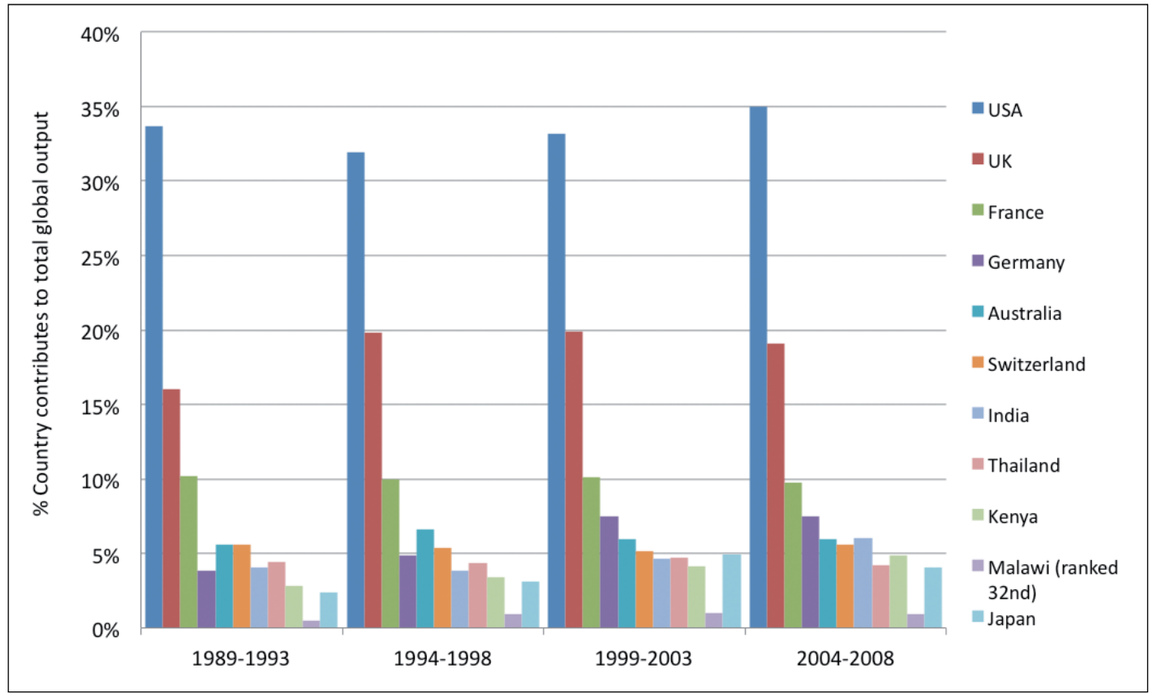


Figure 3 Malaria papers linked with 'top ten most productive' countries, 1989–2008 (five-year periods)[30]



31. Analysis of the subject focus of malaria-related publication output over time shows that much of the output, not surprisingly, has been published predominantly in 'tropical medicine' and 'parasitology' journals (see Figure 4). Although over the past two decades there has been an increase in the volume of malaria-related papers across all subject areas, the most striking growth has been in journals focusing on the basic sciences – specifically 'medicinal chemistry', 'biochemistry/molecular biology' and 'microbiology' (see Figure 4 and Table 3, Annex D).

32. In terms of world publication outputs within the field of malaria, the number of malaria-related papers appearing in 'immunology'-related journals has declined over the past 20 years – from 8.8 per cent of the world total (between 1989 and 1993) to 3.1 per cent (between 2004 and 2008).

33. Moving beyond the volume of output, citation analysis[31] is helpful to identify from where high-quality, highly cited research originates. Citation data for 20 years (1989–2008) were used to determine the origins and affiliation of the most highly cited malaria papers worldwide. Over the whole period, most of the prolific institutions are located in high-income countries, particularly the UK and the USA. Of the 20 institutions listed in Table 4, Annex D, nine institutions are UK-based and five are USA-based.

34. The University of Oxford and London School of Hygiene and Tropical Medicine (LSHTM) are linked to the most highly cited papers in malaria research worldwide over the 20-year period.[32] The University of Liverpool[33] is ranked sixth after KEMRI (Kenya), Mahidol University (Thailand) and the US National Institute of Allergy and Infectious Diseases, reflecting the strength of UK research in and commitment to malaria.

27 The time trend of malaria papers linked to the 'top ten most productive' countries was modified to include Malawi (ranked 32nd) and exclude Japan (ranked tenth) because the Wellcome Trust is interested in outputs linked to the Wellcome Trust Research Programme in Malawi.

28 The data for the USA have been reduced by a factor of three to bring them into a common range.

29 The significant increase in research papers from China over the past decade, as evidenced in the human genetics 1990–2009 portfolio review, has yet to be demonstrated in malaria-related research using this method.

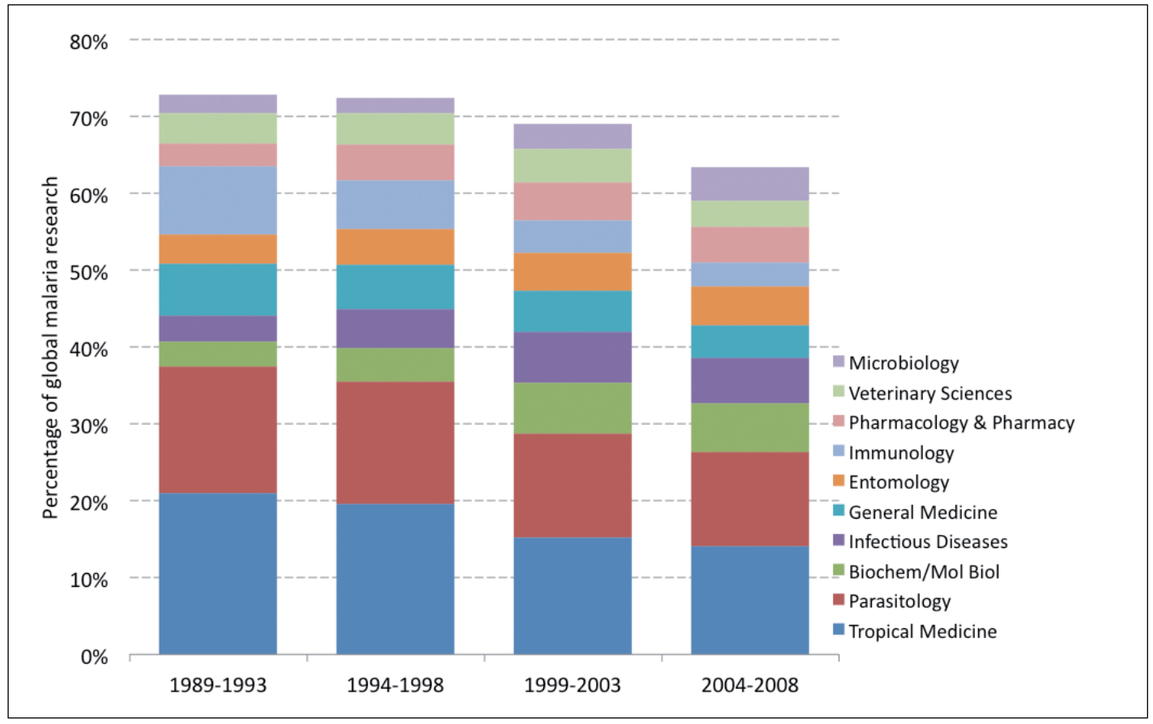
30 Malaria papers linked to the 'top ten most productive' countries was modified to include Malawi (ranked 32nd) and exclude Japan (ranked tenth) because the Wellcome Trust is interested in outputs linked to the Wellcome Trust Research Programme in Malawi.

31 In this analysis, 'highly cited papers' are those papers with an average rebased impact of at least four (i.e. they have received at least four times as many citations by the end of 2008 as the average paper published in that year in the same subject area).

32 The Universities of Oxford and Liverpool and the LSHTM have well-known tropical medicine centres or schools, including: the MALAWI-Liverpool-Wellcome Trust Research Programme based in Blantyre; the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme in Thailand; the KEMRI-Wellcome Trust Research Programme (a partnership between KEMRI, University of Oxford and the Wellcome Trust); and the Joint Malaria Programme (a collaboration between the National Institute for Medical Research of Tanzania, the Kilimanjaro Christian Medical College, the LSHTM and the University of Copenhagen).

33 University of Liverpool includes Liverpool School of Tropical Medicine, the MALAWI-Liverpool-Wellcome Trust Research Programme based in Blantyre and the Liverpool Wellcome Trust Tropical Centre.

Figure 4 **Malaria papers published in five-year periods by subject category (1989–2008)**



Data: Thomson Reuters 2009; Analysis: Evidence, Thomson Reuters (Scientific UK).

35. The top five authors in terms of producing the most highly cited papers in malaria research worldwide, Nick White, Brian Greenwood, Kevin Marsh, Bob Snow and Adrian Hill (See Table 5, Annex D) – all of whom have received significant funding from the Wellcome Trust over this period (see Table 5, Annex C) – are linked to the top three institutions (see Table 4, Annex D).

36. In 2009, the journal *Lab Times* published an analysis of papers from 1996 to 2007, which showed that Wellcome Trust-funded researchers feature strongly in author citation in the parasitology field – including the top seven.[34] Nick White and Kevin Marsh were the two most cited.

34 Neumann R. Publication analysis 1996–2007: parasitology. Lab Times 2009;3:38–40. Only journals relevant to parasitology were included in the analysis.

3. Looking back: the Wellcome Trust and malaria

You [Wellcome Trust] have picked the right people and you have supported them, and it has paid off very well and how do you replicate that, I don't know. But that is genius.
Wellcome Trust Expert Group on malaria, April 2010

37. Over the past few decades, considerable progress has been made in our knowledge of malaria, most of which has resulted from funding basic, curiosity-driven research. However, much of the advance, in terms of tangible impacts upon health, has come from a better understanding of how to measure, prevent and treat malaria in people using existing tools (including long-lasting insecticide-treated bednets and indoor residual spraying), approaches for the clinical management of malaria, and developing and validating effective treatments for malaria such as intermittent preventative treatment during pregnancy, artemisinin combination treatment, artesunate–mefloquine fixed-dose combination, artesunate for severe malaria and dihydroartemisinin-piperaquine.

38. This review highlighted four broad areas where the Wellcome Trust is thought to have had a significant impact on the field of malaria:

- the sustained provision of project and people-based funding for malaria-focused research leaders and young researchers in the field who, in turn, have delivered a range of breakthroughs in our knowledge of and approach to tackling malaria
- the support of genomic science at the WTSI, which is enhancing our understanding of the basic biology of malaria
- the support of research capacity building and infrastructure in malaria-endemic regions (particularly through the MOPs), which have helped to deliver important clinical investigation studies and tangible impacts on the malaria burden
- the involvement with and support of multi-agency, cross-sector partnerships and collaborations that have shaped the direction of malaria – both within and outside the field. Advances in knowledge in malaria research associated with Wellcome Trust funding are set out in Table 2 and Timeline (Annex E).

3.1 Building research capacity and infrastructure

In terms of capacity building, the Trust has been absolutely central, because they have committed long-term significant resources. It is only now, 20 years down the line, that there is a really strong cohort of African scientists coming through.
Wellcome Trust Expert Group on malaria, April 2010

39. Since the establishment of the Wellcome Trust Laboratories by Henry Foy at the Kenyatta Hospital in Nairobi during the late 1940s, the Wellcome Trust has worked to build capacity and expertise in malaria research. The Expert Group highlighted that one of the Trust's major strengths is its ability to provide sustained support for research capacity and infrastructure – as it has done for malaria research – both inside and outside the UK.

40. Over the past two decades, the Wellcome Trust has supported malaria researchers through all stages of their careers through personal and institution-based grants (see Tables 5, 5a, and Table 6, Annex C). The Wellcome Trust has thus contributed to the formation of a new generation of malaria researchers and excellent research leaders, many of whom are now informing national and international policy and directing research efforts, both in the UK and overseas (see case studies).

41. Between the financial years 1989/90 and 2007/08, the Wellcome Trust committed approximately £189m[35] to malaria-focused research across all its funding divisions. During this time, an additional £120m was allocated for core support and infrastructure at Wellcome Trust Centres and the MOPs, as well as a further £8.8m on malaria-focused research through the WTSI (see Tables 3 and 3a, Annex C). As described in section 2, the Wellcome Trust has been in the top five global funders of R&D for new products for all four years of the G-FINDER study – disbursing an estimated $28m, $27m, $27m and $34m in funding during the financial years 2007, 2008, 2009 and 2010, respectively.[36,37]

35 Excludes Wellcome Trust funding for infrastructure at Wellcome Trust Centres and MOPs (52 grants, £120m).

36 Overall, malaria was the second highest neglected disease area funded ($468m in 2007, $540m in 2008 and $595m in 2009) after HIV/AIDS ($1.08bn in 2007, $ 1.16bn in 2008 and $1.14bn in 2009). In 2010, malaria was the third highest neglected disease area funded ($547m in 2010) after HIV/AIDS ($1.1bn in 2010) and tuberculosis ($6bn in 2010). The Bill and Melinda Gates Foundation ranked as top malaria funder in 2007 ($124m), 2008 ($173m) and 2009 ($182m) of the G-FINDER study. In 2010, the Bill and Melinda Gates Foundation ranked third ($87m). The US NIH was 2010's largest funder of malaria R&D.

37 Wellcome Trust grant data in this review are not comparable with G-FINDER grant data. G-FINDER grant data include disbursements made only for active primary grants. Wellcome Trust funding data include all active and completed grants between the

42. Through its funding divisions, the Wellcome Trust has awarded 515 grants,[38] mainly in responsive mode, to malaria-focused projects – accounting for £189m, representing just over 3 per cent of the Trust's funding commitment over this time (see Tables 3 and 3a, Annex C). Of this, approximately two-fifths (42 per cent by number; 42 per cent by value; 216 grants; £80m) of malaria grant funding has been careers based, supporting individual researchers doing malaria-based projects via personal support schemes (Table 1 and Figure 2, Annex C). These personal support schemes include studentships (£9m), early career fellowships (£8m), and Intermediate (£25m) and Senior/Principal research fellowships (£38m).

43. The larger proportion of funds (58 per cent by number, 58 per cent by value; 299 grants; £109m) has been allocated to research and project support (equipment, university awards, strategic awards, and project and programme grants; Table 1, Annex C). Over the 20-year period, approximately three-fifths (61 per cent by number; 60 per cent by value; 314 grants; £114m) of Wellcome Trust funding for malaria research (excluding Wellcome Trust grants for infrastructure at Wellcome Trust Centres and MOPs) has been allocated to UK institutions, whereas 39 per cent of funding (201 grants; £75m) has been committed to non-UK-based malaria research (see Table 2 and Figure 3, Annex C). Of the 201 grants[39] featuring non-UK based malaria research, 159 (£47m) grants were based in low- and middle-income countries; 79 of these grants were fellowships totalling £32m in grant funding (see Table 2, and Figure 3b, Annex B).

44. Several centres providing the facility for research and training on malaria and other tropical diseases have been a core part of the Wellcome Trust's capacity building strategy around malaria.

3.1.1 UK Wellcome Trust Centres for Research in Clinical Tropical Medicine

45. Wellcome Trust Centres for Research in Clinical Tropical Medicine provide an environment that enables clinicians and health professionals to pursue research and undertake clinical training in national and international public health and tropical medicine. In addition, they provide a UK base for researchers engaged in projects outside the UK and support exchanges between clinical scientists. There is also a close relationship between these UK centres and the MOPs (section 3.3). In 1995, the Wellcome Trust established four UK centres:

- the Wellcome Trust Bloomsbury Centres for Research in Clinical Tropical Medicine, comprising the LSHTM; UCL (Institute of Child Health)[40]; Institute of Psychiatry, London; Barts and the London School of Medicine and Dentistry; and St George's University of London
- the Wellcome Centre for Clinical Tropical Medicine at Imperial College London[41] with St Mary's Hospital
- the Liverpool Wellcome Trust Tropical Centre[42]
- the Wellcome Trust Centre for Research in Clinical Tropical Medicine at Oxford.[43]

3.1.2 Wellcome Trust Centre for Molecular Parasitology

46. Through its support of the Wellcome Trust Centre for Molecular Parasitology (WTCMP) at the University of Glasgow, the Trust has helped to develop UK capacity in malaria parasitology. The WTCMP was first established in 1987 as a Wellcome Trust Unit (the Wellcome Trust's contribution was £1.1m) to study the molecular genetics of parasites, including *Trypanosoma*, *Leishmania* and *Trichomonas*, under the direction of Professor Andrew Tait and Professor David Barry. In 2002, the French National Institute of Health and Medical Research (INSERM) team led by Professor Christian Doerig (now based at the Department of Microbiology, Monash University, Victoria, Australia) joined the WTCMP and in 2004, INSERM established the Malaria Research Unit. In 2006, the WTCMP co-located to the multidisciplinary Glasgow Biomedical Centre, and in 2008, after a successful bid for a Wellcome Trust Strategic Award, core support for the WTCMP was renewed (£2.7m). In 2011, under the direction of Professor David Barry, malaria parasitology remained a key component of the research undertaken at the centre.

47. In addition, the WTCMP – together with the Institute of Infection, Immunity and Inflammation within the College of Medical, Veterinary and Life Sciences (MVLS) at the University of Glasgow – hosts the European Virtual Institute for Malaria Research (EVIMalaR).[44] EVIMalaR is a European Commission-funded network that combines 55 of the European Union's leading malaria research groups from 28 institutions with six leading African institutions, the International Centre for Genetic Engineering and Biotechnology from India and representation of the Australian Malaria Research Network. This virtual institute is directed by Professor Andy Waters, a Wellcome Trust Principal Research Fellow.

48. Recently, research funded through EVIMalaR and three other EU projects[45] led by Professor Christian Doerig (who still maintains strong links with the WTCMP) and Professor Andy Waters at the WTCMP has discovered that chemotherapy drugs originally designed to inhibit key signalling pathways (PAK-MEK) in cancer cells can also kill blood stages of the malaria parasite *P. falciparum*. This finding is expected to have major implications for future antimalarial drug discovery strategies.[46]

3.1.3 Wellcome Trust funding for the History of Medicine

49. Through its History of Medicine funding programme, the Trust has played an important part in supporting research into the history of malaria research in the UK and more broadly. Historians at the Wellcome Unit for the History of Medicine, which was established at Oxford University in 1972, have conducted several studies on the history of the disease and its control, including the *History of Malaria and Its Control in Twentieth-century East Africa* and *The History of Malaria in England*. Other studies supported through Wellcome's History of Medicine grants include 'History of anti-malarial policy in colonial South India' (Queen Mary, University of London) and 'Stagnation and salvation: a cultural history of malaria in Rome and the Campagna, 1859–1939' (the Indian Institute of Technology). Such historically based studies provide new insights into our understanding of malaria today and the strategies that have been developed to address the disease over time. Such work provides an important context for the successes and failures in malaria treatment and prevention to date and helps to engage new audiences with the history of malaria and its relevance to today's world. In total, the Trust has contributed just over £0.4m to history of malaria research over the past two decades.

financial years 1989/1990 and 2007/2008.

38 Excludes Wellcome Trust grants for infrastructure at Wellcome Trust Centres and MOPs (52 grants, £120m).

39 Excludes the 40 Wellcome Trust grants for infrastructure at Wellcome Trust Centres and MOPs.

40 **wbc.lshtm.ac.uk/**

41 **www3.imperial.ac.uk/clinicaltropicalmedicine**

42 **www.liverpoolwttc.org.uk/**

43 **www.tropicalmedicine.ox.ac.uk/uk-centre**

44 **www.evimalar.org**

45 AntiMal Sixth Framework Programme (FP6) Malaria Initiative, Biology and Pathology of Malaria Parasite Network of Excellence, and FP7 MALSIG.

46 Sicard A et al. Activation of a PAK-MEK signalling pathway in malaria parasite-infected erythrocytes. Cell Microbiol 2011;13(6):836–45.

Table 2 Advances in knowledge in malaria research associated with Wellcome Trust funding

Key date	Who	Discovery or impact
1983	White NJ et al. Severe hypoglycemia and hyperinsulemia in falciparum malaria. N Engl J Med 1983;309:61-66.	Demonstration of malaria hypoglycaemia. Helped shape the initial approach to the clinical management of cerebral malaria.
1988	Taylor TE et al. Blood glucose levels in Malawian children before and during the administration of intravenous quinine in severe falciparum. N Engl J Med 1988;319:1040–7.	Demonstration that hypoglycaemia is a frequent complication of falciparum malaria in children. Important in shaping the initial approach to the clinical management of cerebral malaria.
1989	Molyneux ME et al. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Q J Med 1989;71:441–459.	Blantyre Coma Score first described.
1992	Roberts D et al. Rapid switching to multiple antigenic and adhesive phenotypes in malaria. Nature 1992;357(6380):689–92.	Demonstration of antigenic and functional heterogeneity in malaria.
1992	Trang TTM et al. Acute renal failure in severe falciparum malaria. Clin Infect Dis 1992;15:874–80.	First description of natural history of acute renal failure in severe malaria.
1992	White NJ et al. Comparison of artemether and chloroquine for severe malaria in Gambian children. Lancet 1992;339:317–21.	First evaluation of artemisinin derivatives in Africa.
1993	Nosten F et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993;341:1054–6.	Discovery of halofantrine cardiotoxicity.
1994	Turner GD et al. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration. Am J Pathol 1994;145:1057–69.	Identification of ICAM-1 as the cytoadherence receptor in the brain in cerebral malaria.
1995	Smith JD et al. Switches in expression of Plasmodium falciparum var genes correlate with changes in antigenic and cytoadherent phenotypes of infected erythrocytes. Cell 1995;82:100–110.	Demonstration that antigenic variation expression correlates with *var* gene expression.
1996	Mai NTH et al. Post-malaria neurological syndrome. Lancet 1996;348:917–21.	Description of the post-malaria neurological syndrome.
1996	Price RN et al. The effects of artemisinin derivatives on malaria transmissability. Lancet 1996;347:1654–8.	Artemisinins shown to reduce gametocyte carriage.
1997	Dondorp AM et al. Prognostic significance of reduced red cell deformability in severe falciparum malaria. Am J Trop Med Hyg 1997;57:507–11.	Discovery of a major pathological process in severe malaria.
1999	Gupta et al. Immunity to non-cerebral severe malaria is acquired after one or two infections. Nat Med 1999;5(3):340–3.	Demonstration that immunity against non-cerebral severe malaria develops with the first and second infections.
1999	Silamut K et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. Am J Path 1999;155:395–410.	Definitive description of the distribution of microvascular sequestration in cerebral malaria.
1999	Nosten FR et al. Effects of Plasmodium vivax malaria in pregnancy. Lancet 1999;354:546–9.	First detailed description of the effects of vivax malaria during pregnancy.
2000	Chotivanich K et al. The mechanisms of parasite clearance after antimalarial treatment of Plasmodium falciparum malaria. J Infect Dis 2000;182:629–33.	Discovery of the mechanism of parasite clearance after artemisinin derivative treatment.
2002	Phu NH et al. Hemofiltration and peritoneal dialysis in infection associated acute renal failure in Vietnam. N Engl J Med 2002;347:895–902.	Haemofiltration reduces the mortality of malaria acute renal failure.
2002	Medana IM et al. Axonal injury in cerebral malaria. Am J Pathol. 2002;160:655–66.	Discovery of neuropathological process that may explain reversible coma in cerebral malaria.
2002	Gardner MJ et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 2002;419:498–511.	Completion and publication of the genome sequence of *P. falciparum*.
2002	Holt RA et al. The genome sequence of the malaria mosquito Anopheles gambiae. Science 2002;298(5591):129–49.	Completion and publication of the genome sequence of *Anopheles gambiae*.
2003	Kriek N. Characterisation of the pathway for the transport of cytoadherence-mediating protein, PfEMP1, to the host cell surface in malaria parasite-infected erythrocytes. Mol Microbiol 2003;50(4):1215–27.	Delineation of the transport mechanism for the delivery of the crucial parasite virulence factor, PfEMP1, to the erythrocyte surface.
2004	Stepniewska K et al. The in vivo assessment of antimalarial drug efficacy in falciparum malaria; the duration of follow-up. Antimicrob Agents Chemother 2004;48:4271–80.	Paper that underpinned changes in the WHO guidelines on antimalarial assessment.
2004	Hien TT et al. Dihydroartemisinin-piperaquine against multidrug resistant falciparum malaria in Viet Nam: randomized clinical trial. Lancet 2004;363:18–22.	First publication on a major new ACT.
2004	Price RN et al. Mefloquine resistance in Plasmodium falciparum results from increased pfmdr1 gene copy number. Lancet 2004;364:438–47.	Molecular basis of mefloquine resistance described.
2004	Horrocks et al. Variable var transition rates underlie antigenic variation in malaria. Edited by Louis H Miller, National Institutes of Health, Rockville, MD, July 2004, vol. 101, no. 30, 11129–34.	Demonstration that variable *var* transition rates have important implications for the underlying molecular mechanisms of antigenic variation in malaria.
2004	Roper. Intercontinental spread of pyrimethamine-resistant malaria. Science 2004;305(5687):1124.	Demonstration that pyrimethamine-resistant malaria parasites originally arrived in Africa from South-east Asia.
2004	Mayxay M et al. Short communication: an assessment of the use of malaria rapid tests by village health volunteers in rural Laos. Trop Med Int Health 2004;9(3):325–9.	Demonstration that two malaria diagnostic kits, ParacheckPf and OptiMAL, have low error rates and can be used with minimal training.
2004	Taylor TE et al. Nat Med 2004;10:143–145. Differentiating the pathologies of cerebral malaria by postmortem parasite counts.	First description of the link to malaria retinopathy. Demonstration that 25 per cent of the patients who satisfy the standard clinical case definition of cerebral malaria die for reasons unrelated to malaria.
2004	Singh B et al. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet 2004;363(9414):1017–24.	Discovery of the fifth malaria species, *Plasmodium knowlesi*, infecting humans.
2005	Webster DP et al. Enhanced T cell-mediated protection against malaria in human challenges by using the recombinant poxviruses FP9 and modified vaccinia virus Ankara. PNAS 2005:4836–4841.	Two-stage vaccine delivery programme is used to drive powerful cell-based immune responses (those based on T cells, as opposed to B-cell-based antibody responses).
2005	Dondorp A et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487);717–25.	Largest clinical trial to assess artesunate as a treatment for severe malaria, SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), found that using artesunate reduced the number of deaths by more than a third when compared with quinine.
2005	www.malariagen.net/	MalariaGEN established.
2005	Smith DL et al. The entomological inoculation rate and Plasmodium falciparum infection in African children. Nature 2005;438:492–95.	Demonstration that 80 per cent of all new malaria infections are concentrated in just one-fifth of the population in children in Africa.
2005	Bull PC et al. Plasmodium falciparum variant surface antigen expression patterns during malaria. PLoS 2005;1(3):202–13.	Demonstration that information on *var* expression patterns can be used as a tool to investigate how host and parasite adapt to one another as immunity develops.
2005	The Malaria Atlas Project established.	See Table 8, Annex C.
2006	WHO's guidelines for the Treatment of Malaria (2006); Guidelines for the treatment of malaria, second edition, World Health Organization, 2010; Guidelines for the treatment of malaria, World Health Organization, 2006.	ACTs recommended by WHO as first-line treatment for falciparum malaria. The minimum clinical efficacy threshold was raised from 75 per cent at 14 days to 90 per cent at 28 days.

Key date	Who	Discovery or impact
2007	Imwong M et al. Relapses of Plasmodium vivax infection usually result from activation of heterologous hypnozoites. J Infect Dis 2007;195:927–33.	Critical insight into the biology of vivax relapses.
2007	Abdisalan M. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med 2007:1341–1348.	Demonstration that rapid scaling up of ITN coverage can be achieved through mass distribution campaigns. The Kenyan Government initiated a programme to provide 3.4 million treated nets free to as many young children as possible over a two-week period. Coverage rose to two-thirds of all children sleeping under a treated net.
2007	Killeen GF et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med 2007;4:e229.	New guidelines on insecticide-treated mosquito nets issued by WHO. The policy was informed by research examining the positive impact of distributing free bednets.
2008	Draper S. Effective induction of high-titer antibodies by viral vector vaccines. Nat Med 2008;14(8):819–21.	Demonstration of the use of modified cold and pox viruses to deliver a malaria vaccine that offers complete protection from the disease in animals and also strongly limits the growth of human malaria *in vitro*.
2008	Maier AG et al. Exported proteins required for virulence and rigidity of Plasmodium falciparum-infected human erythrocytes. Cell 2008:134(1);48–61.	Identification of eight new proteins that transport PfEMP1.
2008	Reece S et al. Sex ratio adjustment and kin discrimination in malaria parasites. Nature 2008;453:609–614.	Demonstration of sex allocation theory in malaria parasites.
2008	Newton P et al. Fake artesunate in SE Asia. Lancet 2001;357:1948–50.	Operation Jupiter discovers fake ACT drugs in Southern China.
2008	Dondorp AM et al. Direct in vivo assessment of microcirculatory dysfunction in severe falciparum malaria. J Infect Dis 2008;197:79–84.	First direct visualisation and quantitative assessment of sequestration in vivo.
2008	Pain et al. Genome of the simian and human malaria parasite Plasmodium knowlesi. Nature 2008;455:799–803.	Genome of *P. knowlesi* decoded, revealing a host range from monkeys to man.
2008	McGready et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated Plasmodium falciparum treatment in pregnancy. PLoS Med 2008;5(12):e253.	Development of an antenatal care system that has eliminated maternal malaria-related mortality.
2008	Bejon P et al. Efficacy of RTS,S/AS01E: Clinical malaria in 5 to 17 month old children. N Engl J Med 2008;359. Abdulla S et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. N Eng J Med 2008; 359:2533–44.	Two phase II studies demonstrate that the RTS,S vaccine candidate provides infants and young children with significant protection against malaria.
2009	Gomes et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009;373(9663):557–566.	Largest ever community-based study of severe malaria showed that pre-referral rectal artesunate reduced mortality in children by 25 per cent.
2009	Hay SI et al. A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 2009;6:e48.	Generation of a global map of *P. falciparum* endemicity for the year 2007. The first malaria map to be published in 40 years.
2009	Povelones M et al. Leucine-rich repeat protein complex activates mosquito complement in defense against Plasmodium parasites. Science 2009;324(5924):258–261.	Demonstration that mosquito's defence against malaria is due to their immune system mounting an effective attack on the malaria parasite.
2009	Beare NA et al. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. J Infect Dis 2009;199(2):263–71.	Demonstration that impaired perfusion occurs in most children with cerebral malaria, giving insight into the pathogenesis of malaria.
2009	Dondorp AM et al. Artemisinin resistance in Plasmodium falciparum malaria. New Eng J Med 2009;361:455–67.	Artemisinin resistance first described in western Cambodia.
2009	Malaria Genomics Epidemiology Network. A global network for investigating the genomic epidemiology of malaria. Nature 2008;456:732–7.	Demonstration that a DNA-based assay could be designed to trace resistance in *Anopheles funestus*.

Key date	Who	Discovery or impact
2009	Wondji SW et al. Two duplicated P450 genes are associated with pyrethroid resistance in Anopheles funestus, a major malaria vector. Genome Res 2009,19(3):452–459.	Identification of two duplicated P450-specific mosquito genes associated with pyrethroid resistance in *Anopheles funestus*.
2009	Noor AM et al. The use of insecticide treated nets by age: implications for universal coverage in Africa. BMC Public Health 2009;9:369.	Demonstration that older children, between the ages of 5 and 19 years, are the least well protected by insecticide-treated mosquito nets in Africa.
2009	Daneshvar C et al. Clinical and laboratory features of human Plasmodium knowlesi infection. Clin Infect Dis 2009;49(6):852–60.	Demonstration of the clinical and laboratory features of human *P. knowlesi*.
2009	Geissbühler Y et al. Microbial larvicide application by a large-scale, community-based program reduces malaria infection prevalence in urban Dar es Salaam, Tanzania. PLoS one 2009;4(3).	Demonstration of the effectiveness of a large-scale, community-based program using microbial larvicide.
2009	Warimwe G et al. Plasmodium falciparum var gene expression is modified by host immunity. PNAS 2009;106(51):21801–6.	Demonstration that *P. falciparum var* gene expression is associated with low host immunity.
2009	Neumann R. Publication analysis 1996–2007: parasitology. Lab Times 2009;3:38–40	Wellcome Trust-funded malaria researchers are among most cited authors.
2009/ 2010	Rottmann M. Spiroindolones, a potent compound class for the treatment of malaria. Science 2010; 329(5996):1175–80.	Development of a new antimalarial drug candidate, NITD609.
2010	Liu W et al. Origin of the human malaria parasite Plasmodium falciparum in gorillas. Nature 2010;467:420–5.	Demonstration that the human malaria parasite *P. falciparum* originated from infected gorillas.
2010	Smithuis F et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis 2010;10(10):673–81.	First comparison of all available fixed-dose combination treatments for falciparum malaria.
2010	Dondorp et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010;376(9753):1647–57.	Largest ever study in severe malaria, AQUAMAT (African quinine versus artesunate malaria trial), showed that artesunate reduces the mortality of severe malaria in African children by 22 per cent compared with quinine and is highly cost-effective.
2010	McAuley CF et al. High mortality from Plasmodium falciparum malaria in children living with sickle cell anemia on the coast of Kenya. Blood 2010;116:1663–8.	Demonstration of the high risk of death in African children with sickle cell anaemia.
2010	Sutherland CJ et al. Two nonrecombining sympatric forms of the human malaria parasite Plasmodium ovale occur globally. J Infect Dis 2010;201:1544–50.	Discovery of separate species.
2011	Crosnier et al. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. Nature 2011;480;(7378):534–7.	Identification of basigin, a receptor essential for erythrocyte invasion by *P. falciparum*.
2011	Gething PW et al. A new world malaria map: Plasmodium falciparum endemicity in 2010. Malaria J 2011;10:378.	Generation of a global malaria map of *P. falciparum* endemicity for the year 2010.
2011	Douglas AD et al. The blood-stage malaria antigen PfRH5 is susceptible to vaccine-inducible cross-strain neutralizing antibody. Nat Comms 2011;2:601.	Identification of a new candidate malaria vaccine with the potential to neutralise all the tested strains of *P. falciparum*.

3.2 Development in genomic science: unlocking our understanding of malaria

In terms of basic science, the thing that had the biggest impact is the [P. falciparum] *genome.*
Wellcome Trust Expert Group on malaria, April 2010

50. The WTSI was established in 1992 and was initially funded jointly by the MRC[47] and the Wellcome Trust with a primary mission to map, sequence and decode the human genome and to further our knowledge of the genomes of other organisms. Since its inception, the Wellcome Trust has committed over £740m to the WTSI with £8.8m (1 per cent) of this to fund malaria research (see Table 3, Annex C).

51. The UK's contribution to the Human Genome Project (HGP) was led by the WTSI, with one-third of the human genome sequenced there. The technological advances that facilitated the large-scale sequencing of the HGP have enabled scientists to sequence the genomes of numerous important human and animal pathogens, including those important to malaria.

52. In 1995, the Wellcome Trust made the decision to establish the Pathogen Genomics Programme at the WTSI (formerly known as the Pathogen Sequencing Unit[48]), led by Bart Barrell, to sequence the genomes of organisms relevant to human and animal health. Through this programme, the WTSI has played a leading role in:

i. The first multicentre international basic science collaboration in the malaria field – the Malaria Genome Project[49] (see Table 8, Annex C). The completion of this six-year project to sequence the genome of the *P. falciparum* parasite, by an international collaboration of scientists from the USA and the UK, was a major breakthrough in the fight against malaria. This landmark achievement was carried out between three sequencing centres: the WTSI (UK), the Institute for Genomic Research (USA) and Stanford University (USA).[50] Results of the work were published in *Nature* in 2002.[51]
ii. The International Anopheles Genome Project, an international consortium of scientists that sequenced the complete genome of *Anopheles gambiae* – the principal vector of malaria in Africa, which transmits the parasite to humans – described in Holt *et al.* (2002),[52] with revisions described in Sharakhova *et al.* (2007).[53] The genome was sequenced by Celera Genomics (USA) and Genoscope, and annotated by Celera and Ensembl – the latter being a joint collaboration between the European Bioinformatics Institute and the WTSI (UK). The European Molecular Biology Laboratory (EMBL, Germany), the Institute of Molecular Biology and Biotechnology (IMBB, Greece), the Institute Pasteur in Paris, the Institute for Genomic Research (TIGR, USA), and the Universities of Iowa (USA), Rome (Italy) and Notre Dame (USA) also contributed to the collaboration.

53. Completion of the genome sequences of *A. gambiae* and *P. falciparum*, together with the human genome, which was published in *Nature* in 2001[54] by the International Human Genome Consortium, has provided researchers with a detailed insight into the three components of the malaria transmission cycle (humans, parasites and mosquitoes) and new opportunities to tackle questions that could not have been easily addressed before.

54. The genome sequence of *Plasmodium* has enabled a better understanding of parasite adhesion and the proteins involved, including PfEMP1 and rifin proteins, host–parasite interactions, the pathological basis of malaria, and the development of immunity to the parasite. With advances in sequencing technology and bioinformatics, these genomes have provided a catalogue of potential vaccine candidates and significantly reduced gene screening times: what once would have taken decades of work can now be completed within a couple of years.

55. In 2011, there were encouraging advances in the clinical applications of genomics at the WTSI. A protein interaction screening approach called AVEXIS (avidity-based extracellular interaction screen) discovered a component of human red blood cells – the basigin receptor – that seems to be crucial for the malaria parasite *P. falciparum* to complete its life cycle within the human body. *P. falciparum* relies on the basigin receptor to invade the cells by binding a protein, *P. falciparum* reticulocyte-binding protein homologue (PfRH5), to the receptor. Identification of the basigin receptor offers a potential new focus for vaccine development.[55] The importance of this key discovery was confirmed in a paper published in the journal *Nature Communications* in December 2011.[56] A team of scientists from the Jenner Institute[57] at the University of Oxford, working with colleagues from the WTSI and KEMRI, demonstrated that a vaccine they have developed targeting a full-length PfRH5 induces an antibody response in animal models that is capable of neutralising all the tested strains of the *P. falciparum* parasite. The Jenner Malaria Vaccine Programme, led by Professor Adrian Hill, a Wellcome Trust Principal Research Fellow, has been at the forefront of development of malaria vaccines and has pioneered the use of prime boosting vaccination strategies and conducted the first clinical trials using this regime.[58,59,60]

56. The vast amount of data in biological databases generated by the WTSI and other genome centres has created a need for improvements in sequence technologies, methods of data storage and analysis tools to handle, organise, share, interpret and compare (comparative genomics) the information being generated. Through the WTSI, by providing open-source software, the Wellcome Trust is working to support malaria research groups across the world, especially in malaria-endemic countries.

57. In 2005, the Wellcome Trust (together with Professor Dominic Kwiatkowski, who leads the malaria programme at the WTSI) initiated the development of one of the world's largest resources for analysis of genetic susceptibility to infectious disease – the international Malaria Genomic Epidemiology Network[61] (MalariaGEN; Table 8, Annex C). MalariaGEN is a partnership of malaria researchers in 21 countries cofounded by the Wellcome Trust (the Wellcome Trust's contribution was £4.3m[62]) and the Gates Foundation through the Grand Challenges in Global Health Initiative. The consortium is a data-sharing community of researchers across the globe that seeks to discover mechanisms of protective immunity to malaria. The consortium aims to play an important part in the Global Malaria Action Plan, which seeks to eradicate deaths caused by malaria by 2015. In 2009, MalariaGEN published the first genome-wide association study conducted in Africa.[63] MalariaGEN reflects the Wellcome Trust's conviction that open access data and collaboration are fundamental to scientific advance. MalariaGEN is also part of the EVIMalaR network.

47 The MRC contributed approximately £24m to the WTSI for the period up to the end of 2002. Source: WTSI.

48 The Pathogen Sequencing Unit (PSU) was initially funded through individual grants and later through the Wellcome Trust Beowulf Genomics Panel. The Beowulf Panel no longer operates and the PSU has been renamed to the Pathogen Genomics Programme, which is funded through the WTSI.

49 The £18.5m *Plasmodium falciparum* project was funded in the UK by the Wellcome Trust (£8m) and in the USA by the Burroughs Wellcome Fund (£4.9m), the National Institute of Allergy and Infectious Diseases (£2.2m), and the US Department of Defense (£3.4m).

50 Wellcome Trust Sanger Institute: chromosomes 1, 3–9 and 13; TIGR: chromosomes 2, 10, 11 and 14; and Stanford University: chromosome 12.

51 Gardner MJ et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 2002;419:498–511.

52 Holt RA et al. The genome sequence of the malaria mosquito Anopheles gambiae. Science 2002;298(5591):129–49. The sequence is available at **www.ensembl.org/Anopheles_gambiae/**.

53 Sharakhova et al. Update of the Anopheles gambiae PEST genome assembly. Genome Biol 2007;8(1):R5.

54 International Human Genome Consortium. Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.

55 Crosnier C et al. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. Nature 2011;480:534–7.

56 Douglas AD et al. The blood-stage malaria antigen PfRH5 is susceptible to vaccine-inducible cross-strain neutralizing antibody. Nat Comms 2011;2:601.

57 The Jenner Institute is funded through a Strategic Award from the Wellcome Trust.

58 Schneider J et al. Enhanced immunogenicity for CD8+ T cell induction and complete protective efficacy of malaria DNA vaccination by boosting with modified vaccinia virus Ankara. Nat Med 1998;4:397–402.

59 Hill AV et al. DNA-based vaccines for malaria: a heterologous prime-boost immunisation strategy. Dev Biol 2000;104:171–79.

60 McConkey SJ et al. Enhanced T-cell immunogenicity of plasmid DNA vaccines boosted by recombinant modified vaccinia virus Ankara in humans. Nat Med 2003;9:729–35.

61 **www.malariagen.net/**

62 The Wellcome Trust's initial contribution to MalariaGEN was through a Wellcome Trust programme grant worth approximately £4.3m to Professor Dominic Kwiatkowski (Wellcome Trust AS400 grant number: 077383), 'Learning from the human genome how protective immunity against malaria works'.

63 Jallow M et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. Nat Genet 2009;41:657–65.

58. The MRC Centre for Genomics and Global Health (CCGH) is a joint research collaboration between Oxford University, the WTSI, the MRC Laboratories in the Gambia, and the MOPs in Thailand, Vietnam and Kenya. The CCGH acts as the MalariaGEN Resource Centre, providing scientific and operational support for MalariaGEN's research and training activities, with expert teams in sample and data management, informatics, statistics, ethics and programme management. The CCGH also supports the Worldwide Antimalarial Resistance Network[64] data-sharing network.

59. The decision to co-locate the European Bioinformatics Institute at the WTSI in 1996 has also contributed, in part, to building capacity to support the data infrastructure required to underpin malaria genetics research. The WTSI, together with the European Molecular Laboratory–European Bioinformatics Institute, developed the Ensembl[65] web browser, which has been used for the annotation and analysis of vertebrate genomes since 2000, with an initial focus on the human genome. Since 2009, the Ensembl site has been complemented by the creation of a new resource, 'Ensembl Genomes',[66] providing access to genome data from non-invertebrate species. Ensembl Genomes now includes data from malarial parasites (genus *Plasmodium*, available through Ensembl Protists), the malarial vector (*Anopheles gambiae*, available through Ensembl Metazoa) and the human host (in Ensembl), enabling the analysis of all three genomes through an integrated interface.

60. Wellcome has played a key part in the creation, development and upkeep of powerful open source genomic comparison and analysis tools, research resources and databases that are used by the international malaria research community, including (see Table 8, Annex C for details):

- Ensembl/Ensembl Genomes
- Artemis/Artemis Comparison Tool
- Gene^{DB}
- LookSeq
- MapSeq/pf
- MalariaGEN

64 The Worldwide Antimalarial Resistance Network aims to optimise the use of antimalarial drugs by providing quality-assured information on drug resistance through partnership with the WHO and research groups, national control programs and surveillance networks in over 20 countries. The network is funded by the Bill and Melinda Gates Foundation.

65 **www.ensembl.org/**

66 **www.ensemblgenomes.org/**

3.3 Investment in research capacity building and infrastructure in malaria-endemic regions

It is the fact you supported people where the problem was, and the Wellcome Trust got people to go out to where the problem was.
Wellcome Trust Expert Group on malaria, April 2010

The Trust has been flexible and understanding of that [the nature and difficulties associated with research in malaria-endemic regions] and has been in it for the long run. I think that is very important, the long-term support, and not just supporting when things go well, because things don't always go well. So it is that long-term support for people as well as the projects that has been a very important part of it.
Wellcome Trust Expert Group on malaria, April 2010

61. One of the Trust's major strengths is thought to have been its ability to build research capacity and fund research in malaria-endemic countries. Through its MOPs in South-east Asia and Africa, the Trust has made a long-term investment in research, which has proven to have a direct benefit on human health. Through the Trust's long-term investment, the MOPs have established themselves as world-leading centres for malaria and tropical disease-based research. They are responsible for several important discoveries and clinical studies that have delivered key proven and cost-effective interventions that continue to reduce the burden of malaria morbidity and mortality and feed directly into local and international policy (Table 7, Annex C). The programmes also have important international links, participating in research networks such as the Worldwide Antimalarial Resistance Network and the Malaria in Pregnancy Consortium.

62. The KEMRI-Wellcome Trust Research Programme, directed by Professor Kevin Marsh, is based in Kilifi and Nairobi, Kenya (see KEMRI case study and Table 7, Annex C).[67] In 2010, the Wellcome Trust awarded £32.5m to the Programme to support research activities through to 2015. Professor Bob Snow at the programme has spearheaded efforts through the Malaria Atlas Project to quantify the global burden of malaria and has begun to provide definitive maps of all malaria-endemic regions of the world. The Kenya Programme delivered the first comprehensive characterisation of severe malaria in African children, insight into the clinical features and neurological effects of malaria, and evidence supporting the use of insecticide-treated mosquito nets. As one of the trial sites it played a part in bringing the potential malaria vaccine candidate RTS,S to phase III clinical trials. The first results from the ongoing phase III clinical trials, in which the Programme is also participating, were published in the *New England Journal of Medicine* in October 2011 and showed that RTS,S reduces the risk of malaria by half in African children aged from 5 months to 17 months.

63. Established in 1995, the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, directed by Professor Robert Heyderman, is the Trust's MOP in Blantyre, Malawi.[68] Its current core grant of £8.8m over five years was awarded after a site visit in January 2008. The Programme is primarily located at the University of Malawi's College of Medicine in Blantyre. A separate laboratory at the Queen Elizabeth Central Hospital in Blantyre forms an integrated research unit. The Programme also has field sites at the shore of Lake Malawi and in the Shire Valley. This allows scientists, clinicians and public health specialists to work together and respond to local health priorities. The Programme has strong links with the University of Liverpool and the Liverpool School of Tropical Medicine and works closely with the Malawian Ministry of Health on Malawi's malaria control programmes.

64. The Programme has helped to advance malaria treatment and monitoring, notably through the development of the Blantyre Coma Score, a system that helps monitor children in malaria-induced coma. Other clinical research at the facility includes the identification of distinctive retinopathy unique to severe malaria (which could lead to improved specificity of clinical diagnosis), trialling of antimalarial therapies at different sites around the country, the evaluation of strategies to delay the emergence of resistance to antimalarial drugs and the description of the pathogenesis of cerebral malaria using a unique collection of post-mortem brain material.

65. The Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme based in Bangkok, Thailand, under the direction of Professor Nick Day, was established in 1979 by scientists from Mahidol University in Bangkok and the University of Oxford in the UK. The Trust has provided £21.6m of funding to the Programme since 2005, including approximately £3m of core funding each year. The Programme conducts research of direct benefit to communities throughout South-east Asia and beyond. Field research extends across Thailand and includes the Shoklo Malaria Research Unit in Mae Sot directed by Professor Francois Nosten. The Programme also includes the Wellcome Trust-Mahosot Hospital-Oxford Tropical Medicine Research Collaboration, based in Laos, run in collaboration with Mahosot Hospital in Vientiane.

66. This MOP has made major contributions to the understanding and treatment of malaria worldwide. The Shoklo Malaria Research Unit pioneered the development, evaluation and introduction of ACTs and has optimised treatments for women during pregnancy. Researchers at the Programme have assessed the efficacy of antimalarial drugs in patients, conducted detailed clinical, pharmacological and parasitological assessments of emerging artemisinin resistance in Cambodia, and provided pharmacokinetic/pharmacodynamic rationale for antimalarial treatment.

67 **www.kemri-wellcome.org/**

68 **www.mlw.medcol.mw/**

67. The Trust provided support for the Thailand Programme to conduct the largest randomised artemisinin trials in adults and in children; in 2005, Nick White (see case study) and colleagues published the results of the SEAQUAMAT (South-east Asian quinine artesunate malaria trial),[69] which showed that artesunate (given by injection) reduced the mortality of severe malaria by more than one-third in adults. This subsequently formed the basis of the WHO's treatment guidelines for adults.[70] This was followed by the Wellcome Trust-funded AQUAMAT (African quinine versus artesunate malaria trial) study[71] – the largest ever clinical trial among patients hospitalised with severe malaria. The results of this trial led the WHO to revise its guidelines for the treatment of the disease in African children. Artesunate remains the first-line treatment for all severe malaria.

68. The Vietnam Research Programme and Oxford University Clinical Research Unit was established in Ho Chi Minh City in 1991 and in Hanoi in 2006 and is directed by Professor Jeremy Farrar. Professor Tran Tinh Hien, Vice Director of the Programme, has made seminal contributions to malaria research and had a major role in the development and assessment of the artemisinin derivatives over the past 25 years. He was one of the first clinicians to assess these drugs outside China and has continued to play a leading part globally in a broad range of infectious diseases. In 2010, Professor Hien was awarded the 2010 Mackay Medal (**www.rstmh.org/awards/medals/medals-available-2010/donald-mackay-medal**) by the Royal Society of Tropical Medicine and Hygiene for his ground-breaking work in infectious diseases in Vietnam for over 20 years, and in 2011 he was made an Honorary Member of the American Society of Tropical Medicine and Hygiene.[72] The Wellcome Trust has supported the Programme for almost 20 years and its core support has been extended through to 2015. One of the core research areas at the Unit is monitoring and understanding drug resistance in *P. falciparum* and *P. vivax*. The Vietnam Programme has made major contributions to researching malaria: these include establishing the use of artemisinin derivatives for the treatment of falciparum malaria and establishing the burden of vivax malaria in South-east Asia (showing that *P. vivax*, which was previously considered relatively harmless, is common and can cause disease).

69. In the past ten years, the Wellcome Trust has introduced several programmes designed specifically to further strengthen research infrastructure and capacity in resource-poor regions. These programmes aim to complement work underway in many of the existing MOPs and build networks and links outside the 'North'. Although these have no specific research area focus, it is likely that newly trained researchers will work in research areas of local and national importance – and, hence, malaria.

70. The Health Research Capacity Strengthening initiative began with an agreement in 2004 between the Wellcome Trust and the UK Department for International Development (DFID) to commit £10m each towards a joint programme to help strengthen the capacity for generating new health research knowledge within Kenya and Malawi and to improve evidence-based decision making, policy formulation and implementation. In Kenya and Malawi, priorities have been developed exclusively by a National Task Force – purposely without any predetermined direction from the funders – to meet local health research needs. This required the establishment of new grant-giving entities, and steady progress is being made. Organisations in both countries are now making awards using transparent, merit-based peer-review processes.

71. In 2009, the Wellcome Trust introduced its African Institutions Initiative[73] to enroll African scholars and institutions as leaders in efforts to rebuild research capacity in Africa. A total of £30m has been provided to seven African-led international consortia,[74] which represent 51 African institutions in 18 countries, in partnership with research countries in Australia, Denmark, Norway, Switzerland, the USA and the UK.

69 Dondorp A. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

70 WHO. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010. WHO. Guidelines for the Treatment of Malaria. Geneva: World Health Organization; 2006.

71 Dondorp et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010;376(9753):1647–57.

72 Arnold K et al. A randomized comparative study of artemisinine (qinghaosu) suppositories and oral quinine in acute falciparum malaria. Trans R Soc Trop Med Hyg 1990;84(4):499–502. Hien TT et al. Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria. Trans R Soc Trop Med Hyg 1992;86(6):582–3.

73 The African Institutions Initiative was not included in our funding analysis because it was established in financial year 2009. The funding analysis covered Wellcome Trust financial years 1989/1990 and 2007/2008. The Health Research Capacity Strengthening initiative was also not included in our funding analysis. The funding analysis covered Wellcome Trust financial years 1989/1990 and 2007/2008.

74 The seven African-led consortia are: Consortium for Advanced Research Training in Africa (CARTA); One Health Initiative, African Research Consortium for Ecosystem and Population Health; One Medicine Africa-UK Research Capacity Development Partnership Programme for Infectious Diseases in Southern Africa (SACIDS consortium); Research Institute for Infectious Diseases of Poverty (IIDP); Southern Africa Consortium for Research Excellence (SACORE); Strengthening Research Capacity in Environmental Health (SNOWS); and Training Health Researchers into Vocational Excellence in East Africa (THRiVE).

72. The Wellcome Trust's Strategic Awards are also thought to have kick-started a period of sustained investment in research and training in Africa by responding to the needs of local researchers (several of which have been malaria focused), providing substantial funding to give talented researchers access to training and the experience needed to conduct research at a world-class level. Recipients of Strategic Awards include Professor Kevin Marsh, Director of the KEMRI–Wellcome Trust Research Programme (£8m, to develop research capacity and leadership in East Africa) and Professor Brian Greenwood at the LSHTM (£7m, towards the Malaria Capacity Development Consortium, or MCDC, to support training for African scientists to undertake high-quality malaria research in African universities).

73. The MCDC, which was established in 2008, is a partnership of four European and five African partners.[75] The secretariat of the consortium, under the direction of Professor Brian Greenwood and Professor David Schellenberg, is hosted by the LSHTM. In 2008, the MCDC was awarded a Strategic Award (£7m) to build on the successful doctoral and postdoctoral capacity development programme funded previously by the Bill and Melinda Gates Foundation through the Gates Malaria Partnership.[76] Today, this Wellcome Trust Strategic Award supports approximately 20 African PhD students. The MCDC has also received an award of $5m from the Bill and Melinda Gates Foundation, which will allow it to sustain the investment in the investigators who were previously trained through the Gates Malaria Partnership.

3.4 Support for multi-agency, cross-sector partnerships and collaborations

The Trust certainly has made a contribution [to international collaborations]. You funded the first international collaboration to map the genome and then you did the functional genomics initiative.
Wellcome Trust Expert Group on Malaria, April 2010

The Dakar meeting was very important; for me, that was the turning point for malaria research, that was the beginning, and the fact that Dr Varmus went to Dakar for a week and then went to Mali for a week had a huge impact.
Wellcome Trust Expert Group on Malaria, April 2010

74. The Wellcome Trust has played an important part in several malaria-focused international cross-sector partnerships over the past two decades. As the Multilateral Initiative on Malaria's first Secretariat (1997–1999), the Wellcome Trust had a crucial role in shaping the Initiative during its first few years of operation. The MIM, founded in 1997, is a coordinated international collaboration of individuals, funding partners and four self-governing institutions (the MIM/TDR,[77] MIMCom,[78] MR4[79] and the MIM Secretariat), tackling malaria through strengthening research capacity in Africa and increasing international communication and cooperation.

75. As the first coordinating member of the MIM, the Wellcome Trust helped to support the coordination of malaria research internationally and increased training opportunities for researchers in Africa. The infrastructure for African Centres put together by MIM motivated African scientists to maximise the use of resources.[80]

76. The NIH (under the direction of Dr Harold Varmus) convened the first MIM conference in Dakar, Senegal, in January 1997; this was thought to have been a key turning point in the fight against malaria. The MIM has become a pre-eminent international research collaboration – helping to build and support research capacity across the world (Table 8, Annex C).

77. With the emergence of resistance to artemisinin-based drugs, the need to pursue new pharmacological leads remains. Participating in public–private research collaborations has been an integral part of the Trust's efforts to catalyse action against artemisinin-resistant parasites. The Wellcome Trust has been working through several public–private partnerships to help accelerate drug development for malaria (Table 8, Annex C).

75 The four European partners are: Center for Medical Parasitology, University of Copenhagen; DBL – Centre for Health Research and Development, University of Copenhagen; Liverpool School of Tropical Medicine; and the LSHTM. The five African universities are: College of Medicine, University of Malawi (CoM), and the Wellcome Trust Clinical Research Programme, Blantyre, Malawi, Kilimanjaro Christian Medical College, Moshi (KCMC), and the Joint Malaria Programme (JMP) Tanzania, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, Faculty of Medicine and School of Public Health, Makerere University, Kampala, Uganda, and the Ministry of Health, Uganda, and the Faculty of Medicine, Université Cheikh Anta Diop (University of Dakar), Senegal and the Ministry of Health, Senegal.

76 The Gates Malaria Partnership was funded by a BMGF award ($40m) to the London School of Hygiene and Tropical Medicine in 2000.

77 **www.mimalaria.org/eng/aboutmim.asp#MIMTdr**

78 The MIM internet communication arm. **www.mimalaria.org/eng/aboutmim.asp#MIMTdr**

79 Malaria Research Reference Reagent Resource Center. **www.mimalaria.org/eng/aboutmim.asp#MIMTdr**

80 Review of the Multilateral Initiative on Malaria (MIM). Final Report. Bethesda: MIM Secretariat; 2010.

78. The Wellcome Trust has led several initiatives to transform the drug discovery pipeline for malaria. It was a founding member of the PDP funders group (which also includes DFID, USAID, the Bill and Melinda Gates Foundation, and others) and is a member of the WHO Malvac Malaria Vaccine Group. It has also provided continued support for Medicines for Malaria Venture, which was established in 1999 as a PDP dedicated to delivering new affordable antimalarial drugs in malaria-endemic countries. In 2005, the Wellcome Trust and DFID made a joint commitment to provide £10m each to MMV over five years (together providing approximately 18 per cent of MMV's funding). The Trust provided a further award of £5m to MMV in 2011. Other MMV funders include the Bill and Melinda Gates Foundation, USAID, and several European development agencies.

79. To date, MMV has registered three medicines – Guilin's artesunate and Coartem® Dispersible and Sigma-tau's DHA-piperaquine. Another ACT, artesunate-pyronaridine, is awaiting regulatory approval by the European Medicines Agency. Coartem® Dispersible, a child-friendly form of the ACT Coartem, was developed by Novartis in partnership with MMV and launched in 2009. In the 11 years since its inception, MMV has built a robust pipeline of malaria drugs, including drugs to tackle *P. vivax,* comprising over 50 projects. Its importance was recognised by the Expert Group.

The MMV has been extraordinarily successful, it has brought in academia and all the pharmaceutical companies so the Trust should take some credit for this; they have been very supportive.
Wellcome Trust Expert Group on malaria, April 2010

80. Through a Strategic Translation Award, the Wellcome Trust supports the Novartis Institute for Tropical Diseases (NITD): Malaria Drug Discovery, a five-year partnership dedicated to identifying a preclinical small molecule to provide a single-dose treatment for malaria caused by *P. falciparum* and identifying a new treatment modality for *P. vivax*.[81] The Wellcome Trust, the Singapore Economic Development Board and the MMV pledged over £10m to the Institute. Although NITD[82] will manage the programme, they will also conduct research jointly with several institutions, including the Genomics Institute of the Novartis Research Foundation and the Swiss Tropical and Public Health Institute. A potential drug candidate, called NITD609, developed by the international collaboration has been approved as a preclinical candidate and is ready for phase I studies in humans.

81. The Dundee Drug Discovery Unit (DDU) based at the University of Dundee is also supported through a Strategic Translation Award. In 2006, with funding worth approximately £8.1m, a group led by Professor Mike Ferguson and Professor Alan Fairlamb instigated a drug discovery effort with the aim of translating basic research discoveries into candidate drugs (for tropical neglected diseases) ready for clinical trials.

82. The funding has been used to appoint key personnel from the biotechnology sector and industry to lead the creation of a drug screening and medicinal chemistry operation of comparable capability to that found in a small company. Professor Paul Wyatt, Head of Drug Discovery, was recruited from Astex Technologies, and Professor Julie Frearson (who headed the screening facility) was attracted from Cambridge-based drug discovery company Biofocus Ltd (now BioFocus DPI, a Galapagos company). A compound library has now been amassed and the robotics for screening installed; the first assays were run during 2006.

83. In 2008, the Wellcome Trust's Seeding Drug Discovery Initiative awarded Professor Stephen Ward and Dr Giancarlo Biagini (Liverpool School of Tropical Medicine) and Professor Paul O'Neil (Liverpool University) £1.4m to develop inhibitors to a potential drug target in malaria – an enzyme known as alternative complex 1 (or PfNDH2), which is found in the electron transport chain of the malaria parasite *P. falciparum*.[83]

81 Wellcome Trust Strategic Translation Award (£6.4m) to Professor Alex Matter, NITD.

82 The NITD is a public–private partnership between Novartis and the Singapore Economic Development Board that was set up in 2002.

83 Wellcome Trust (Seeding Drug Discovery). 'Alternative complex I as a new drug target against malaria' was not included in our funding analysis as the award was allocated in Wellcome Trust financial year 2009. The funding analysis covered Wellcome Trust financial years 1989/1990 and 2007/2008. The 'Alternative complex I as a new drug target against malaria' grant was granted an extension in 2010 until 2011.

4. Looking forward: speculations on the future of malaria research

84. In terms of addressing the global burden of malaria over the past two decades, the main impact has come from an improved understanding of how to measure, prevent and treat malaria in individuals using existing tools – predominantly in the field.

85. Increased R&D funding, enhanced global partnerships and coordinated efforts to control malaria (i.e. the Global Fund, MIM, RBM and MDGs) through scaled-up evidence-based interventions – such as insecticide-treated bednets, indoor residual spraying, intermittent preventative treatment in pregnant women, RDTs, and the diagnosis and treatment of infected persons with ACTs – are having an impact upon malaria morbidity and mortality.

86. In terms of the Wellcome Trust, as described in the previous section, its primary role has been through its contribution to research into measuring, preventing and treating malaria. Research conducted through the MOPs has provided evidence to support international policies for malaria control, including the use of insecticide-treated bednets[84,85] and changes in treatment for both severe and uncomplicated malaria, which has led to the global adoption of ACTs as first-line treatment.[86,87] Through its funding for UK basic research into malaria and through the MOPs, Wellcome has generated substantial on-the-ground research capacity, community links and scientific leadership in places where malaria is endemic and research can be integrated into national research and healthcare systems.

87. The Wellcome Trust's investment in basic biomedical, epidemiological and genetic research has also contributed to some of the most important breakthroughs in our understanding of malaria. In particular, the characterisation of the laboratory and clinical features of *Plasmodium knowlesi* – now recognised as a significant cause of the disease alongside the five other *Plasmodium* species;[88,89,90] the Malaria Atlas Project, which provided the first comprehensive description and burden of the disease worldwide;[91] the Malaria Genome Project, which completed the sequence of the genome of the *P. falciparum* parasite; MalariaGEN – part of the Grand Challenges in Global Health Initiative – which looked at individuals' malaria resistant factors through genome-wide association studies for the first time in Africa;[92] the analysis of the *var* genes of *P. falciparum*, now known to be central to the parasite's pathogenicity;[93] and the development of prime-boosting strategies for malaria vaccine development.[94]

88. The Wellcome Trust has also made major contributions to research that has dramatically changed the way malaria is assessed and treated, including research that has: established artesunate as the treatment of choice for severe malaria; developed pre-referral rectal treatment; defined the optimum methods of assessment; discovered mechanisms of action; defined antimalarial pharmacodynamics; led the field in pharmacokinetic/pharmacodynamic modelling, resistance modelling and clinical trial design; introduced ACT; and conducted pivotal early trials for all the currently available ACTs.

89. Despite this progress, malaria remains an endemic disease in many low- and middle-income countries. Emerging resistance to artemisinin-based compounds, the lack of an effective vaccine, expanding and maintaining coverage of insecticide-treated bednet and indoor residual spraying programmes, the overdependence on pyrethroids (a class of insecticide) and the shortfall in resources mean that much more needs to be done to ensure sustained progress if the long-term goal of global eradication is to be achieved. Furthermore, ongoing global climate policy debates over the impact that climate change might have upon the epidemiology and global burden of malaria means that it remains a priority on the research and public health agenda.[95] Predictive modelling studies have reported that rising global temperatures are also affecting existing mortality and morbidity rates[96] and will increase the global range and intensity of malaria in the future. Research conducted by the Malaria Atlas Project challenges this notion, however, suggesting any failure to reduce the malaria burden in the future would be difficult to attribute to climate change[97] and concluding that effectively scaling up existing malaria control interventions could potentially outweigh the negative effects of global warming as much as ten-fold.

90. Through this review, several challenges for malaria researchers and their funders have emerged. The following challenges are by no means exhaustive and (as with any review or consultation) a different review, informed by consultation with different experts, might have reached a different set of conclusions and priorities. Nevertheless, we believe that by addressing some of the research needs highlighted – and by building on existing infrastructures, critical mass and collaborations – the Wellcome Trust and other funders will help to maximise the impact of malaria-focused research in reducing the burden of the disease.

4.1 Ensure continued support for underpinning research into basic immune and biological mechanisms

What can be done with malaria parasites now, in the lab, is quite staggering, compared to what was possible ten, particularly 20 years ago, experiments were just beyond thought. Now, I think essentially if you want to do something with the rodent areas, you can do it, and I think that has transformed a lot of the understanding of the basic biology.
Wellcome Trust Expert Group on malaria, April 2010

We have been hampered in the malaria immunology world by equating vaccines with immunology and there has not been enough investment into looking at basic immunology.
Wellcome Trust Expert Group on malaria, April 2010

I think the understanding of the pathology, the physiology and the drugs are not as advanced as I thought they would be.
Wellcome Trust Expert Group on malaria, April 2010

91. During the past decade, many of the advances in basic malaria research have opened doors and enhanced our understanding of both the basic biology of the parasite and the host-protective immune response. Breakthroughs include: the characterisation of the laboratory and clinical features of the *Plasmodium* species; *in vitro* culture, which facilitated research into the molecular biology of the parasite; the discovery of VAR2CSA antigens, which helped us to understand why pregnant women were susceptible; and, most recently, genome sequencing of all three organisms involved in the transmission of malaria – the parasite *P. falciparum*, the mosquito vector *Anopheles gambiae* and the human host.

92. Studies on the contribution of human genetic factors, most notably the sickle cell trait that offers protection against malaria, have provided insight into the nature of adaptation of human populations in malaria-endemic countries. Other human genetic polymorphisms providing a protective effect against malaria have been identified, including haemoglobin S, haemoglobin B, haemoglobin E, thalassaemias and glucose-6-phosphate.[98]

93. More recently, there has been substantial progress towards licensing the first malaria vaccine candidate, RTS,S (also known as RTS,S/AS), developed by PATH MVI and GlaxoSmithKline (Timeline). The first set of results from a large-scale phase III trial of RTS,S, published in the *New England Journal of Medicine*,[99] show that the malaria vaccine candidate provides significant protection against clinical and severe malaria to young African children.

84 Killeen GF et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med 2007;4:e229.

85 Nevill CG et al. Insecticide-treated bed nets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. Trop Med Int Health 1996;1(2):139–46.

86 WHO. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010.

87 Dondorp A. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

88 The six *Plasmodium* species are *P. falciparum*, *P. vivax*, *P. knowlesi*, *P. malariae* and *P. ovale*. *P. ovale* has been shown by genetic methods to consist of two separate species, *P. ovale curtisi* and P. *ovale wallikeri.* Sutherland CJ et al. Two nonrecombining sympatric forms of the human malaria parasite Plasmodium ovale occur globally. J Infect Dis 2010;201(10):1544–50.

89 Singh B et al. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet 2004;363(9414):1017–24.

90 Cox-Singh J and Singh B. Knowlesi malaria: newly emergent and of public health importance? Trends Parasitol 2008;24(9):406–10.

91 **www.map.ox.ac.uk/**

92 Jallow M et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. Nat Genet 2009;41:657–65.

93 Smith JD et al. Switches in expression of Plasmodium falciparum var genes correlate with changes in antigenic and cytoadherent phenotypes of infected erythrocytes. Cell 1995;82:100–110.

94 Hill AV et al. DNA-based vaccines for malaria: a heterologous prime-boost immunisation strategy. Dev Biol 2000; 104:171–179.

95 Patz JA et al. Impact of regional climate change on human health. Nature 2005;438:310–7.

96 Parry ML et al (eds). Climate Change 2007: Impacts, adaptation and vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge: Cambridge University Press; 2007.

97 Gething PW et al. Climate change and the global malaria recession. Nature 2010;465(7296):342–5.

98 Kwiatkowski DP. How malaria has affected the human genome and what genetics can teach us about malaria. Am J Hum Genet 2005;77:171–92.

99 The RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863–75.

94. The Expert Group identified several basic research areas where a focus by the Wellcome Trust and other key funders would make a substantial impact on our understanding of the biology, biochemistry, immunology and pathobiology of malaria, specifically:

- the basic biology of all species of the *Plasmodium* parasite, particularly *P. vivax*
- the basic metabolic functions of the *Plasmodium* species, including metabolomics, lipidomics and glycomics
- the complex mechanisms underlying the immunobiology of malaria
- robust model systems to support human immunological research.

95. Human malaria is caused mainly by five species of the protozoan parasite *Plasmodium* (*Plasmodium falciparum*, *Plasmodium vivax*, two species of *Plasmodium ovale*, and *Plasmodium malariae*), of which *P. falciparum* and *P. vivax* are the most virulent and responsible for most malaria infection globally.[100] A sixth species, *Plasmodium knowlesi*, a malaria parasite of long-tailed macaque monkeys (*Macaca fascicularis*), can also infect humans. A detailed understanding of the biology of all these parasites is required to support the development of effective interventions in the long term.

We have been thinking very much about models and P. falciparum *but* P. falciparum *is only one species. We do need to think in the future of other species.*
Wellcome Trust Expert Group on malaria, April 2010

96. *Plasmodium* parasites have complex life cycles with multiple stages. In the infective stage, known as the sporozoite stage, the parasites are transmitted to the human host with a vector (*Anopheles* mosquito) bite. In the pre-erythrocytic stage, the sporozoite undergoes many rounds of asexual divisions and matures into merozoites in the liver cells. During the erythrocytic stage, the parasites invade red blood cells as merozoites, where they undergo several stages of replication and development before invading new red blood cells; in the sexual stage, susceptible mosquitoes ingest infected blood (gametocytes) from the human host. The parasite completes its maturation inside the insect's gut, finally migrating to the mosquito's salivary glands because it is through the saliva that it will enter a new human host. In some *Plasmodium* species, such as *P. vivax* and *P. ovale*, the parasite has the ability to remain dormant in the liver of its host in a form known as the hypnozoite. This dormant parasite stage in the liver can result in multiple relapses of infection and is the most enigmatic and least understood phase of the life cycle.

97. The Expert Group described a need for more research into the last phase of the parasite's life cycle – the sexual stage – given the importance of gametocytes in transmission. As elimination and eradication efforts ramp up, transmission-blocking vaccines targeting the sexual stage of the parasite will be important for reducing transmission in areas of low prevalence and to prevent the spread and development of parasites resistant to vaccines. This will require an improved understanding of basic gametocyte biology.

98. Much of the research effort against *Plasmodium* has been focused on *P. falciparum*[101] (accounting for 45 per cent of total malaria R&D, compared to 3 per cent for *P. vivax*, in 2007–2009). Although *P. vivax* is less virulent than *P. falciparum* in terms of mortality, from a public health viewpoint it is highly significant – it is the most geographically widespread of the species. Worldwide, an estimated 130 to 390 million people are infected every year and 2.6 billion people are at risk of infection.[102,103] Clinical relapses with debilitating effects can occur because of the liver hypnozoites.[104] Primaquine is the only licenced drug available that can prevent such relapses (tafenoquine is still investigational), but its mechanism of action is still poorly understood. To prevent vivax malaria, the Expert Group identified three broad areas where increased research efforts are required:

- the *P. vivax* liver stages (exo-erythrocytic stage), the hypnozoite and other biological processes exclusive to *P. vivax*
- the biology of the vectors in sustaining *P. vivax* transmission and the ecological diversity of host–vector and host–parasite interactions (necessary to develop effective community-based interventions to disrupt the transmission of malaria)
- the mechanism of action of current anti-relapse drugs, particularly primaquine, and ways of optimising their safety and effectiveness (see section 4.3).

I think the other major parasite, Plasmodium vivax*, has been woefully neglected. In the last couple of years it has surfaced, it has caught people's attention and it is a growing field.*
Wellcome Trust Expert Group on malaria, April 2010

99. Because of the complexity of the *Plasmodium* life cycle, the innate immune response to malaria is still poorly understood. Difficulty arises from *Plasmodium*'s intimate relationship with the human host, its adaptability and its ability to evade the host immune response using sophisticated mechanisms (such as host erythrocyte modification and antigenic variability using cell surface proteins, such as PfEMP1,[105] made by the *var* gene family). Furthermore, *Plasmodium*'s several life stages make the selection of important antigens for a viable effective vaccine to malaria a huge challenge.

One of the reasons why pathogenesis hasn't moved forward is that for Plasmodium falciparum*, we think that cytoadherence is an important thing, and we know quite a bit about it, but we haven't been able to make that link with disease because it is a complicated system.*
Wellcome Trust Expert Group on malaria, April 2010

100. The adaptability of *Plasmodium* species, in particular *P. falciparum*, is evidenced through the development of resistance to antimalarial drugs. Chloroquine resistance was first reported in 1961 (Timeline). Since then, the occurrence of resistance has increased for all antimalarials. More recently, artemisinin resistance has been reported in western Cambodia (Timeline).

101. Although many proteins involved in *Plasmodium*'s lifecycle have been identified – including the host cell invasion proteins MSP1, AMA1,EBA-175, TRAP and CTRP and the host cell modification proteins PfEMP1, KAHRP and PfEMP2 – much still remains to be learned about the cellular and molecular biology underlying these mechanisms and the host immune response.[106,107] If we are to develop effective drugs and vaccines to block these vital stages within *Plasmodium*'s life cycle, it is essential to bridge the gaps in our understanding of the host immune response to malaria.

102. Deciphering the *Plasmodium* genome and proteome has accelerated drug development by identifying those genes essential for *Plasmodium* to survive and those involved in the metabolic pathways of these complex host–parasite interactions. For example, the MEP (2-C-methyl-D-erythritol 4-phosphate) pathway has been identified as a new target for potential new antimalarials, including fosmidomycin.[108] However, approximately 60 per cent of the 5400 *P. falciparum* genes still encode proteins of unknown function.[109]

103. Although the presence and components of many of the *Plasmodium* metabolic pathways can be predicted through genomic analysis using *Plasmodium* gene finding programmes such as PHAT, GeneFinder, GlimmerM and Hexamer, these can only generate gene function predictions[110] and require further experimental and biological validation. The Expert Group emphasised that we still know very little about the basic metabolic functions of the *Plasmodium* species, including metabolomics, lipidomics and glycomics. Given the potential that a greater understanding of the parasites' metabolic pathways can offer to malaria pathogenesis, the Wellcome Trust and other funders might consider how to support this area in the future.

We know very little about the lipids, we know very little about the carbohydrates or the metabolics of the parasite and those are three areas which are not yet investigated in appropriate depth and we could be missing very substantial parts of very important information.
Wellcome Trust Expert Group on malaria, April 2010

104. The Expert Group emphasised the relative lack of understanding of the complex mechanisms underlying the immunobiology of malaria, such as modes of action, reactivities of antibodies, the role of cytokines, activation of the host's natural defence mechanisms (innate immune factors) by *Plasmodium* antigens and identification of pertinent innate receptors, among others. The perceived lack of knowledge of the immunologic mechanisms was thought to be in part because of a lack of direct funding for basic immunology. In addition, there was a feeling that in recent years, immunologic research has focused on vaccine development.

100 White NJ. Malaria. In GC Cook and A Zumia (ed.). Mansonis Tropical Diseases. 21st edn. Philadelphia: WB Saunders; 2003. pp 1205–96.

101 PATH. Staying the Course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

102 Hay SI et al. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis 2004;4:327–36.

103 Guerra CA et al. Mapping the global extent of malaria in 2005. Trends Parasitol 2006;22:353–8.

104 Baird JK. Neglect of Plasmodium vivax malaria. Trends Parasitol 2007;23:533–9.

105 Smith JD et al. Decoding the language of var genes and Plasmodium falciparum sequestration. Trends Parasitol 2001;17:538–45.

106 Iyer J et al. Invasion of host cells by malaria parasites: a tale of two protein families. Molec Microbiol 2007;65:231–49.

107 Baum J et al. Host-cell invasion by malaria parasites: insights from Plasmodium and Toxoplasma. Trends Parasitol 2008;24(12):557–63.

108 Jomaa H et al. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. Science 1999;285:1573–6.

109 **www.plasmodb.org**, version 5.4

110 Bahl A et al. PlasmoDB: the Plasmodium genome resource. A database integrating experimental and computational data. Nucleic Acids Res 2003;31(1):212–5.

105. Another barrier thought to be impeding understanding of the host immune response is the absence of effective model systems to investigate human malaria and assess potential vaccine candidates.[111] Research into the biology of malaria has relied on four species of rodent malaria (*Plasmodium yoelii*, *Plasmodium berghei*, *Plasmodium chabaudi* and *Plasmodium vinckei*), which have been used extensively to complement research on *P. falciparum* – the only human malaria parasite that has been successfully cultured continually *ex vivo.* A culture system is available for the blood forms of *P. falciparum*, which has greatly assisted drug and vaccine trials against these stages of this species. However, no culture methods are available for the stages of the parasite in the liver or for any of the other human malaria species. Although model rodent malaria systems are valued for the study of human malaria, it remains difficult to make inferences about human malaria based on their results.

106. More robust model systems – that not only mimic the human immune system but also allow experimental animal studies to interact closely with human infection studies – would be a valuable complement to basic research on the pathogenesis and clinical manifestations of malaria. To this end, as in many areas of biosciences research, encouraging basic malaria researchers to collaborate with more clinical- and vaccine-focused malaria researchers would help to take the field forward.

I have a plea, if we keep going with vaccines that we actually try to incorporate some basic track research alongside the vaccine. So if something fails you don't have to go right back to the drawing board, you have got a whole lot of basic research going on and actually that doesn't get funded, when research is going towards vaccines, what gets funded is just the vaccine but not the parallel work that is necessary.
Wellcome Trust Expert Group on malaria, April 2010

107. The Expert Group described a shift in culture and emphasis within the malaria research community – towards more translational research. In recent years, the proportion of global malaria R&D funding directed to product development has increased.[112] Although the importance of translational research and the 'game-changing' part played by public–private partnerships (such as MMV) must not be underestimated, the Expert Group emphasised that sustaining their impact in the long term will require underpinning, basic research. The experts urged the Wellcome Trust and other key funders to maintain 'blue skies' research, through mechanisms such as the Investigator Awards scheme.

There has been a step change, I think the public–private partnerships coming in have changed the landscape and I think everybody is now talking about translational research and people are getting their heads around what translational research actually means and doing some of that.
Wellcome Trust Expert Group on malaria, April 2010

I have a plea from the Trust's side not to stop the tap on the 'blue skies' research because if we stop that tap, the translational end would never happen.
Wellcome Trust Expert Group on malaria, April 2010

4.2 The importance of clinical research and clinical investigation

I would like to support having more clinical investigations. The bureaucratic obstacles and the impediments are huge. They have become more expensive and more difficult, and as a result less and less people are doing it. Apart from the last clinical trial of vaccines, which still had a core base of large international organisations, very few people are doing clinical investigations any more.
Wellcome Trust Expert Group on malaria, April 2010

108. In recent decades, many of the most important impacts on human malaria morbidity and mortality have been achieved through clinical and intervention-based research. Current recommendations for the treatment and clinical management of uncomplicated[113] and severe[114] malaria in adults, children and individuals at high risk, particularly pregnant women (i.e. ACTs, intravenous artesunate and pre-referral rectal artesunate) have arisen from clinical investigations – of which the Wellcome Trust has been a key supporter over this time.

109. The Expert Group described concern over the limited number of clinical investigations currently underway, particularly in malaria-endemic regions. The perceived increasing number of obstacles confronting clinical researchers – including costs, regulatory burdens, and patient participation and recruitment protocols – and the dearth of good morbidity and surveillance data are all thought to be adding to the complexities of conducting clinical investigations on malaria.

110. The Expert Group were in agreement that supporting capacity for clinical research is crucial if we are to continue to deliver improvements in human health and to complement the ongoing, high-quality basic science research effort. More resources should be given to understanding the pathology, physiology and pathophysiology of the disease. In terms of severe malaria in particular, given the complex pathophysiology of the infection involving multiple organ systems, the management of patients presents a broad range of clinical challenges. This is particularly true in endemic regions, where access to diagnostic and therapeutic tools may be limited. The Expert Group agreed that clinical research into the pathophysiology of acidosis, anaemia, renal failure and pulmonary oedema is likely to meet the clinical challenges associated with severe malaria and deliver patient benefits.

4.3 Ensure a pipeline of antimalarial drugs

One of the things we must have in malaria is a pipeline of medicines, because the parasite is going to get resistant.
Wellcome Trust Expert Group on malaria, April 2010

We are using medicines but on a very flimsy knowledge base. We don't know enough about the work up to malaria, the pharmacokinetics and we are probably using the wrong dosing and so on. So there is a need to strengthen that knowledge base, which I think is an area that easily gets overlooked in the rush to use these tools.
Wellcome Trust Expert Group on malaria, April 2010

111. Despite the recent development of several new antimalarial drugs against *P. falciparum* (including artesunate–amodiaquine, artesunate–mefloquine, Coartem® Dispersible for children and Pyramax®) and approximately 27 candidates in various clinical stages of development worldwide,[115] the Expert Group felt it likely – if not inevitable – that the malaria parasite will develop resistance to these and other major drugs in the future. Furthermore, other *Plasmodium* species (particularly *P. vivax*) are likely to become more prevalent as control measures against *P. falciparum* become more effective. The Expert Group maintained that the least expensive and most effective research investment at present would be to optimise the dose regimens for currently available antimalarial drugs. One challenge for the future is to develop novel compounds to combat *P. vivax* and other emerging strains of *Plasmodium*.

112. The Expert Group discussed the implications of emerging and increasing resistance in malaria and emphasised the need for the development of a sustained pipeline of antimalarial drugs. A major threat to malaria control and eradication is the emergence of *Plasmodium* species that are resistant to the currently used artemisinins recommended by the WHO as the first-line treatment for *P. falciparum* malaria in all malaria-endemic regions.[116,117] The emergence of artemisinin resistance on the Thailand–Cambodian border,[118] the risk of it spreading to other regions and the lack of replacement drugs for ACTs mean further investment in research to enhance understanding of drug resistance is needed. Access to quality-assured diagnostics, vector control, and monitoring and surveillance are also important in this (see sections 4.4, 4.5 and 4.6).

113. In summary, the Expert Group highlighted several priorities for malaria drug development and improvement:

- optimising dose regimens for currently available antimalarial drugs
- novel drugs to tackle other malaria parasites, particularly *P. vivax*, which will necessitate a clearer understanding of their resistance mechanisms
- significant investment in building malaria-focused pharmacology and pharmacokinetic research capacity
- the implementation of novel management systems to monitor the use of compounds in the field to protect the drug supply pipeline.

114. In terms of efficacy for antimalarial drugs, the Expert Group described a relative lack of detailed understanding of the pharmacokinetics and pharmacodynamics of antimalarial drugs in human populations, particularly how human genetic variability and the mechanisms of absorption, elimination, distribution, biotransformation and metabolism lead to treatment failure, resistance and certain drug side-effects. The mechanism of

111 Langhorne et al. The relevance of non-human primate and rodent malaria models for humans. Malaria J 2011;10:23.

112 PATH. Staying the Course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

113 Uncomplicated malaria is symptomatic malaria with parasitaemia (<5 per cent of red blood cells infected) and no evidence of vital organ dysfunction.

114 Severe malaria is acute malaria with hyperparasitaemia (5–10 per cent of red blood cells infected).

115 PATH. Staying the Course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

116 Nosten F, White NJ. Artemisinin-based combination treatment of falciparum malaria. Am J Trop Med Hyg 2007;77:181–92.

117 White NJ. Qinghaosu (artemisinin): the price of success. Science 2008;320:330–4.

118 Dondorp AM et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med 2009;361:455–67.

action of primaquine, the only 8-aminoquinoline in clinical use, is still not known, and it was highlighted as a priority drug (in terms of vivax malaria) for optimisation by the Expert Group. The perceived lack of progress in pharmacokinetics was thought to result from a lack of direct funding, a lack of understanding of the basic biological mechanisms and the lack of malaria pharmacologists in the field. The Expert Group recommended supporting research into the pharmacokinetics of antimalarial drugs, particularly because of the key evidence such studies provide for determining optimal drug dosages, drug combinations and usage in a population, and distinguishing between treatment failure caused by resistance and by other causes, such as inadequate drug concentrations. Such information is essential to optimise treatment management and achieve effective delivery across all malaria-endemic regions.

115. The Expert Group discussed the limited amount of evidence available for policy makers to make decisions on how ACTs should be properly executed and deployed in the field. The crucial need for research on how to protect ACTs for as long as possible was emphasised. The ACT Consortium[119] is currently looking at the effectiveness of ACTs over time, the cost-effectiveness of delivery strategies, acceptability, safety and how to improve ACT usage.

4.4 A need to expand the armoury of, and access to, quality-assured diagnostic testing

It [diagnostic testing] will make a huge difference, for a variety of reasons. One is better clinical management, not only of malaria cases but the cases that are negative too. And the other is the use of medicines more rationally. All the indications are that we were over-treating malaria in children in Africa, so provided we have good diagnostic tools, these things will make a huge difference for the better. But we still have a huge challenge, to get quality diagnostic tools out there in the field and that is not a simple task, that is a massive challenge.
Wellcome Trust Expert Group on malaria, April 2010

119 **www.actconsortium.org**

Rapid diagnostic tests. It is not high technology, but it has revolutionised how malaria is going to be managed, and if elimination does happen somewhere then its going to play a key part.
Wellcome Trust Expert Group on malaria, April 2010

116. In 2006, the adoption of ACTs as first-line treatment transformed the global treatment of malaria; however, if patients are misdiagnosed with malaria and incorrectly treated, these drugs may become ineffective. The prompt and accurate diagnosis of malaria is pivotal for effective clinical case management and control, to ensure appropriate drug treatment, and to prevent presumptive treatment of malaria, which is widespread in endemic areas. The availability of effective, high-quality diagnostic tools is key to facilitate this.

117. Historically, microscopy – diagnosis via microscope analysis – has been the main method of confirming a diagnosis of malaria. In most malaria-endemic regions, however, microscopy in a clinic setting is not practical. The development of RDTs, which require less equipment and training and can be used in the field, has made a massive difference to the clinical management of malaria. Malaria RDTs, also known as 'dipsticks' or 'malaria rapid diagnostic devices', were introduced in 1995 (Timeline) and have the potential to greatly improve the management of malaria infections when a high-quality microscopy diagnosis is not readily available.

118. The introduction of RDTs (followed by the endorsement of the WHO and inclusion in their guideline on universal diagnostic testing[120,121]) before being treated was identified as a major step change in the clinical management of malaria. Over the past few years, the number of RDTs available, the interest in scaling-up diagnosis and the number of new diagnostic screening tools in development – based on technologies such as loop-mediated isothermal amplification, PCR, digital microscopy and serology – has rapidly increased.[122]

120 WHO. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010.

121 RDTS detect malaria antigen in a drop of human blood. One example is histidine-rich protein 2 (HRP-2), which is specific for *P. falciparum*.

122 PATH. Staying the Course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

119. Although the Expert Group acknowledged the important role of the Foundation for Innovative New Diagnostics[123] and WHO in driving the development and implementation of high-quality diagnostic tests in malaria-endemic countries, and although African countries and other regions[124] are currently deploying RDTs in the community setting, the Expert Group emphasised that accurate malaria diagnosis in remote low-resource areas still remains a major issue.

120. Malaria RDTs used in remote and low-resource areas face more challenges than those used in the traditional laboratory setting: the plethora of issues – such as thermal stability, sensitivity and specificity (which depends on parasite density, the population tested, the preparation and interpretation of the RDTs, and the quality of the reference standard), transport, sample collection and storage, shelf life, variability and community-level diagnosis – mean malaria RDTs used in the field need to be more robust, and quality assurance is more difficult to implement and maintain. Therefore, achieving high-quality diagnosis in the field is a huge challenge because the planning and financial resources for training, monitoring and quality control programmes must be adequate. As a result, there is currently a lack of RDT accuracy and reproducibility in the field setting.

121. In working to reduce the clinical impact of malaria, it is essential to have quality-assured RDT-based diagnosis, reporting, screening and monitoring of incidence rates to inform national malaria programmes of the effectiveness of control strategies. The role of healthcare professionals in this is also crucial; appropriately trained community healthcare workers are essential to ensure RDTs are prepared and interpreted accurately.

122. More research is required to evolve and improve the range of RDTs, including the development of novel low-cost diagnostics that can detect very low levels of malaria parasites in asymptomatic individuals, and to support their availability and access in testing in low-resource settings.

RDTs have some huge challenges to face and quality assurance of these tests is proving to be much more difficult than we thought.
Wellcome Trust Expert Group on malaria, April 2010

123 **www.finddiagnostics.org**

124 Sixteen African countries are deploying RDTs at the community level, as are 22 countries in other regions. WHO. World Malaria Report. Geneva: World Health Organization; 2010.

4.5 A need for improved and novel vector control tools

123. Prevention of malaria transmission by the *Anopheles* vector is one of the fundamental measures of the Global Malaria Control Strategy.[125] Key interventions currently recommended for vector control include the use of insecticide-treated bednets, long-lasting insecticide-treated mosquito nets, indoor residual spraying, insecticide-treated materials and integrated vector management.[126,127,128,129] Field trials of insecticide-treated bednets and indoor residual spraying have demonstrated that they are most effective when applied with high coverage rates.[130,131,132] However, the combination of logistical challenges associated with the distribution of insecticide-treated bednets and the rise of insecticide resistance threatens to undermine the effectiveness of treated bednets.[133] Furthermore, the dependence on a single class of insecticides – the pyrethroids – in bednet impregnation makes insecticide resistance more likely; therefore, the development of new insecticides is crucial.

124. The Expert Group raised and discussed several research needs for the future of malaria vector control, specifically:

- More research into vector biology, to support the discovery of alternative insecticides to pyrethroids and new vector control tools including, for example, the potential to genetically modify mosquitoes that would be resistant to malaria and drive out natural malaria-carrying mosquitoes.
- A better understanding of how community health services can be best mobilised to implement measures such as insecticide-treated bednets and

125 WHO. A Global Strategy for Malaria Control. Geneva: World Health Organization; 1993.

126 WHO. Instructions for treatment and use of insecticide-treated mosquito nets. Geneva: World Health Organization; 2002.

127 WHO. Indoor Residual Spraying. Use of indoor residual spraying for scaling up global malaria control and elimination. Geneva: World Health Organization; 2006.

128 WHO. Malaria Vector Control and Personal Protection. Geneva: World Health Organization; 2006.

129 WHO. Insecticide-treated Mosquito Nets: A WHO position statement. Geneva: World Health Organization; 2007.

130 Pluess B et al. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev 2010;14(4):CD006657.

131 Killeen GF et al. Preventing childhood malaria in Africa by protecting adults and mosquitoes with insecticide-treated nets. PLoS Med 2007;4.

132 Lindblade KA et al. Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide-treated bed nets: 4 to 6 years follow-up. JAMA 2004;291;2571–80.

133 Ranson H et al. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol 2011;27(2):91–8.

long-lasting insecticide-treated mosquito nets. Studies have shown that removing the costs to recipients for insecticide-treated bednets reduces inequity and increases coverage,[134] although there are variations and more research is needed to explore how best to identify and access marginalised communities.

- A greater understanding of the optimum uses and applications of the range of vector control methods that exist. For example, the use of indoor residual spraying alone should be compared with its use in combination with insecticide-treated bednets.
- One of the main challenges of any malaria control programme is sustaining the effort involved, particularly when low levels of malaria have been achieved. The Expert Group argued that an increased capacity to scale-up and improve the maintenance of existing vector control measures and ensure their regular and proper use is essential. Currently, the total resources available to scale-up recommended vector control interventions fall short of what is needed.
- Another challenge is the relative lack of senior entomologists working in the field and the limited pipeline of trained junior researchers entering the field. There is an opportunity for funders – including the Wellcome Trust – to consider how to support capacity building and training strategies to address these gaps within the malaria research community.

125. In the area of vector control, the Expert Group emphasised the potential of collaborations between industry and academia to develop effective insecticides and consider the development of a supply of effective vector control tools. The group cited the example of the Innovative Vector Control Consortium (IVCC, which was funded by the Gates Foundation with an initial award of $50.7m and established in 2005) as a potential model to follow.[135] Initially established as a research consortium, the IVCC has evolved into a PDP and registered as a not-for-profit company and charity in 2008. IVCC's aim is to "enable partnerships for the accelerated development and delivery of new products and tools that increase the effectiveness and efficiency of the control of insects which transmit disease". By bringing together relevant expertise and technical resources from across sectors, the IVCC hopes to transcend the barriers that have blocked innovation in the development of vector control products.

4.6 Enhanced information systems, tools and technologies

Even more important than modelling is the impact of GIS and that kind of technology on disease control. That is a field that has grown hugely – the geographic measuring systems. But its application and control has been dismal. This is an area where I think there is a huge gap. I wouldn't put my money on modelling; I would put it on getting better information systems.
Wellcome Trust Expert Group on malaria, April 2010

There is a big gap in what I might call monitoring, evaluation research…We are going to end up with problems, because we are not getting the right large scale feed through of information of what is going on in these large scale programmes.
Wellcome Trust Expert Group on malaria, April 2010

It is becoming more and more important to recognise the focality of malaria, we have known it all along, but it is an area where we haven't put any practical value to. Even in high transmission areas like Africa, the straw that breaks the back of this camel is going to be focal and local malaria, which we are not looking at.
Wellcome Trust Expert Group on malaria, April 2010

The epidemiologists as well, they are very important too. What Bob Snow has done in the Malaria Atlas Project revolutionised it.
Wellcome Trust Expert Group on malaria, April 2010

126. Surveillance of malaria incidence and mortality is essential for monitoring the progress of malaria control programs nationally and internationally, and for recognising malaria focality – which is vital for malaria immunisation and transmission control. As important as having high-quality diagnostic tools for malaria is the need to capture accurate malaria incidence data across populations.

127. The Expert Group described a dearth in accurate malaria surveillance systems. This has perhaps become more acute over time: although funding via large prevention programmes is thought to be responsible for major reductions in the burden of malaria in many areas, the ability to precisely model and quantify those reductions remains difficult. The Expert Group described the continuing importance of 'shoe-leather epidemiologists', who are crucial in building the picture of malaria incidence by personally tracing every contact, in resource-poor settings. To have people adequately trained in the capture of high-quality data and in interpreting and mapping incidence using reliable health information and surveillance systems is a priority.

128. This has been further highlighted in a recent study, led by researchers at the IHME, which indicated that malaria mortality data is possibly double previous estimates by WHO for 2010.[136] Such large variation in incidence estimates emphasises the limitations of existing data sources for assessing malaria mortality over time and underscores the need to improve methods for future estimates of malaria disease burden.

129. Geographic information systems (GIS) and technology-based surveillance support tools are being used increasingly to map and model the incidence and prevalence of malaria across parts of the world. However, such mapping technologies can only be used effectively where the underlying incidence data are reliable and complete, where there is adequate information infrastructure, and where staff are trained to interpret the data; in many resource-poor and malaria-endemic settings, none of these criteria for the success of GIS-related technologies are fulfilled.

130. Investments to help build a cadre of researchers to deliver high-quality surveillance and epidemiology are crucial, as are technology and information systems to support surveillance. Consequently, it was recommended that support should be provided to address the gap in health information systems. This, again, is an area where collaboration between researchers, information technology providers and industry could have a major impact.

4.7 Integrated databases to enable research data sharing

Getting people to put their data into shared databases as early as possible, I think that would transform the way research is done in the field, to get data out, to share and properly archive databases.
Wellcome Trust Expert Group on malaria, April 2010

This is a host parasite vector interface and if we really are going to understand the complexity of the disease, then we are going to have to, at some stage, do something akin to a systems biology approach that is able to handle all of those information streams, and that is a huge challenge.
Wellcome Trust Expert Group on malaria, April 2010

131. Since the sequencing of the human genome, the malaria community has embraced the principles of open access for malaria research data. In the fight against malaria, data are highly significant – from genomic sequencing data on pathogen and vectors to serotypes and incidence data.

132. Several genome-based databases with a focus on malaria parasites already exist, such as PlasmoDB[137] and Vectorbase,[138] but these are not currently integrated; the Expert Group extolled the potential benefits of having shared, publicly accessible databases. Although the development of integrated databases would be a huge challenge, bringing together diverse data sets from the host, parasite and vector research communities is likely to yield several benefits, including:

- enabling the exchange of robust information (both positive and negative) between the host, pathogen and vector communities
- facilitating data sharing between basic and clinical scientists
- enabling the malaria research community to share clinical trial data
- enabling the efficient exchange of immunology data
- helping to facilitate a systems biology approach to malaria research
- providing a deeper understanding of the complex host–pathogen system
- increasing the speed at which new drugs are developed.

134 Noor AM et al. Insecticide treated net coverage in Africa: mapping progress in 2000–2007. Lancet 2009;373:58–67.

135 **www.ivcc.com/index.htm**

136 Murray CJL et al. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2011;379(9814):413–31.

137 Aurrecoechea C. PlasmoDB: a functional genomic database for malaria parasites. Nucleic Acids Res 2009;37(suppl. 1):D539–43.

138 A cloning vector sequence database.

133. There is a precedent for such collaboration within the malaria community, as evidenced in the *P. falciparum* database MapSeq/pf.[139] MapSeq/pf is a database of genome variation in the malaria parasite *P. falciparum* in populations around the world, which enables the interrogation of more than 300 genomes simultaneously. Malaria researchers around the world have contributed samples and data to the MapSeq/pf project. The MapSeq/pf project is primarily funded by the Wellcome Trust, which is currently bearing most of the sequencing costs. MapSeq/pf also receives funds from other bodies, notably the MRC, the Bill and Melinda Gates Foundation, and the NIH in the USA.

134. The development of any public, integrated database necessarily requires management, curation and associated governance and access policies to ensure researcher confidence in the data. To do this requires adequate investment in infrastructure and the training of database managers, systems analysts and other information technologists.

We do need more database managers and database curators who are going to be able to look after these [shared databases].
Wellcome Trust Expert Group on malaria, April 2010

In relation to databases, we are going to need systems analysts to distinguish them from modellers, as a group. We are going to need those and they are going to need the infrastructure, which is non-existent, to get them started. I think that is something we do have to look to.
Wellcome Trust Expert Group on malaria, April 2010

4.8 A need to strengthen research capacity and support training

One of the problems is that, for a lot of young African scientists, there are lots of PhD programmes and ways to train, but there is actually nothing to go back to, other than the Wellcome Trust type units. And that is not enough.
Wellcome Trust Expert Group on malaria, April 2010

When you are getting down to these more unusual situations with things not working, it is going to be absolutely critical to have competent entomologists and they really have just gone.
Wellcome Trust Expert Group on malaria, April 2010

135. The Expert Group agreed that the future of malaria research will involve improving the current tools for prevention, diagnosis and treatment and developing new approaches to combat the disease. To do this requires a focus on both short-term and long-term capacity development – both human and infrastructure and systems capacity. In the short term, it is essential that researchers are equipped with the training to enable them to use existing tools and knowledge effectively. In the longer term, it is important that there are sufficient highly skilled researchers and technicians across all aspects of malaria research.

136. As described, researchers to help us understand and combat malaria are required in several traditional and emerging disciplines. The Expert Group described a relative shortage of junior malariologists and those specialising in parasitology, immunology, pathology and pharmacology. Researchers with skills in community and health services research are important to aid in the development of effective prevention and treatment delivery programmes and to work with governments and healthcare providers in endemic countries. In addition, there is an emerging need for bioinformaticians and information science researchers to complement the work of basic-focused malaria researchers.

137. The Expert Group commended the research and capacity-strengthening activities of the Wellcome Trust in Africa, such as the Health Research Capacity Strengthening Initiative and the African Institution Initiative, which has a significant focus on the training and mentorship of junior researchers. In addition, the Expert Group emphasised the need for improved coordination between the researchers working in the field in endemic countries and their international counterparts to ensure that research findings and expertise are shared, to maximise the opportunities for collaboration and minimise the potential for duplication.

139 **www.sanger.ac.uk/MapSeq/**

138. Interestingly, although the benefits of 'big', collaborative science on the global burden of malaria are thought to be substantial, the need to ensure that science organised in this way does not negatively affect a junior researcher's career remains a challenge. Working collaboratively within consortia on a subject like malaria can deliver timely results and avoid duplication; however, it is argued that consortia can restrict scientific independence and limit career paths for young researchers. This issue is not unique to the field of malaria, but its potential impact is perhaps more acute given the need to sustain a pipeline of researchers to prevent the progress made to date being reversed; it remains crucial that new researchers are attracted to work in the field. It was agreed that it is the responsibility of institutions moving towards collaborative 'big science' to have career development strategies in place for the younger generation of malaria researchers coming through.

What we are missing from the vector biology community is senior and mid-senior level people, we lost a generation and we have a tiny number of people who are now trying to mentor others coming through and it is an almost impossible task.
Wellcome Trust Expert Group on malaria, April 2010

4.9 A recognition of the importance of international, multi-sector collaborations to tackle malaria

If malaria hadn't got into the Global Fund we would still be struggling around.
Wellcome Trust Expert Group on malaria, April 2010

139. Over the past decade or so, several international collaborations, public–private partnerships and PDPs have been established to combat malaria. The focus of these collaborations has ranged from basic science (the focus of the Malaria Genome Project) to the delivery of vaccines and drugs in malaria-endemic regions (the focus of PATH MVI). These collaborations are thought to be making a crucial difference in the effort to combat diseases because they bring together relevant experts that are required to address the complexities of disease treatment and prevention.

140. PDPs bring together public sector funding with private sector funding and manage the contributions towards a common objective. The majority of PDPs work as non-profit organisations, whereby activities are outsourced to academic or private sector partners, with the PDP bringing together expertise and providing public funding, technical oversight and portfolio management. Each PDP focuses on specific types of technologies (e.g. drugs, vaccines or diagnostics), and some PDPs limit themselves to a specific disease area.[140]

141. Established in 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria (often called 'the Global Fund') is an international public–private partnership organization that aims to "attract and disburse additional resources to prevent and treat HIV and AIDS, tuberculosis and malaria". The Global Fund has been the world's largest financier of anti-AIDS, TB and malaria programs and at the end of 2010 had approved funding of $21.7bn that supported more than 600 programs in 150 countries; the Expert Group emphasised the important role of the Global Fund in helping to bring money to the field of malaria over the past decade. The global financial crisis has severely dented the availability of funding via the Global Fund, which has since decided to cancel round 11 of grant funding.[141]

142. The Expert Group recommended that public, private and philanthropic funders should continue to seek out opportunities to work together to minimise the risk of over-reliance on one funder or sector and to ensure a well-balanced, diverse, responsive and flexible portfolio of malaria-related research funding across the globe.

I think the R&D funding has largely been dissociated from the Global Fund, up to now. We are in the middle of the Global Fund, resources have been spent on research and in some ways, the biggest threat to malaria is the possibility of the Global Fund drying up; 'drying up' is too harsh a word, but there is a huge threat. There is a possibility that they will not be able to sustain this funding.
Wellcome Trust Expert Group on malaria, April 2010

140 DfID. 2010. Product Development Partnerships: Lessons from PDPs established to create new health technologies for neglected diseases. **www.dfid.gov.uk/Documents/publications1/hdrc/lssns-pdps-estb-dev-new-hlth-tech-negl-diseases.pdf**

141 **www.theglobalfund.org/en/**

I think the real challenge for the upstream research funders is to try and retain the diversity in thinking, which I think is the most fundamental thing we risk, because everything is turned into a more efficient machinery, to deliver, we risk dampening that diversity and innovation and herding the scientists, which is a real danger.
Wellcome Trust Expert Group on malaria, April 2010

4.10 To ensure consideration of the social, political and ethical implications of malaria-related research

143. Looking ahead, the Trust and other funders of malaria-related research need to continue to engage with the social, political and ethical implications of research. To ensure global funds for malaria R&D are coordinated effectively and used to their best effect, funders need to maintain an active, open dialogue.

144. Research diagnosis and treatment regimens necessarily carry with them a need to consider patient benefit. Research that involves the participation of individuals from low- and middle-income countries – and where patient benefit may not be immediate – raises important ethical considerations around issues including informed consent and benefit sharing. Such research must always respect the cultural and social context.

145. In addition, many of the barriers to the implementation of malaria research findings and recommendations are political and economic. A key challenge for the Wellcome Trust and other funders and partners in malaria research support is to ensure that interventions of demonstrated effectiveness are taken up into health policy and practice at the local and global level; research findings can be difficult to translate easily and immediately into resource-poor settings. Funders also need to work to ensure that malaria drugs can be made available to those most in need at affordable prices and to address the growing problem of counterfeit medicines. Funders need to continue to explore mechanisms by which they can support researchers and other organisations to ensure the maximum utility of research in practice.

146. It is important in going forward with malaria research that such contexts and considerations are not lost in the pursuit of knowledge.

4.11 To support dialogue with relevant policy and public stakeholders

147. The Expert Group emphasised the importance and value of raising public awareness of the problems of malaria and the continued need to deliver public awareness campaigns. Like many aspects considered in this review, it is something that has become more prominent in recent years.

148. Public engagement activities play a major part in increasing the impact of malaria prevention and control strategies, and international campaigns such as RBM, United Against Malaria[142] and World Malaria Day[143] are needed to inform, enhance and sustain the delivery of malaria control strategies to achieve universal coverage and eventual elimination.

149. Public consultation, participation and open dialogue, upstream in the research process, ensure the development of appropriate, culturally relevant technologies. Continued public discussion can generate a bottom-up demand for such interventions. Engagement activities along with cultural and social research can help determine the most appropriate way to engage with particular communities, to conduct research and to design health promotion strategies.

150. Through its international engagement work, the Trust stimulates dialogue about health research and its impact on the public. Furthermore, all Wellcome Trust MOPs are encouraged to have community engagement or communications staff to facilitate interactions between researchers, local communities, policy actors and the media.

142 **unitedagainstmalaria.org/**
143 **www.worldmalariaday.org**

Dr Gerry Killeen: Mosquito control

Dr Gerry Killeen. *Dr Gerry Killeen*

Summary

Reducing mosquito numbers and avoiding mosquito bites are key to reducing malaria transmission. The *Anopheles gambiae* mosquito is the main transmitter ('vector') of *Plasmodium falciparum* malaria and so is responsible for more deaths worldwide than any other animal. Dr Gerry Killeen has conducted field research in Africa since 2000, working to identify new ways to control the mosquitoes that transmit malaria and better ways to use current methods.

Background

The World Health Organization's malaria control strategy emphasises the importance of targeting a range of vectors using a combination of interventions – including distributing insecticide-treated bednets, spraying insecticides indoors and killing insect larvae. But implementing and maintaining effective vector interventions on a large scale can be challenging. A range of coordinated, evidence-based interventions are needed to break the malaria transmission cycle at a local level. High-quality field-based research by well-trained local scientists is crucial to achieving this, and novel complementary interventions are needed to eliminate malaria transmission in endemic areas.

Dr Gerry Killeen works to identify, develop and validate appropriate vector control tools that will be effective in parts of Africa where malaria is endemic and resources scarce. His work promotes evidence-based policy and will help to ensure the most effective strategies are implemented, quickly.

A biochemist, Dr Killeen started developing mathematical models of malaria transmission during his postdoctoral research at Tulane University in New Orleans. Inspired by F L Soper's quest to rid north-east Brazil of the *A. gambiae* mosquito, he moved to East Africa – first Kenya, then Tanzania. Since 2000 he has conducted field research, mostly in isolated rural settings, working with the Ifakara Health Institute and the International Centre for Insect Physiology and Ecology. He holds a Readership at the Liverpool School of Tropical Medicine and leads the Biomedical and Environmental Thematic Group at the Ifakara Health Institute in Tanzania.

Since being awarded a Wellcome Trust Intermediate Fellowship in 2005, Dr Killeen has modernised and validated Soper's neglected vector control strategy, first used more than 50 years ago. He now hopes to make further improvements and roll it out on a large scale.

Advance

Dr Killeen realised that currently used insect-trapping methods (principally human landing catch trapping, which is labour-intensive and exposes the collector to the risk of malaria infection) were unsuitable for monitoring mosquito behaviour on a large scale. He tested a series of tent traps that could provide an affordable, practical and informative trapping method. Since validating this method, he has used it in a variety of field studies to monitor mosquito behaviour in urban Dar es Salaam, as well as in Ifakara and other parts of rural Tanzania.

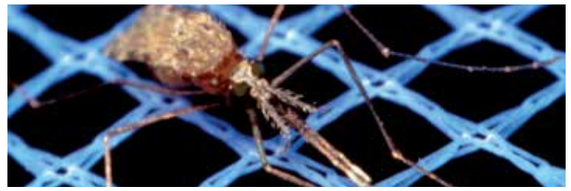
His research has revealed that bednet use and indoor spraying were changing the behaviour of the insect vectors and forcing them to feed outdoors. This demonstrated the need for novel interventions that target larval stages to complement indoor vector control measures targeting adult mosquitoes.

Free distribution of insecticide-treated bednets to reduce malaria transmission is a high priority for national malaria control programmes. However, in most countries only vulnerable groups such as children and pregnant women are being targeted. In 2007 Dr Killeen published research to show that complete coverage of the whole population, not just vulnerable groups, with insecticide-treated bednets was necessary to have a significant impact on malaria disease burden. The evidence provided by Dr Killeen's study led directly to rapid changes in WHO guidelines for bednet distribution, emphasising the need for over 80 per cent coverage with long-lasting insecticide-treated nets in national malaria control programmes.

In Dar es Salaam, mosquito surveillance and control in the Urban Malaria Control Programme is delegated to community members known as community-owned resource persons (CORPs). Dr Killeen and colleagues from the Ifakara Health Institute, Durham University, Harvard University, the Swiss Tropical Institute and the Liverpool School of Tropical Medicine have developed a programme of community-based surveillance and larviciding (killing larvae) in 15 urban wards covering 55 km^2 of Dar es Salaam.

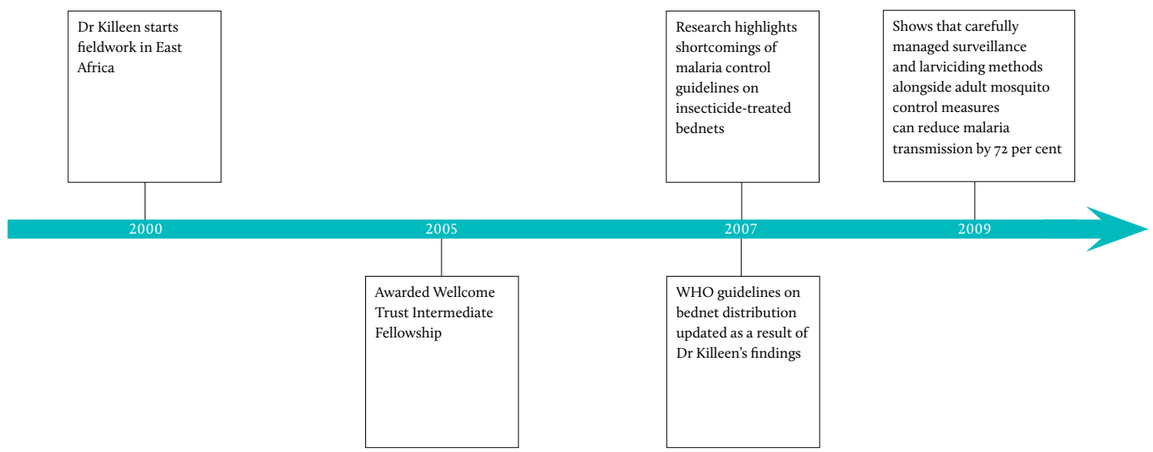
One study closely monitored inoculation rates and malaria infection prevalence for a year. This revealed that larviciding as an adjunct to existing insecticide-treated bednets reduced malaria transmission by 72 per cent. Dr Killeen now plans to modernise the intervention further to make use of locally available technologies, such as mobile phone reporting, and to integrate local management and evaluation teams so the intervention can be scaled up to a multi-country trial.

Dr Killeen is committed to working in low-income countries and applying basic science to practical programmes that will affect the lives of millions of people. Central to this is his desire to build research capacity and nurture local scientific talent. Several of his students have been successful applicants to the Trust's Master's Fellowship scheme, and this has helped to provide the incentive needed for young Africans to compete at the highest level. The research base Dr Killeen has established in Tanzania helps to build local research capacity, boasting a team including 20 Kenyan and Tanzanian postgraduate researchers, three postdoctoral researchers and two academic staff (including Dr Killeen). His goal is to develop not only the technologies and knowledge but also the expertise and training base that Africa will need to eliminate malaria in the long term.



An *Anopheles* mosquito on the mesh of a bednet. *Wellcome Images*

Timeline of Dr Gerry Killleen



References

Russell TL et al. Impact of promoting long-lasting insecticide treatments of bednets upon malaria transmission in a rural Tanzanian setting with pre-existing high coverage with untreated nets. Malar J 2010;9:187.

Castro MC et al. The importance of drains for the larval development of lymphatic filariasis and malaria vectors in Dar es Salaam, Tanzania. PLoS Negl Trop Dis 2010;4:e693.

Devine GJ, Killeen GF. The potential of a new larviciding method for the control of malaria vectors. Malar J 2010;9:142.

Okumu FO et al. Development and field evaluation of a synthetic mosquito lure that is more attractive than humans. PLoS ONE 2010;5:e8951.

Govella NJ et al. Insecticide treated nets can reduce malaria transmission by mosquitoes which feed outdoors. Am J Trop Med Hyg 2010;82:415–9.

Ogoma SB et al. Window screening, ceilings and closed eaves as sustainable ways to control malaria in Dar es Salaam, Tanzania. Malar J 2009;8:221.

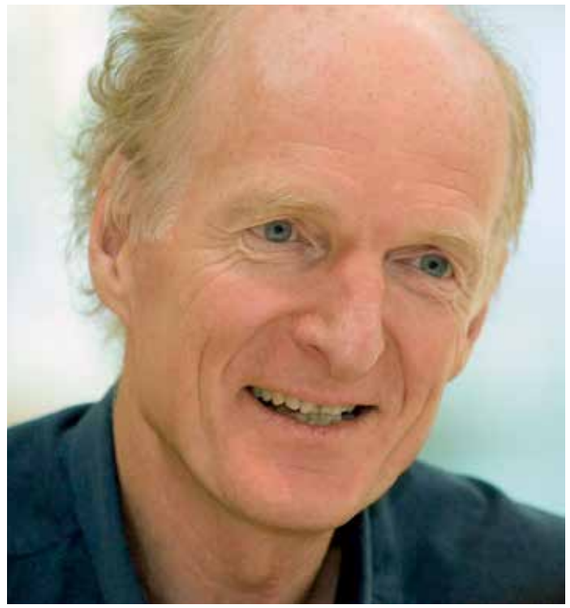
Govella NJ et al. A new tent trap for sampling exophagic and endophagic members of the Anopheles gambiae complex. Malar J 2009;8:157.

Geissbühler Y et al. Microbial larvicide application by a large-scale, community-based program reduces malaria infection prevalence in urban Dar es Salaam, Tanzania. PLoS ONE 2009;4:e5107.

Killeen GF et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med 2007;4:e229.

Killeen GF et al. Infectiousness of malaria-endemic human populations to vector mosquitoes. Am J Trop Med Hyg 2006;75(Suppl 2):38–45.

Professor Nick White:
On the front line of the fight against malaria



Professor Nick White. *Wellcome Library, London*

Summary

Professor Nick White has been a key figure in developing and validating effective treatments for malaria, including widespread use of artemisinin-based antimalarial drugs. His extensive research has provided the evidence to support changes in treatment for both severe and uncomplicated malaria and has led to the introduction and global adoption of artemisinin-based combination therapies (ACTs). Now, as artemisinin resistance begins to emerge, he is well placed to face the new challenges in the fight against malaria parasites.

Background

Professor White has lived and worked in South-east Asia for almost 30 years. His career in malaria research began in earnest when, in 1980, he was awarded a lectureship in tropical medicine funded by the Wellcome Trust and moved to work in Thailand with the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme. He became Director of the Programme in 1986 and Chairman in 2001. In 1991, he founded the Wellcome Trust Clinical Research Unit in Vietnam. Professor White has been a Wellcome Trust Principal Research Fellow since 1992. He is Professor at both Mahidol and Oxford Universities and an Honorary Consultant Physician at the John Radcliffe Hospital in Oxford, and he sits on several World Health Organization (WHO) advisory panels.

The Programme in Thailand has, from the outset, focused on clinical research relevant to improving patient health. It has played a key part in building local research capacity by training clinical scientists from across the region and building world-class clinical research infrastructure. Research activity within the programme has led to fundamental improvements in the health of people living in Thailand and other parts of South-east Asia, as well as further afield. Professor White's contribution to these achievements has been recognised in a number of awards, including an OBE. He was also identified as the world's third most influential malaria researcher in a survey of citations in publications between 1995 and 2005. And in a survey of papers published between 1996 and 2007 by European parasitologists, he was by far the most highly cited researcher.

Advance

Professor White's malaria research has examined the disease-causing characteristics of the malaria parasite and how antimalarial drugs work. In the 1980s, Professor White established the correct dosage regimens for severe malaria drugs.

In the 1990s, he went on to develop the theoretical basis for assessing antimalarial drugs in patients and how they could be adapted to field conditions. This led, through a series of large clinical trials, to the development of optimum treatment regimens for drug-resistant malaria and ultimately artemisinin combination therapy (ACT), the current first-line treatment for *Plasmodium falciparum* malaria throughout the world. As a result of the widespread use of ACTs, deaths from malaria in Vietnam have dropped from around 1500 per year in the 1990s to around 100 each year now. And since the introduction of ACTs to refugee camps along the Thai–Myanmar border, cases of malaria within the camps have fallen by 90 per cent.

Professor White's team of Trust-funded researchers developed and tested the use of ACTs in the 1990s. They carried out extensive clinical trials to test the effectiveness of different artemisinin derivatives given in combination with additional antimalarials such as mefloquine. They found that artemesinin derivatives were highly effective at killing *P. falciparum* parasites and caused fewer side-effects than existing antimalarials.

Professor White and colleagues have also carried out some of the largest clinical trials in the world to test the effectiveness of artesunate, a water-soluble derivative of artemesinin that can be injected. These trials have been key to driving changes from quinoline-based medications to ACTs.

In a worrying development, they have also provided the first comprehensive evidence that artemisinin-resistant *P. falciparum* parasites are circulating in Cambodia; the team is developing novel methods to detect these.

In light of this and new evidence that fake artemisinin drugs are being circulated, Professor White's research teams are developing methods to detect and tackle counterfeit and substandard antimalarial medicines. They are also looking for new and more effective antimalarial medications.

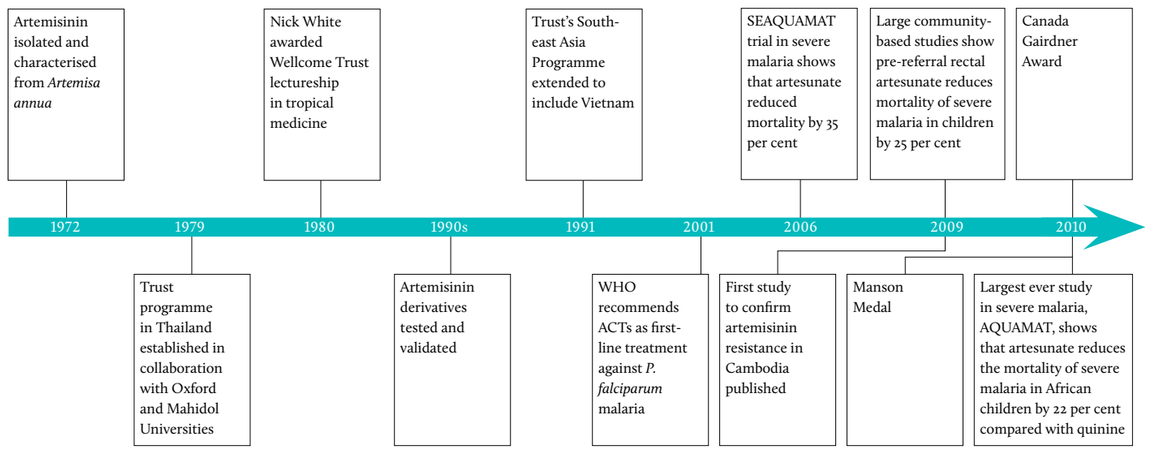
Elsewhere, Professor White and colleague François Nosten have demonstrated that women in late pregnancy are being systematically under-dosed with current antimalarial treatments. His clinical studies have shown that artemisinins are safe for use during pregnancy. These findings have led to changes in recommendations for antimalarial treatment during pregnancy.

He and his colleagues have also developed mathematical models to quantify the impact of different antimalarial treatment choices and implementation strategies. The models have provided a useful tool to inform the design of treatment policies.

Clinical teams within the Wellcome Trust Programme have made comprehensive descriptions of severe malaria that have provided the basis for the first WHO severe malaria management guidelines. And, in a landmark paper published in 2005, researchers from the Programme showed that treatment with artesunate reduced mortality by 35 per cent compared with quinine treatment.

In 2010, in the largest ever study in severe malaria (AQUAMAT), Professor White's team showed that artesunate reduced the mortality of severe malaria in African children by 22 per cent compared with quinine.

Timeline of Professor Nick White



References

Hutagalung R et al. A randomized trial of artemether-lumefantrine versus mefloquine-artesunate for the treatment of uncomplicated multi-drug resistant Plasmodium falciparum on the western border of Thailand. Malar J 2005;4:46.

Chotivanich K et al. Transmission-blocking activities of quinine, primaquine, and artesunate. Antimicrob Agents Chemother 2006;50(6):1927–30.

van Vugt M et al. Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug resistant falciparum malaria. Antimicrob Agents Chemother 1998;42(1):135–9.

McGready R et al. Randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated Plasmodium falciparum treatment in pregnancy. PLoS Med 2008;5(12):e253.

Boni MF et al. Mathematical models for a new era of malaria eradication. PLoS Med 2008;5(11):e231.

Dondorp A. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

Dondorp AM et al. Artemisinin-resistant Plasmodium falciparum malaria. N Engl J Med 2009;361:455–67.

Brockman A et al. Field evaluation of a novel colorimetric method – double-site enzyme-linked lactate dehydrogenase immunodetection assay – to determine drug susceptibilities of Plasmodium falciparum clinical isolates from northwestern Thailand. Antimicrob Agents Chemother 2004;48(4):1426–9.

Gomes MF et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009;373(9663):557–66.

Dondorp et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010;376(9753):1647–57.

Professor Chris Newbold: Malaria and immunity

Professor Chris Newbold. *Wellcome Library, London*

Summary

For more than 20 years, Professor Chris Newbold has studied antigenic variation in the malaria parasite and how it contributes to host immunity and parasite virulence. A key contributor to the Malaria Genome Project, his team was also the first to clone genes for the variant antigen *var*, now known to be central to the *Plasmodium falciparum* parasite's pathogenicity. His work drove a sea change in thinking about malaria and how immunity to the parasite develops.

Background

Plasmodium falciparum is the most virulent malaria parasite species that infects humans and is responsible for 1–2 million childhood deaths in sub-Saharan Africa alone.

For more than 20 years, Professor Newbold has been interested in antigenic variation in the parasite. Following postdoctoral research at the National Institute for Medical Research in Mill Hill, London, he moved to the University of Oxford in 1984, becoming Professor of Tropical Medicine in 1997.

The Wellcome Trust's support for malaria research has been key to his research. Trust programmes such as the Functional Genomics Development Initiative have helped Professor Newbold and his collaborators to characterise key molecular components of the parasite that drive its invasion into host red blood cells. The malaria-mapping project laid the foundations for the *P. falciparum* genome-sequencing Malaria Genome Project, which began in 1996 with funding from an international consortium that included the Trust.

Professor Newbold holds an honorary faculty position at the Wellcome Trust Sanger Institute, which has been at the core of his work to understand gene regulation in the parasite for many years, and he played a key part in establishing basic science research at the KEMRI–Wellcome Trust Research Programme in Kilifi, Kenya.

Advance

Professor Newbold had a key role in the Malaria Genome Project, acting as coordinator for its UK arm. The impact of the Project, completed in 2002, is hard to overstate. The *Nature* paper containing the annotated sequence has been cited more than 1800 times. The sequence data have transformed the research field and enabled and encouraged many young investigators to develop new ideas to address some of the seemingly intractable questions facing malaria researchers. *Plasmodium* species sequencing projects continue to form a significant element of Professor Newbold's research as comparisons between related species improve our understanding of the function of different *Plasmodium* genes.

The Trust-funded Functional Genomics Development Initiative followed soon after the Malaria Genome Project and enabled Professor Newbold and his colleagues to identify the molecular machinery that allows the parasite to invade host red blood cells. A number of these molecules, including a calcium-dependent protein kinase, are being characterised and investigated in the hope that specific inhibitors might be developed as potential novel therapeutics.

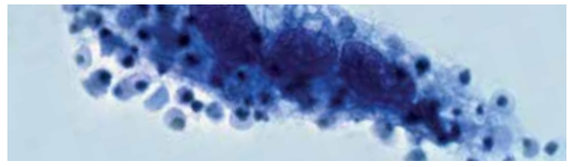
Professor Newbold's team was the first to clone the *var* genes of *P. falciparum,* now known to be central to the parasite's pathogenicity. His work sparked a transformation in people's thinking about malaria and how immunity to the parasite develops. He went on to show that the parasite can rapidly switch its antigenic and adhesive phenotypes *in vitro* and identified host-cell surface molecules, including ICAM on endothelial cells, that act as receptors for malaria-infected red blood cells.

Much of Professor Newbold's research on immunity to severe malaria has been performed in collaboration with researchers at the KEMRI–Wellcome Trust Research Programme. The team demonstrated that immunity to severe malaria is acquired rapidly after only one or two infections and that antibodies to *var* gene products such as PfEMP1 are important in generating effective immunity to malaria.

Recently, in collaboration with researchers in the Gambia, his team has explored the transcriptional regulation of gene activity in isolates of *P. falciparum* from people with malaria. As part of the study, the team developed new statistical methods that are now freely available to other researchers to help to account for parasites at different stages of the life cycle within the host. They identified two transcriptional clusters that are likely to correlate with sexual and asexual stages of the parasite's life cycle.

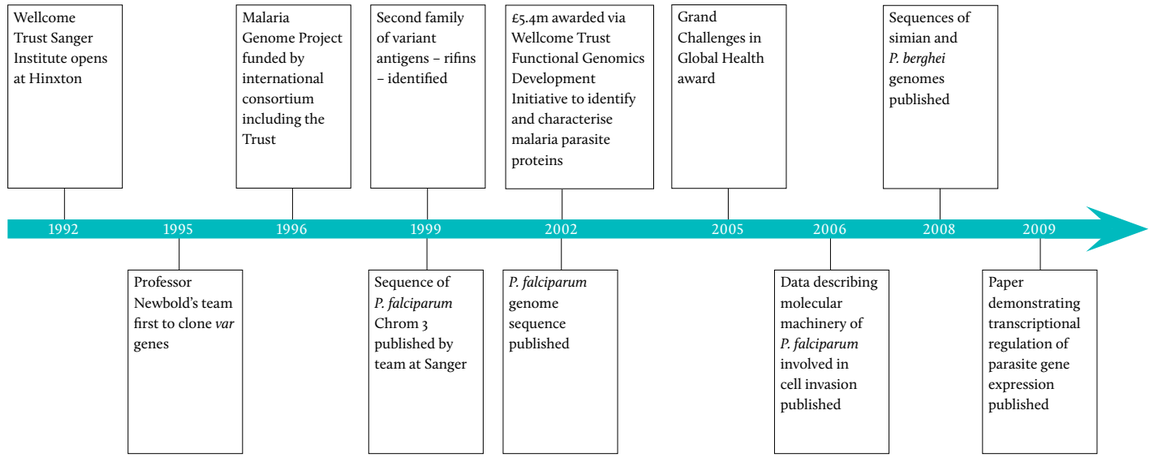
Professor Newbold's research has made a significant impact on the malaria research community and on our understanding of malaria genetics and gene function. His work in malaria-endemic areas such as Kenya has helped our understanding of how people develop immunity to malaria and what causes disease symptoms. This information will inform future developments that may lead to new treatments and/or vaccines that protect against the disease. His research continues to explore how antigenic variation affects immunity to malaria infection and severity of disease. The arrival of new sequencing technologies will allow researchers to explore in ever greater detail the molecular machinery involved in the parasite's complex life cycle. Professor Newbold's team is particularly interested in the transcriptional regulation of gene expression and has identified non-coding RNAs that may be important.

In addition, the team is studying the population biology of *Plasmodium* species field isolates in order to understand in more detail how drug resistance spreads and to find ways to combat it. The wealth of *Plasmodium* sequence data that has been accumulating since the first annotated draft of the genome was published in 2002 has helped Professor Newbold and collaborators to identify and update a quarter of the gene models within the *P. falciparum* genome and will allow a much more accurate and detailed analysis of the genome to be published in the near future.



Cytoadherence in *P. falciparum* malaria. *Wellcome Images*

Timeline of Professor Chris Newbold



References

Smith JD et al. Switches in expression of Plasmodium faciparum var genes correlate with changes in antigenic and cytoadherent phenotypes of infected erythrocytes. Cell 1995;82:101–10.

Gupta S et al. Immunity to non-cerebral severe malaria is acquired after one or two infections. Nat Med 1999;5(3):340–3.

Kyes SA et al. Rifins: a second family of clonally variant proteins expressed on the surface of red cells infected with Plasmodium falciparum. Proc Natl Acad Sci USA 1999;96(16):9333–8.

Bowman S et al. The complete nucleotide sequence of chromosome 3 of Plasmodium falciparum. Nature 1999;400(6744):532–8.

Smith JD et al. Identification of a Plasmodium falciparum intercellular adhesion molecule-1 binding domain: a parasite adhesion trait implicated in cerebral malaria. Proc Natl Acad Sci USA 2000;97(4):1766–71.

Gardner MJ et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 2002;419(6909):498–511.

Kriek N et al. Characterization of the pathway for the transport of cytoadherence-mediating protein, PfEMP1, to the host cell surface in malaria parasite-infected erythrocytes. Mol Microbiol 2003;50(4):1215–27.

Bull PC et al. Plasmodium falciparum antigenic variation: relationships between in vivo selection, acquired antibody response, and disease severity. J Infect Dis 2005;192(6):1119–26.

Pain A et al. The genome of the simian and human malaria parasite Plasmodium knowlesi. Nature 2008;455(7214):799–803.

Jaco E et al. Statistical estimation of cell-cycle progression and lineage commitment in Plasmodium falciparum reveals a homogeneous pattern of transcription in ex vivo culture. Proc Natl Acad Sci USA 2009;106(18):7559–64.

Professor Dominic Kwiatkowski: Malaria variation

Professor Dominic Kwiatkowski. *Wellcome Library, London*

Summary

Genome science provides new approaches to study how malaria parasites develop resistance to the drugs used to treat the disease and why some people are able to resist malaria better than others. Professor Dominic Kwiatkowski is developing global partnerships that enable researchers in malaria-endemic countries to use these new technologies and translate them into practical applications for malaria control.

Background

Malaria is caused by *Plasmodium* parasites that invade human red blood cells and are transmitted from one person to another by bloodsucking *Anopheles* mosquitoes. There is an ongoing evolutionary arms race between the malaria parasites, the mosquito vector and the human host. Parasite populations are continually evolving ways to resist the drugs that are used to treat the disease; mosquito populations develop resistance to insecticides; and some people have genetic factors that confer natural resistance to malaria.

The pace of innovation in this area of research has increased rapidly over the past decade. A crucial milestone was the publication of the first human genome sequence, shortly followed by the genome sequences of *Plasmodium falciparum* and *Anopheles gambiae*. Important recent advances include new technologies for large-scale genome sequencing, and new statistical methods for genome-wide analysis of genotype–phenotype associations and recent evolutionary selection.

Professor Dominic Kwiatkowski leads the Wellcome Trust Sanger Institute's Malaria Programme, which brings together population-based studies and experimental genetic approaches to investigate the clinical and biological consequences of genome variation in the parasite, vector and host. A major focus of his work is to build the global research partnerships that are needed to conduct large-scale genomic epidemiological studies. These include studies of the human genetic factors that determine protective immunity against malaria and studies of the parasite genetic factors and evolutionary mechanisms responsible for the emergence and global spread of new forms of antimalarial drug resistance.

Professor Kwiatkowski originally trained as a paediatrician before embarking on his research career in the 1980s, initially funded by a Wellcome Trust training fellowship for medical and dental graduates. After a period of research in the USA, he worked for several years with Professor Brian Greenwood at the MRC Laboratories in the Gambia. He joined the University of Oxford in 1989 and since 1998 has been an MRC Clinical Research Professor, a position he now complements with his role at the Sanger Institute.

In 2007, he was appointed as Director of the MRC Centre for Genomics and Global Health, which provides support and training in genetics, statistics, informatics and ethics for researchers in low-income countries. Since 2008, he has also been Director of Informatics for the Worldwide Antimalarial Resistance Network, a global partnership of clinicians, researchers and public health agencies with major funding from the Bill and Melinda Gates Foundation.

Advance

In the Gambia, Professor Kwiatkowski established the critical role of cytokines (cell signalling proteins secreted by the immune system) in malaria fever and discovered key biomarkers of cerebral malaria. He developed mathematical models of host–parasite population dynamics and directed a large therapeutic intervention study in severe childhood malaria, which included one of the world's first clinical trials of anti-cytokine therapy.

In 1994, his laboratory in Oxford reported the first evidence that variations in a person's cytokine genes affect their susceptibility to infectious disease and went on to discover various molecular mechanisms through which common genetic variants affect these genes. His group's work has included a number of methodological innovations, including a way to investigate how natural variants affect transcriptional regulation *in vivo*.

Professor Kwiatkowski initiated a multi-centre case-control study of malaria in 1996. In 2005, this developed into the Malaria Genomic Epidemiology Network (MalariaGEN), a partnership of malaria researchers in 21 countries, co-funded by the Wellcome Trust and the Gates Foundation through the Grand Challenges in Global Health initiative. MalariaGEN is one of the world's largest resources for the analysis of genetic susceptibility to infectious disease and in 2009 published the first genome-wide association study conducted in Africa. His research team is now working to translate new approaches in genomics, statistics and computer science into tools that will help to reduce the massive burden of disease in low-income countries. Malaria remains the main focus of their work, as a classic example of natural selection in action. Understanding the evolutionary processes and biological mechanisms that confer human resistance to malaria and parasite resistance to antimalarial drugs could provide vital insights and new tools to assist global efforts to control malaria.

This is scientifically and technically challenging at multiple levels. For example, one of the team's major projects is a trans-ethnic genome-wide association study of human resistance to severe malaria, in partnership with researchers working at 12 different locations in Africa, Asia and Australasia. Because of the great genetic diversity of human populations in Africa, this requires the development of new statistical methods and the optimisation of genotyping platforms. Another large partnership project is to sequence the genome of *Plasmodium falciparum* samples from around the world. The aim is to sequence thousands of genomes each year, which requires technological innovations to achieve large-scale genome sequencing of field samples at low cost.

A key area of the work is to develop web-based tools that enable researchers in malaria-endemic countries to analyse and share data on the samples that they have collected, and to make large-scale genomic data accessible and useful to clinical researchers and epidemiologists in malaria-endemic countries. Professor Kwiatkowski's team is also working with partners around the world to develop principles and policies for data sharing that respect principles of ownership and ethics, as well as a commitment to research capacity building in malaria-endemic countries, leading to equitable and sustainable global research networks.

Their ultimate goal is to develop cost-effective genome-based technologies that could provide early warning of the emergence and spread of new forms of drug resistance. In addition, by improving understanding of natural mechanisms of disease resistance, their findings could aid development of a malaria vaccine.

References

Teo YY et al. Methodological challenges of genome-wide association analysis in Africa. Nat Rev Genet 2010;11:149–60.

Manske HM, Kwiatkowski DP. LookSeq: a browser-based viewer for deep sequencing data. Genome Res 2009;19:2125–32.

Jallow M et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. Nat Genet 2009;41:657–65.

Malaria Genomic Epidemiology Network. A global network for investigating the genomic epidemiology of malaria. Nature 2008;456:732–7.

Chokshi DA et al. Data sharing and intellectual property in a genomic epidemiology network: policies for large-scale research collaboration. Bull World Health Organ 2006;84:382–7.

Knight JC et al. In vivo characterization of regulatory polymorphisms by allele-specific quantification of RNA polymerase loading. Nat Genet 2003;33:469–75.

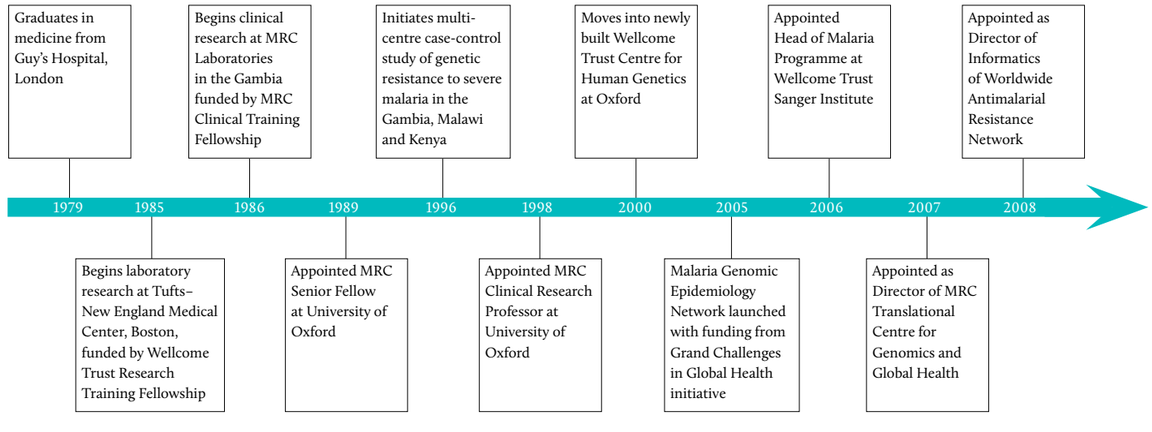
van Hensbroek MB et al. A trial of artemether or quinine in children with cerebral malaria. N Engl J Med 1996;335:69–75.

McGuire W. Variation in the TNF-alpha promoter region associated with susceptibility to cerebral malaria. Nature 1994;371:508–10.

Kwiatkowski D, Nowak M. Periodic and chaotic host-parasite interactions in human malaria. Proc Natl Acad Sci USA 1991;88:5111–3.

Kwiatkowski D et al. TNF concentration in fatal cerebral, non-fatal cerebral, and uncomplicated Plasmodium falciparum malaria. Lancet 1990;336:1201–4.

Timeline of Professor Dominic Kwiatkowski



The Kenya Medical Research Institute in Kilifi, Kenya. *Wellcome Library, London*

Background

- The KEMRI–Wellcome Trust Research Programme is well known internationally for its work tackling malaria and other infectious diseases, particularly bacterial and viral childhood infections.
- With links to the Trust since the 1940s, the Programme was formally established in 1989, in partnership with the Kenya Medical Research Institute (KEMRI).
- The Programme has two sites. In Nairobi, a unit is based at the capital's Kenyatta Hospital and has strong links with the Ministry of Health, facilitating the translation of research findings into medical policy. The unit in coastal Kilifi (an hour's drive from Kenya's second-largest city, Mombasa) is based in a busy district hospital, serving over half a million people and linking basic studies to clinical applications with local relevance.

Discoveries

- Recent research at the Programme includes a new global malaria atlas and studies on the clinical features and neurological effects of malaria, antimalarial drug resistance, treatments for acute respiratory infections, the natural history of sickle-cell disease, a large genetic birth cohort study, the management of severe malnutrition and paediatric HIV infection, and the epidemiology of epilepsy.
- The Malaria Atlas Project provides the first comprehensive description of the epidemiology and burden of the disease worldwide, at regional, continental and global scales.
- Studies have delivered the first comprehensive characterisation of severe malaria in African children and provided evidence that the influence of HIV, severe malnutrition and bacteraemia are over-represented in severe malaria.

Translation

- Through the recently established Clinical Trial Facility, Kilifi served as one of two sites involved in a phase II trial of a new malaria vaccine candidate, RTS,S, which has shown significant protection in young children. This has led to a phase III trial in which the Programme is also participating.
- The Kenya Programme has contributed to the growing body of evidence supporting the use of insecticide-treated bednets to prevent diseases, such as malaria, spread by mosquitoes. Researchers carried out one of the four large-scale trials on which current international policy is based, but the Programme has also demonstrated that millions of African children remain unprotected by the nets.

Research leaders

- Strong community links are at the heart of the Programme, with an emphasis on capacity building and training to build scientific leadership and create a critical mass of support from trained research and non-research staff.
- The Programme employs over 600 people, 95 per cent of whom are Kenyan. Of the 100 scientists in the Programme, 75 are East African.
- A £9 million Strategic Award from the Wellcome Trust is helping to train local researchers in areas such as translational research, social science and clinical trials.

Research environment

- The Programme conducts basic and clinical research in parallel, with results feeding directly into local and international health policy, and aims to expand the country's capacity to conduct multidisciplinary research that is strong, sustainable and internationally competitive.
- Although malaria remains a major focus of research at the Programme, there are many complex interactions with other diseases and with predisposing factors at the individual, community or health system level. Research is therefore organised under four broad themes:
  - clinical sciences, including bedside research, developmental medicine and disability, and therapeutics
  - epidemiological and human genetics research on infectious diseases, including malaria, HIV and pneumonia, and non-infectious diseases such as epilepsy, sickle-cell disease and malnutrition
  - pathogen and vector biology, involving basic science research on immunity, pathogenesis and drug targets
  - social, behavioural and public health research, where social scientists, health economists and others study the social and behavioural aspects of healthcare at different levels, helping to shape local policy.
- Working with the community, researchers are also looking at local perceptions of research and the consent process, helping to raise awareness of medical ethics in resource-poor countries.

Influence

- The Programme plays a key part in a number of regional initiatives, such as the Network for Surveillance of Pneumococcal Disease in the East African Region (netSPEAR) and the East African Network for Monitoring Antimalarial Treatment (EANMAT, looking in particular at antimalarial drug resistance).
- It also has increasing links with researchers and institutions around the region, with research projects based in neighbouring countries such as Somalia and Uganda. For example, in Dar es Salaam, Tanzania, the Programme is studying a large cohort of people with sickle-cell disease to define the natural history of the disease and to improve treatment and management.
- Clinical and therapeutic research from the Programme directly informs the Kenyan Government's malaria guidelines for hospital care for children and newborns.

The Kenya Medical Research Institute Clinical Trial Facility in Kilifi, Kenya. *Wellcome Library, London*

- The Programme helped the Kenyan Ministry of Health to establish its 2001 National Malaria Strategy and runs an in-depth demographic surveillance survey as part of INDEPTH, an international organisation evaluating populations and their health in low-income countries.
- Policy researchers have conducted extensive studies on paediatric admissions in health systems. They developed a 'shopkeeper training programme' for improving the treatment of childhood fevers in rural areas, which was adopted as a national programme and has had a major influence on programmes in other African countries.

Key publications

Marsh K et al. Indicators of life threatening malaria in African children. N Engl J Med 1995;332(21):1399–404.

Nevill CG et al. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. Trop Med Int Health 1996;1(2):139–46.

Snow RW et al. Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. Lancet 1997;349(9066):1650–4.

Marsh VM et al. Changing home treatment of childhood fevers by training shop keepers in rural Kenya. Trop Med Int Health 1999;4(5):383–9.

Snow RW et al. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature 2005;434(7030):214–7.

O'Meara WP et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet 2008 372(9649):1555–62.

Bejon P et al. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N Engl J Med 2008;359(24):2521–32.

Abuya T et al. Impact of ministry of health interventions on private medicine retailer knowledge and practices on anti-malarial treatment in Kenya. Am J Trop Med Hyg 2009;80(6):905–13.

Noor AM et al. Insecticide treated net coverage in Africa: mapping progress in 2000-07. Lancet 2009;373(9657):58–67.

Hay SI et al. A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 2009;6(3):e1000048.

Annex A: Membership of the Wellcome Trust Expert Group on Malaria

Professor Dan Colley (Chair)	Professor of Microbiology and Director of the Center for Tropical and Emerging Diseases, University of Georgia, Athens, Georgia, USA
Professor Brian Greenwood	Manson Professor of Clinical Tropical Medicine at the London School of Hygiene and Tropical Medicine, London, UK
Professor Nick White	Chairman of The Wellcome Trust South-east Asian MOPs and Professor of Tropical Medicine at the University of Oxford, UK, and Mahidol University, Bangkok, Thailand
Dr Kamini Mendis	Coordinator, WHO, Global Malaria Programme, Geneva, Switzerland and, after October 2010, Independent Consultant on malaria and tropical medicine, Columbo, Sri Lanka
Professor Janet Hemingway	Director of the Liverpool School of Tropical Medicine, Liverpool, UK
Professor Andy Waters	Professor of Molecular and Developmental Parasitology, Institute of Infection, Immunity and Inflammation, College of Medical Veterinary and Life Sciences, and Wellcome Trust Centre for Molecular Parasitology, University of Glasgow, Glasgow, Scotland
Professor Alister Craig	Chair in Molecular Parasitology, Liverpool School of Tropical Medicine, Liverpool, UK
Professor Robert Sinden	Emeritus Professor, Imperial College London, London, UK
Professor Chris Newbold	Head of the Molecular Parasitology Group at the Weatherall Institute of Molecular Medicine at Oxford University and Honorary Faculty member at the Wellcome Trust Sanger Institute, Cambridge, UK
Professor Jean Langhorne	Division of Parasitology, National Institute for Medical Research, London, UK

Annex B: Methodology

1. As part of moves to strengthen the Wellcome Trust's evaluation activity, in 2008, the Assessment and Evaluation team developed an approach to review the impact of its funding at a subject, portfolio level. Finding the optimum way to review the impact of scientific research – and to use such information in strategic decision making – remains a significant challenge. In this portfolio review, we do not attempt to provide an assessment of the impact of awards at an individual grant and/or funding scheme level but instead we take a macro, holistic view of the development of a field over time and consider the Wellcome Trust's role within this.

2. The specific aims of the portfolio review were three-fold:

   1. to identify the key landmarks and influences on the malaria research landscape over the past two decades (1990–2009)
   2. to consider the key features of the Wellcome Trust's impact on this malaria research landscape
   3. to consider the current and future direction of malaria and consider where there may be opportunities for Wellcome Trust strategy and funding.

3. To provide some boundaries and restrict the scope of the analysis, this review focuses on human malaria infection research, encompassing parasite and vector biology, host response and pathogenesis, resources and infrastructure, drug development, diagnostics, evaluation and resistance, epidemiology (surveillance and distribution), vaccinology, health services, ethics and policy research, prevention and control (including vector control), research design, technology and methodology, and the history of malaria.

4. On this basis, over the 20-year timeframe (1990–2009), support for malaria has accounted for £189m,[144] representing just over 3 per cent of the Trust's total funding commitment over this time. During this time, an additional £120m (52 grants) was allocated for core support and infrastructure at Wellcome Trust Centres and the Trust's MOPs; much of the work undertaken in these Centres and MOPs has played a part in facilitating malaria-focused research and providing training and research capacity development. In addition, the WTSI spend on malaria-focused research during this time period was £8.8m.

144 Wellcome Trust funding commitment between the financial years 1989/1990 and 2007/2008.

5. In addition, in doing this review of a portfolio of funding - adopting a more macro approach to a review, looking at trends across the field and bringing subject experts into the heart of a review – we hope to test whether this approach is valuable to the Wellcome Trust and strategy more generally.

6. Finding the optimum way to review the impact of scientific research – and to use such information in strategic decision making – remains a major challenge. When attempting to assess the impact of a particular funding stream or funder over a substantial amount of time, we made the decision not to review on a micro basis (by looking at individual grants) but instead to take a macro, holistic view of the development of the field over time and consider the part that the Wellcome Trust and its funding has played within the field. We know that the Wellcome Trust has committed a substantial amount of its funding for malaria and specifically malaria-focused research over a long period. Support for malaria remains a cornerstone of its research funding strategy.

7. The review involved three complementary streams:

   - a landscape analysis
   - narrative case studies
   - an Expert Group

Landscape analysis

8. The landscape analysis had three components:

   - the Wellcome Trust funding analysis
   - an international scientific, policy and funding landscape analysis
   - a bibliometric analysis

Wellcome Trust funding analysis

9. A search of the Wellcome Trust's AS400 Grants System was conducted to identify malaria-related funding provided by the Wellcome Trust from 1990 onwards. This involved a search for specific search terms, as identified by Wellcome Trust Science Funding Staff. The full list of grants was then manually filtered to identify grants with a 'malaria' focus. After accounting for grant extensions and WTSI-based grants,[145] a total of 515 individual

145 Only a small minority of WTSI grants feature on the WT AS400 grant system. Wellcome Trust Sanger Institute data are, therefore, provided directly by WTSI, unless otherwise stated.

grants with a malaria focus have been funded by the Wellcome Trust over this time. An additional 52 grants were allocated for core support and infrastructure at Wellcome Trust Centres and the Trust's MOPs. In terms of the total financial value of funding committed by the Wellcome Trust, supplements and extensions to grants were included.

International scientific, policy and funding landscape analysis

10. To provide context to the development of malaria research over the time period under investigation, a Timeline of key events was produced by Wellcome Trust staff. The Timeline contains key historical scientific advances and/or 'firsts' that have taken place or had a major impact on malaria-related research, focusing particularly on 1990 to the present day. Each event on the Timeline has been classified as a 'scientific advance and knowledge', a 'policy development' or a 'funding development'.

11. The Timeline was used as a prompt during the consultation with the Wellcome Trust Expert Group, and their feedback on the content was invited; the revised version of the Timeline is included in Annex E.

Bibliometric analysis

12. To identify key trends in the type, nature and location of malaria research over this period, an analysis of publication outputs was conducted. This bibliometric analysis was conducted by Evidence, a Thomson Reuters business, and draws on the databases underlying the Web of Science, which include comprehensive coverage of more than 10 000 journals. All research papers included within the databases are allocated by Thomson Reuters to one or more of 253 different subject categories according to which journal the paper is published in; however, it is not possible to easily identify papers concerning malaria from these journal subject categories alone, so a subject filter was created[146] based on the following keywords and phrases:

    #1 malaria*
    #2 plasmodium
    #3 anopheles
    #4 "black water fever"

13. As such, the final dataset is thought to be a good proximate dataset for the field of malaria research. It contained 34 197 papers published over the period 1989–2008.[147]

14. In addition to information on the volume and origins of malaria research publications, a citation analysis was conducted to provide insight into the quality of papers emerging over the period. To account for variation in citation practices across fields and the impact of publication date on the number of citations accumulated, Evidence rebase (or normalise) all raw citation data to the world average in the relevant subject field in the year of publication. In the context of this report, 'highly cited papers' refers to those papers with an average rebased impact of at least 4 (i.e. they have received at least four times as many citations as the average paper published in that year in the same subject area).

15. With scientific research becoming an increasingly collaborative and multi-location activity, research papers are often linked to multiple authors based at more than one research institution. This report uses 'integer counting', meaning that any single paper counts as 'one' output for each author, institution and country contributing to its publication. For example, a paper with two authors from Harvard University, one author from the University of Texas and one author from the University of Oxford is counted as one output for each of the four authors concerned, one output for each of the three named institutions, and one output each for the USA and the UK. The tables of top countries, institutions and authors, therefore, will feature an element of double counting.

16. Evidence are able to supply data on UK organisations with a high degree of accuracy because they ensure that organisational name variants are reconciled into one name to counter the limitations of the raw Thomson Reuters address data on the papers themselves. For non-UK data, the tables in this report rely on the raw data, so paper numbers should be considered as indicative rather than absolute, although address reconciliation was effected for 'significant' research organisations. This methodology will have most impact where major organisations have several institutions or research centres (e.g. the MRC will be split into its constituent parts, whereas papers associated with the separate institutes of the National Centre for Scientific Research in France, Spanish National Research Council or the Chinese Academy of Sciences are all indexed under the name of the parent organisation).

Narrative case studies

17. A series of case studies were compiled to tell the story and highlight the key accomplishments of specific Wellcome Trust investments. These narratives were selected to reflect the range of funding types, from major infrastructure and fellowship support to collaborations.

Wellcome Trust Expert Group on Malaria

18. To complement the landscape analyses and case study work, a key component of this portfolio review was the engagement of malaria experts to provide a review of the key influences on the field and an assessment of the Wellcome Trust's role within this. Instead of consulting experts on an individual basis, we tested whether we could usefully employ a cohort of independent subject experts in a group setting.

19. Witness Seminars: in 1990, the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the history of medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history.[148] Among several other initiatives, the format of Witness Seminars was adopted to promote interaction between these different groups. The Witness Seminar is a specialised form of oral history, where several people (approximately 40) associated with a particular set of circumstances or events are invited to come together to discuss, debate and agree or disagree about their memories. The Witness Seminar initiative was led by Professor Tilli Tansey, then at the Wellcome Trust Centre for the History of Medicine, UCL, and after October 2010 at the School of History, Queen Mary, University of London. Further information about Witness Seminars can be found in volumes of *Wellcome Witnesses to Twentieth Century Medicine*.[149]

20. Drawing on the Witness Seminar approach to history and influence mapping, which was originally developed by the Institute of Contemporary British History in 1986, a small number of experts (n = 7, plus a Chair) were invited to debate and discuss the status of malaria research 1990–2009 over the course of an afternoon. Existing and increasing pressures on experts generated by the peer review system embedded into science funding have made it traditionally (and increasingly) difficult to involve experts in post-award review, where arguably they could play a major part in helping to consider future funding allocation at a more strategic level. Experts were selected on the basis of their expertise in the field and, to ensure the maximum relevance to the review's aims, at least half of the experts had a fairly good knowledge of the Trust over the period in question.

21. The Expert Group received a summary of the landscaping and bibliometric analysis in advance of their meeting hosted at the Wellcome Trust in April 2010. Under the Chairmanship of Professor Dan Colley, the discussion was framed around the broad areas of questioning seen in Table A. The meeting was recorded and the tapes transcribed. We found, alongside significant landscape analysis, that allowing our experts to be both retrospective and speculative enabled us to draw out learning from the past with future implications and to consider how this might link to current and potential future funding strategies.

Table A Outline agenda – Expert Group on malaria

Past/retrospective
Key impacts and influences on the field
What have been the key developments in the field – validation of Timeline?
What are the origins of the key developments?
What have been the key impacts within the field?
What have been the key impacts beyond the field?
Role of the Wellcome Trust and key influences on the field
What has been the role of the Wellcome Trust throughout this period?
Present
Field progression
Has field got as far as/gone in the direction you anticipated?
What are the current limiting factors?
Who is driving the agenda?
Future/prospective
Speculation and futures
What are the next big challenges in the field?
What might be Wellcome's role?
What strengths could the Wellcome Trust bring to the field?

146 The filter was created by Wellcome Trust scientific staff in collaboration with Evidence Ltd.

147 Because of the availability of citation data, the period of bibliometric analysis covers the period 1989–2008.

148 See 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicine* published by the Wellcome Trust, the Wellcome Trust Centre for the History of Medicine at University College London and Queen Mary, University of London.

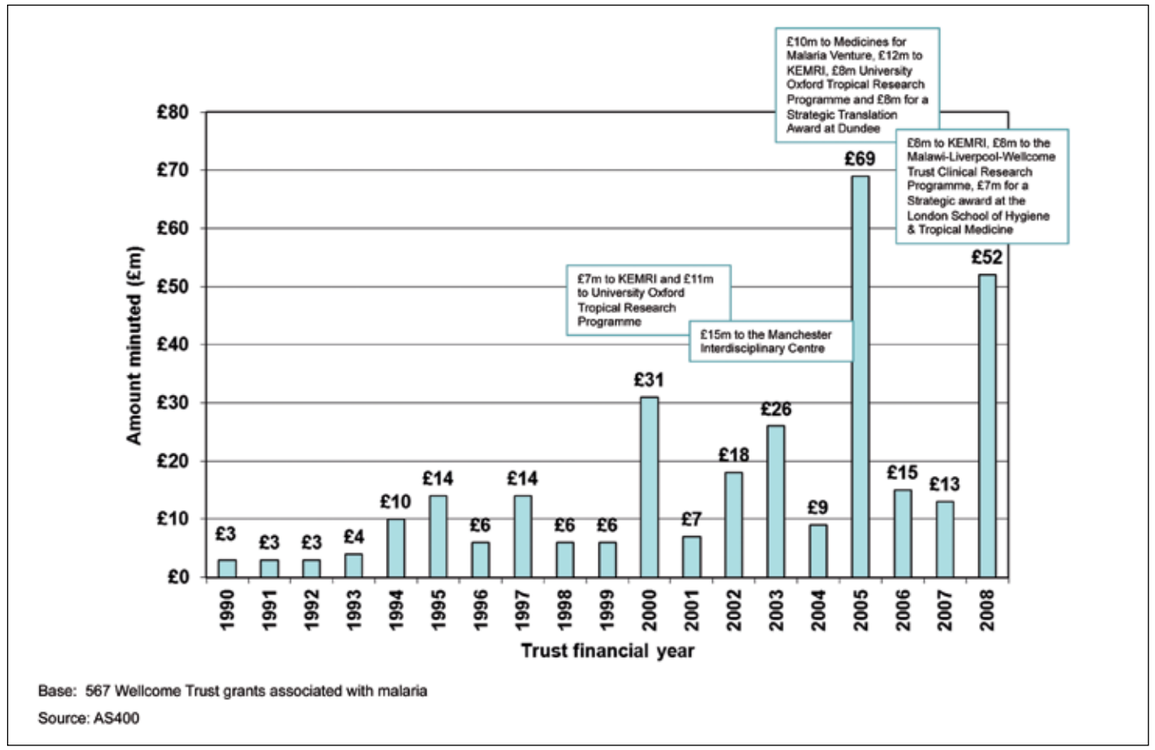
149 **www.history.qmul.ac.uk/research/biomed/index.html**

Annex C: Wellcome Trust funding for malaria

22. Between the financial years 1989/1990 and 2007/2008, the Wellcome Trust has awarded 515 grants,[150] mainly in responsive mode, to malaria-focused projects across all its funding divisions. These grants accounted for £189m, representing just over 3 per cent of the Trust's funding commitment over this time (excluding WTSI, £8.8m; see Table 3 and Table 3a). An additional £120m (52 grants) was allocated for core support and infrastructure at Wellcome Trust Centres and the Trust's MOPs. Approximately two-fifths (42 per cent by number, 42 per cent by value, 216 grants, or £80m) of malaria grant funding has been career-based, supporting individual researchers doing malaria-based projects via personal support schemes (Table 1). These personal support schemes include studentships (£9m), Early Career Fellowships (£8m), Intermediate Fellowships (£25m), and Senior and Principal research fellowships (£38m).

23. The larger proportion of funds (58 per cent by number, 58 per cent by value, 299 grants, or £109m) has been allocated to research and project support (equipment, university awards, strategic awards, and project and programme grants; Table 1). An additional £120m (52 grants) was allocated for core support and infrastructure at Wellcome Trust Centres and the MOPs.

Figure 1 Wellcome Trust grants supporting malaria research, including infrastructure grants to Wellcome Trust Centres and MOPs, 1990–2008



150 Wellcome Trust grant data in this review are not comparable with G-FINDER grant data. G-FINDER grant data include disbursements made only for active primary grants. Wellcome Trust funding data include all active and completed grants between the financial years 1989/1990 and 2007/2008.

Table 1 Wellcome Trust funding for malaria by grant type, excluding Wellcome Trust infrastructure funding for Wellcome Trust Centres and MOPs, 1990–2008[a]

Grant type	Number of grants	Percentage of total malaria grants[b]	Amount (£m)	Percentage of total malaria funding
Personal funding				
Studentship	77	15%	9	5%
Early career fellowship	54	10%	8	4%
Intermediate fellowship	58	11%	25	13%
Senior/principal research fellowship	27	5%	38	20%
Total personal funding	**216**	**42%**	**80**	**42%**
Research funding				
Project	181	35%	54	29%
Programme	21	4%	27	14%
Strategic award	2	0.4%	15	8%
Equipment	30	6%	6	3%
University award	7	1%	3	1%
Other**	58	11%	4	2%
Total research funding	**299**	**58%**	**109**	**58%**
TOTAL	**515**		**189**	

[a] Excludes funding to the WTSI because grant type data are not available in comparable format.

[b] Percentages are rounded and might not equal 100 per cent.

**Other; see Table 1a.

Base: 515 WT grants associated with malaria, excluding WT infrastructure funding for Wellcome Trust Centres and MOPs.

Source: AS400.

Table 1a Wellcome Trust funding for malaria research: other grant types

Other grant types	Number of grants	Amount awarded
Arts Small Awards	1	£28 070
Australian/New Zealand – Research Initiative Award	1	£60 700
European Interlaboratory Collaborative Support	1	£14 200
History of Medicine Research Leave Award	1	£39 444
History of Medicine Travel Grants	2	£2240
History of Medicine Research Expenses	1	£2000
Miscellaneous	1	£1815
PE People Award	1	£30 000
Research Development Grants For New Lecturers	1	£60 490
Sir Henry Wellcome Commemorative Awards	3	£494 677
Symposium	36	£403 632
Taxonomy Research Leave Award	1	£157 346
Technology Development Grant	3	£2 541 121
Vacation Scholarships	1	£660
Wellcome Short-Term Travel Grants	4	£45 349

Table 2 Wellcome Trust funding for non-UK-based malaria research by grant type, excluding infrastructure funding for Wellcome Trust Centres and MOPs, 1990–2008

Grant type	Number of grants	Percentage of total malaria grants[a]	Amount (£m)	Percentage of total malaria funding
Personal funding				
Studentship	10	5%	0.8	1%
Early career fellowship	38	19%	6	8%
Intermediate fellowship	30	15%	13	17%
Senior/principal research fellowship	15	7%	14	19%
Total personal funding	**93***	**46%**	**34**	**45%**
Research funding				
Project	63	31%	22	29%
Programme	7	3%	10	13%
Strategic award	1	0.4%	6	8%
Equipment	8	4%	1	1%
Other	29	14%	0.3	0.4%
Total research funding	**108**	**54**	**39**	**52%**
TOTAL	**201**		**75**	

[a] Percentages are rounded and might not equal 100 per cent.

*Of the 93 grants for non-UK-based personal research associated with malaria, 79 of these grants were fellowships based in low- or middle-income countries.

Base: 201 WT grants for non-UK-based research associated with malaria, excluding WT infrastructure funding for Wellcome Trust Centres and MOPs.

Source: AS400.

Table 3 Wellcome Trust (WT) and Wellcome Trust Sanger Institute (WTSI) funding for malaria research, 1990–2008[a, b, c]

Year	WT grant funding (£m)[d]	WT malaria,[e] including funding for WT Centres and MOPs		WTSI (£m)[b]	WTSI malaria	
		(£m)	Percentage of WT grant funding		(£m)[b]	Percentage of WTSI total funding
1990	53	3	6%			
1991	60	3	5%			
1992	86	3	3%			
1993	437	4	1%	4	0	0%
1994	193	10	5%	9	0	0%
1995	198	14	7%	28	0	0%
1996	168	6	4%	34	0	0%
1997	222	14	6%	16	0.5	3%
1998	212	6	3%	16	0.8	5%
1999	354	6	2%	38	0.5	1%
2000	480	31	6%	59	0.9	2%
2001	388	7	2%	54	0.7	1%
2002	419	18	4%	58	0.5	0.9%
2003	395	26	7%	65	0.4	0.6%
2004	258	9	3%	72	0.3	0.4%
2005	344	69	20%	77	0.4	0.5%
2006	325	15	5%	76	0.2	0.3%
2007	359	13	4%	73	0.9	1%
2008	525	52	10%	76	2.8	4%
TOTAL	**5476**	**309**	**6%**	**754**	**8.8**	**1%**

[a] Data from the Wellcome Trust grants system are 'commitment', and data from the WTSI are 'disbursement'.

[b] All WTSI data provided by the Sanger Institute.

[c] Data are rounded to the nearest £m.

[d] Excludes all funding to the WTSI and WT running costs.

[e] Excludes data to the WTSI.

Base: 567 Wellcome Trust grants associated with malaria, including WT funding for Wellcome Trust Centres and MOPs. The MOPs and WT Centres are included because some of the core support will have been used to support malaria-focused research.

Source: AS400.

Table 3a Wellcome Trust (WT) funding for malaria research, including and excluding infrastructure funding for Wellcome Trust Centres and MOPs, 1990–2008[a, b, c]

Year	WT grant funding (£m)[d]	WT malaria,[e] including infrastructure funding for WT Centres and MOPs		WT malaria, excluding infrastructure funding for WT Centres and MOPs	
		(£m)	Percentage of WT grant funding	(£m)	Percentage of WT grant funding
1990	53	3	6%	3	6%
1991	60	3	5%	2	3%
1992	86	3	3%	2	2%
1993	437	4	1%	3	1%
1994	193	10	5%	8	4%
1995	198	14	7%	11	6%
1996	168	6	4%	4	2%
1997	222	14	6%	7	3%
1998	212	6	3%	6	3%
1999	354	6	2%	6	2%
2000	480	31	6%	12	3%
2001	388	7	2%	7	2%
2002	419	18	4%	18	4%
2003	395	26	7%	8	2%
2004	258	9	3%	9	3%
2005	344	69	20%	38	11%
2006	325	15	5%	15	5%
2007	359	13	4%	11	3%
2008	525	52	10%	19	4%
TOTAL	**5476**	**309**	**6%**	**189**	**3%**

[a] Data from Wellcome Trust grants system are 'commitment', and data from WTSI are 'disbursement'.

[b] All WTSI data provided by Sanger Institute.

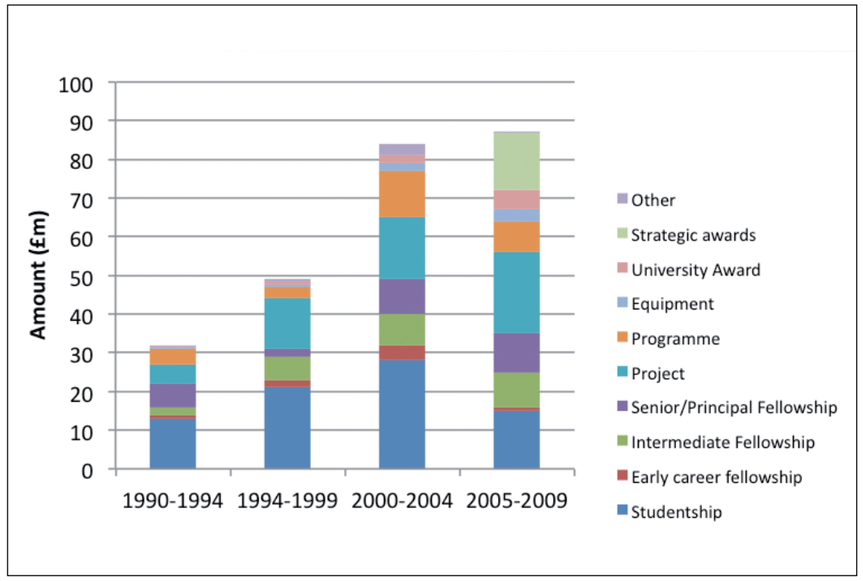
[c] Data are rounded to the nearest £m.

[d] Excludes all funding to the WTSI and WT running costs.

[e] Excludes data to the WTSI.

Base: 567 Wellcome Trust grants associated with malaria, including WT infrastructure funding for Wellcome Trust Centres and MOPs. The MOPs and WT Centres are included because some of the core support will have been used to support malaria-focused research.

Figure 2 Wellcome Trust funding for malaria research by grant type, 1990–2008[a]

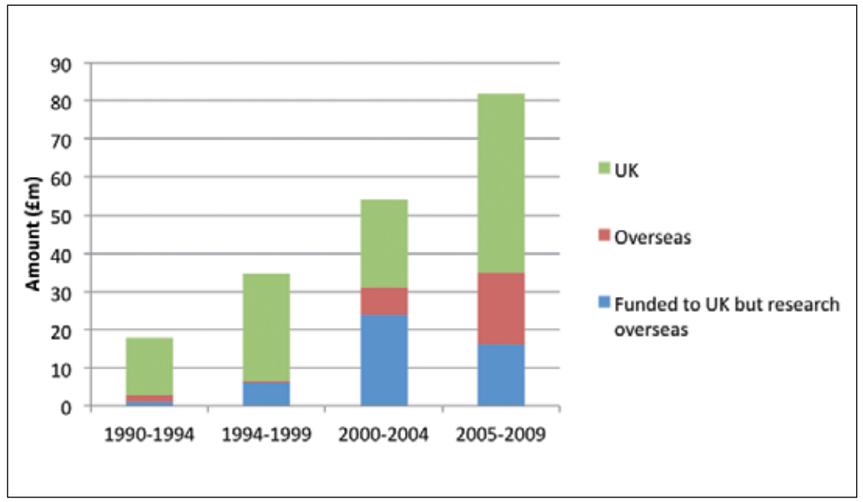


[a] Excludes funding to the WTSI because grant type data are not available in a comparable format.

Base: 515 Wellcome Trust grants associated with malaria, excluding Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

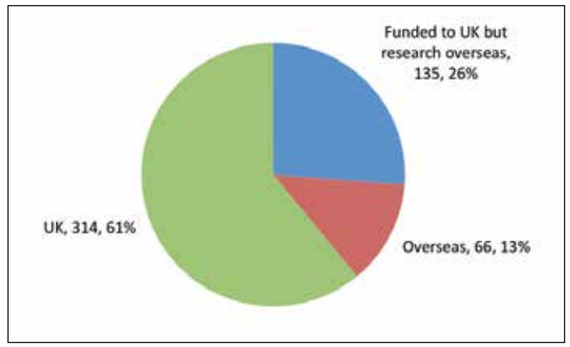
Figure 3 Wellcome Trust funding for non-UK- and UK-based malaria research, 1990–2008



Base: 515 Wellcome Trust grants associated with malaria, excluding Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

Figure 3b Number of Wellcome Trust grants for non-UK- and UK-based malaria research, 1990–2008*

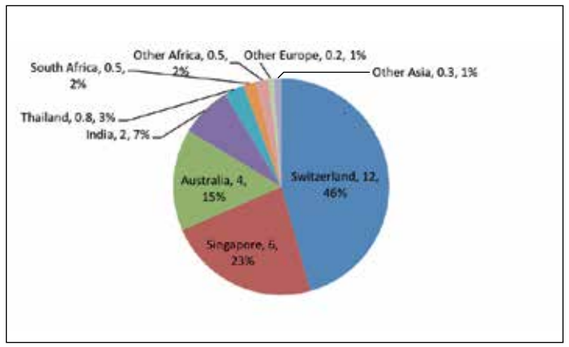


*Of the 201 grants featuring non-UK-based malaria research, 159 grants (£47m) were based in low- or middle-income countries. Of the 66 grants awarded to overseas institutions, 38 (£6.6m) were to low- or middle-income countries, and 20 grants (£5m) were for fellowships.

Base: 515 Wellcome Trust grants associated with malaria, excluding Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

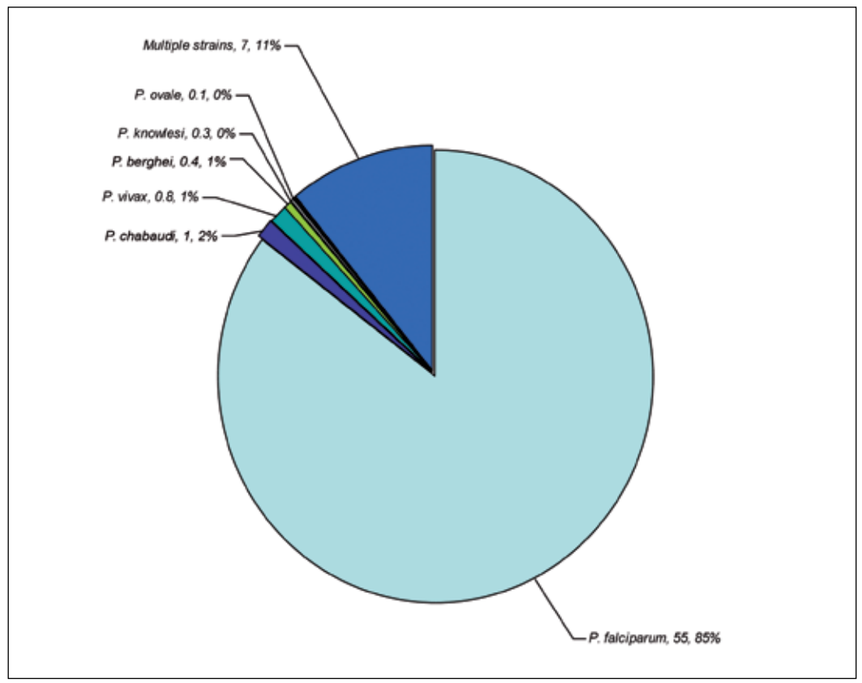
Figure 4 Countries with overseas Wellcome Trust funding in malaria research, 1990–2008 (£m)



Base: 66 Wellcome Trust grants associated with malaria in overseas locations, excluding Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

Figure 5 Strain of malaria specified in Wellcome Trust grants associated with malaria, 1990–2008



Base: 159 Wellcome Trust grants associated with malaria with a strain of malaria specified in the title or abstract.

Source: AS400.

Table 4 Institutions in receipt of the most Wellcome Trust funding for malaria research, including infrastructure grants to Wellcome Trust Centres and MOPs, 1990–2008 (top 20)

Institution	Amount (£m) [a]
University of Oxford, UK	119
KEMRI, Kenya	26
LSHTM, UK	19
University of Manchester, UK	18
University of Glasgow, UK	14
Liverpool School of Tropical Medicine, UK	14
University of Edinburgh, UK	13
University of Dundee, UK	12
University of Liverpool, UK	11
Medicines for Malaria Venture, Switzerland	10
Imperial College London, UK	8
Wellcome Trust Research Unit, Mahidol University, Thailand	7
Novartis Institute for Tropical Disease, Singapore	6
Wellcome Trust Clinical Research Unit, Cho Quan Hospital, Vietnam	4
University of Cambridge, UK	4
University College London, UK	4
St George's University Of London, UK	2
Keele University, UK	2
University of Leeds, UK	2
King's College London, UK	0.8

[a] Data are rounded to the nearest £m.

Base: 567 Wellcome Trust grants associated with malaria, including Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

Table 4a Institutions in receipt of the most Wellcome Trust funding for malaria research, excluding Infrastructure grants to Wellcome Trust Centres and MOPs, 1990–2008 (top 20)

Institution	Amount (£m) [a]
University of Oxford, UK	71
University of Dundee, UK	12
University of Edinburgh, UK	12
University of Liverpool, UK	10
University of Glasgow, UK	10
LSHTM, UK	10
Medicines for Malaria Venture, Switzerland	10
Imperial College London, UK	8
Novartis Institute for Tropical Disease, Singapore	6
Liverpool School of Tropical Medicine, UK	6
University of Cambridge, UK	4
University College London, UK	4
University of Manchester, UK	3
St George's, University of London, UK	2
International Centre Cointrin, Switzerland	2
Royal Melbourne Hospital, Australia	2
Kenya Medical Research Institute, Kenya	2
Keele University, UK	2
University of Leeds, UK	2
International Centre for Genetic Engineering, India	1

[a] Data are rounded to the nearest £m.

Base: 515 Wellcome Trust grants associated with malaria, excluding Wellcome Trust funding for infrastructure at WT Centres and MOPs.

Source: AS400.

Table 5 Researchers in receipt of most Wellcome Trust (research and personal support) funding for malaria research, including infrastructure grants to Wellcome Trust Centres and MOPs, 1990–2008 [a, b] (top ten)

Researcher	Current host institution	Amount (£m) [b]	Grant type
Professor Kevin Marsh	University of Oxford	25	Infectious Disease Fellowship; Senior Research Fellowship; career post in tropical medicine; programme (x2); collaborative project; Strategic Award
Professor Chris Newbold	University of Oxford	15	Programme (x4); project (x9)
Professor Nick White	University of Oxford	13	Project (x4); programme; Strategic Award; Principal Research Fellowship
Professor Adrian Hill	University of Oxford	12	Project (x4); Principal Research Fellowship; Strategic Award
Dr Christopher Hentschel	MMV, Switzerland	12	International Partnership Award (x2)
Professor Michael Ferguson	University of Dundee	8	Strategic Translation Award
Professor Robert Heyderman	Liverpool School of Tropical Medicine	8	Strategic Award
Professor Brian Greenwood	LSHTM	7	Strategic Award
Professor Robert Snow	University of Oxford	6	Collaborative project; project; Senior Research Fellowship (x2); Principal Research Fellowship
Dr Alex Matter	Novartis Institute for Tropical Disease, Singapore	6	Strategic Translation Award

[a] Excludes funding to the WTSI.

[b] Data are rounded to the nearest £m.

Base: 567 WT malaria grants, including infrastructure grants to Wellcome Trust Centres and MOPs.

Source: AS400.

Table 5a Researchers in receipt of most Wellcome Trust (research and personal support) funding for malaria research, excluding infrastructure grants to Wellcome Trust Centres and MOPs, 1990–2008 [a, b] (top ten)

Researcher	Current host institution	Amount (£m) [b]	Grant type
Professor Chris Newbold	University of Oxford	15	Programme (x4); project (x9)
Dr Christopher Hentschel	MMV, Switzerland	12	International partnership award (x2)
Professor Adrian Hill	University of Oxford	9	Project (x4); Principal Research Fellowship
Professor Michael Ferguson	University of Dundee	8	Strategic Translation Award
Professor Robert Snow	University of Oxford	6	Collaborative project; project; Senior Research Fellowship (x2); Principal Research Fellowship
Dr Alex Matter	Novartis Institute for Tropical Disease, Singapore	6	Strategic Translation Award
Professor Malcolm Molyneux	University of Liverpool	5	Programme (x2); project (x3); Research Leave Award (x2)
Professor Andrew Waters	University of Glasgow	5	Principal Research Fellowship
Professor Kevin Marsh	University of Oxford	4	Senior Research Fellowship; career post in tropical medicine; programme; collaborative project
Professor Nick White	University of Oxford	4	Project (x4); Principal Research Fellowship

[a] Excludes funding to the WTSI.

[b] Data are rounded to the nearest £m.

Base: 567 WT malaria grants, including infrastructure grants to Wellcome Trust Centres and MOPs.

Source: AS400.

Table 6 Wellcome Trust Senior and Principal Research Fellows focusing on malaria research funded 1990–2008,[a] including infrastructure grants to Wellcome Trust Centres and MOPs

Year	Researcher	Institution	Grant type
1986	Professor Julian Crampton	University of Liverpool	Senior Research Fellow – basic
1988	Professor Alan Cowman	Royal Melbourne Hospital	Senior Research Fellow – Australia
	Professor Adrian Hill	University of Oxford	Senior Research Fellow – clinical
1989	Professor David Arnot	University of Edinburgh	Senior Research Fellow – basic
1990	Professor Eleanor M Riley	University of Edinburgh	Senior Research Fellow – basic
	Professor Kevin Marsh	University of Oxford	Senior Research Fellow – clinical
1991	Professor Nick White	University of Oxford	Principal Research Fellow –renewed 1999
1992	Dr S Foote	Royal Melbourne Hospital	Senior Research Fellow – Australia
1994	Professor Robert W Snow	University of Oxford	Senior Research Fellow – renewed 2000
	Professor Sanjeev Krishna	St George's University of London	Senior Research Fellow – clinical
1995	Professor Adrian Hill	University of Oxford	Principal Research Fellow – renewed 2005
	Professor Alan Fairlamb	University of Dundee	Principal Research Fellow
2000	Dr Chetan Chitnis	International Centre for Genetic Engineering and Biotechnology, New Delhi	Senior Research Fellow – India
2001	Dr Amit Sharma	International Centre for Genetic Engineering and Biotechnology, New Delhi	Senior Research Fellow – India
	Dr Stephen Rogerson	University of Melbourne	Senior Research Fellow – Australia
2002	Dr Heinrich Hoppe	University of Cape Town	Senior Research Fellow – South Africa
	Dr Pushkar Sharma	National Institute of Immunology, New Delhi	Senior Research Fellow – India
	Dr J Alexandra Rowe	University of Edinburgh	Senior Research Fellow – renewed 2008
2003	Dr Suman Dhar	Jawaharlal Nehru University	Senior Research Fellow – India
	Professor Charles Newton	University College London	Senior Research Fellow – renewed 2008
2004	Professor Sylke Muller	University of Glasgow	Senior Research Fellow – basic
2005	Dr Michael English	University of Oxford	Senior Research Fellow – public health and tropical medicine
	Dr Thomas Williams	University of Oxford	Senior Research Fellow – public health and tropical medicine
2006	Professor Robert Snow	University of Oxford	Principal Research Fellow
	Dr Simon Hay	University of Oxford	Senior Research Fellow – basic
	Dr Steven Sinkins	University of Oxford	Senior Research Fellow – basic
2008	Professor Andrew Waters	University of Glasgow	Principal Research Fellow
	Dr Britta Urban	Liverpool School of Tropical Medicine	Senior Research Fellow – basic

[a] Excludes all funding to the WTSI.

Base: Senior and principal research fellowships in the cohort of 567 Wellcome Trust grants associated with malaria, including infrastructure funding to WT Centres and MOPs.

Source: AS400.

Table 7 Overview of malaria-focused R&D at the Wellcome Trust MOPs

Title	Established	Funding	Aim	Key accomplishments and discoveries (to end 2009)
Major Overseas Programmes				
The Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research (MORU) Chairman: Professor Nick White Director: Professor Nick Day	1979	The Trust provided £21.6m of funding since 2005, including around £3m of core funding each year.	Aims to fight infectious tropical diseases affecting rural communities in Asia and low-income countries elsewhere by creating effective and practical means of diagnosing and treating malaria and other diseases such as typhus, melioidosis and leptospirosis.[151]	• Pioneered the development, evaluation and introduction of ACT, now the frontline treatment for uncomplicated malaria. • Conducted the South-east Asian quinine artesunate malaria trial (SEAQUAMAT), demonstrating that the artemisinin drug artesunate reduced mortality by 35 per cent compared with quinine.[152] This research formed the basis of the WHO's management guidelines in 2006.[153] • Conducted the largest ever study in severe malaria (AQUAMAT), demonstrating that artesunate reduces the mortality of severe malaria in African children by 22 per cent compared with quinine and is highly cost effective.[154] • 2010: Professor Nick White, Chairman of the Wellcome Trust South-east Asian Tropical Medicine Research Programmes, received the Gairdner Award.
Shoklo Malaria Research Unit (SMRU), part of the Wellcome–Mahidol University–Oxford Tropical Medicine Research Programme Director: François Nosten	1986	SMRU has received funding from the pharmaceutical industry, WHO, the European Union and VIHPAL (French Government). In 2000, SMRU (via Oxford University) was awarded a grant from the Bill and Melinda Gates Foundation to extend the control of malaria to the entire Tak Province in collaboration with the Thai Ministry of Health.	Work conducted aims to be of direct benefit to the local community. SMRU also aims to provide information useful to other worldwide populations living with malaria.	• 1991: Nick White was awarded a Principal Research Fellowship. • Provided the first detailed description of the effects of malaria during pregnancy in South-east Asia.[155, 156] • Developed a system of antenatal care that has eliminated maternal malaria-related mortality.[157] • Established the safety of the artemisinin derivatives in pregnancy.[158] • Defined the development of mefloquine drug resistance in this area and produced extensive information (in more than 5000 patients) of its adverse effects and predictors of treatment response.[159] • Assessed the benefit of high-dose halofantrine and discovered its cardiotoxicity.[160] • Treated more than 10 000 patients with artemisinin derivatives (the largest single-centre study in the world). Conducted the first studies to look at a possible cumulative toxicity of this family of drugs in humans. • Documented for the first time the impact of artesunate on the transmission of malaria and the spread of resistance and pioneered the use of ACT.[161,162] • Evaluated the USA-manufactured malaria vaccine SPf66 in its most detailed and carefully conducted trial. • Documented the effects of *P. vivax* in pregnancy.[163] • 2008: Francois Nosten won the Christophe and Rodolphe Merieux Foundation Prize (€400 000) from the Institut de France to honour his ground-breaking malaria research.

151 **www.tropmedres.ac/**

152 Dondorp A. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

153 WHO. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010.

154 Dondorp A et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010;376(9753):1647–57.

155 Nosten F et al. Malaria during pregnancy in an area of unstable endemicity. Trans R Soc Trop Med Hyg 1991;85(4):424–9.

156 Luxemburger C et al. Effects of malaria during pregnancy on infant mortality in an area of low malaria transmission. Am J Epidemiol 2001;154(5):459–65.

157 Tan SO et al. Thrombocytopaenia in pregnant women with malaria on the Thai-Burmese border. Malaria J 2008;7:209.

158 McGready R et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. Trans Royal Soc Trop Med Hyg 1998;92(4):430–3.

159 Nosten F et al. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. Lancet 1991;337:1140–3.

160 Nosten F et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993;341:1054–6.

Title	Established	Funding	Aim	Key accomplishments and discoveries (to end 2009)
Kenya and KEMRI–Wellcome Trust Research Programme Director: Professor Kevin Marsh Quinquennial review in July 2010. See case study.	With links to the Trust since the 1940s, the Programme was formally established in 1989, in partnership with KEMRI.	In 2010, £32.5m was awarded by the Wellcome Trust Major Overseas Programme to support activities for the next five years. The programme has developed a core group of productive researchers who hold £25m of competitively awarded grants and contribute high-quality papers to the scientific literature. In 2008, a £9m Wellcome Trust Strategic Award was awarded to help train local researchers. **Local collaborators:** Ministry of Health; Ministry of Education, Science and Technology; and Kenyatta National Hospital. **National universities and tertiary institutions:** Egerton University; Jomo Kenyatta University of Agriculture and Technology; Kenyatta University; Maseno University; Masinde Muliro University of Science and Technology; and University of Nairobi. **International collaborators:** MRC; Centres for Diseases Control and Prevention (CDC); International Development Research Centre; Japan International Cooperation Agency (JICA); KEMRI–Wellcome Trust, Mahidol University, Bangkok, Thailand; Royal Tropical Institute, Amsterdam; United States Agency for International Development (USAID); Walter Reed Army Institute of Medical Research; World Association of Industrial and Technologist Research Organizations (WAITRO); WHO; and the Drugs for Neglected Diseases Initiative. **Regional collaborators:** Blair Research Centre, Zimbabwe; Ethiopia Health and Nutrition Research Institute, Ethiopia; Makerere University Medical School; Medical Research Council of South Africa; National Institute of Medical Research, Tanzania; Noguchi Memorial Institute of Medical Research, Ghana; Suez Canal University, Egypt; and University of Zambia Medical School, Zambia.[164]	Conducts basic and clinical research in parallel, with results feeding directly into local and international health policy, and aims to expand the country's capacity to conduct multidisciplinary research that is strong, sustainable and internationally competitive.	• 1988: A £0.5m award to Professor David Warrell at the Wellcome-KEMRI/Oxford Malaria Unit, Kilifi, for a study of severe *P. falciparum* malaria in African children. • Developed evidence-based framework for international efforts to define the burden and spatial extents of malaria at regional, continental and global scales. • Demonstrated the key role of immune responses to variant antigens expressed on the malaria-infected red cell surface. • Identified common variant antigens associated with severe malaria and with immunity to disease. • Conducted innovative research on the community perceptions of research and the consent process, stimulating international interest in medical ethics in resource-poor countries.[165] **Translational research and policy formation** • Carried out one of the four key large-scale trials of impregnated bednets on which current international policy is now based. • Carried out a major study on the intermittent preventative treatment of malaria in pregnancy, on which national and international policy is now based. • Developed a training programme for improving the treatment of childhood fevers in rural areas, which has subsequently been adopted as a national programme and has had a major influence on programmes in other African countries. • Provided technical support to the Ministry of Health to establish a National Malaria Strategy, launched by the Government of Kenya in 2001. • Developed Inpatient Care Guidelines for Kenya in collaboration with the Division of Child Health, Ministry of Health, using a substantial body of research evidence generated by the Programme over the past 5–10 years as the standard of care for children in Kenya and used in international guidelines (*Child Advocacy Manual 2002* and *WHO Pocket Book of Hospital Care for Children*, 2004). • Developed and hosted the Network for Surveillance of Pneumococcal Disease in the East African Region (netSPEAR) and the East African Network for Monitoring Antimalarial Treatment (EANMAT), working together with ministries of health, research institutions and international organisations in seven East African countries to provide crucial information for vaccination and drug policy in the region. **Capacity building** • Expanded the PhD training programme. In 2002, the unit was recognised as an Open University sponsoring establishment, and the majority of students are now registered through this mechanism. • 2005: Researched the scale of malaria. Their estimate of 515 million clinical episodes of *P. falciparum* suggests that tackling malaria will require even greater attention than governments and health agencies have anticipated.[166] • 2008: Deaths have fallen by 75 per cent over the past five years. Over longer time frames, 18 years of hospital surveillance data reveal a steady decline in malaria – testament to the success of new drug programmes, the use of insecticide-treated bednets and other measures. • 2008: Clinical trials showed that pregnancy alters the efficacy of antimalarials and that the doses of medicines given to pregnant women were too low – findings that led to a revision of WHO guidelines. • 2008/2009 research brought the malaria vaccine candidate RTS,S/AS closer to phase III clinical trials.

Title	Established	Funding	Aim	Key accomplishments and discoveries (to end 2009)
The Vietnam Research Programme and Oxford University Clinical Research Unit (OUCRU) Chairman: Professor Nick White Director: Professor Jeremy Farrar	1991	The Wellcome Trust has supported the Programme for almost 20 years and recently extended its core support through to 2015.	Monitoring and understanding drug resistance in *P. falciparum* and *P. vivax*.	• Played a major part in establishing the role of artemisinin derivatives for the treatment of falciparum malaria. • Helped to establish the burden of vivax malaria in South-east Asia, showing that vivax – which was previously considered relatively harmless – is common and can cause severe disease.[167] • Has developed strong links with HTD and other hospitals in Ho Chi Minh City, Hanoi and other regions of Vietnam. In February 2006, an OUCRU office in Hanoi was opened.
Malawi–Liverpool–Wellcome Trust Clinical Research Programme Director: Professor Robert Heyderman	1995	2008: The Programme was awarded £8.6m of core funding by the Trust. Core funding from the Wellcome Trust maintains the centre, and Trust-funded research fellowships and project grants have been awarded to many participating biomedical scientists and clinicians.[168]	Focuses on five major multidisciplinary research themes, namely malaria and brain diseases, therapeutics in the tropics, severe bacterial infection, mucosal and vaccine immunity, and health in the population.[169]	• Advanced malaria treatment and monitoring, notably through the development of the Blantyre Coma Score, a system that helps to monitor children in malaria-induced coma. • 2005/2006: Conducted studies that led to the change in policy and practice for LapDap usage, and rectal artesunate for comatose children with malaria. • Conducted the biggest autopsy study ever of children with fatal malaria showing that some, who had died of what seemed to be severe malaria, had received a different diagnosis. This research helped the team to understand the importance of changes in the retina associated with malarial infection, which may lead to improved diagnosis of the disease. • Worked with College of Medicine at the University of Malawi to improve diagnosis and treatment of diseases such as malaria, HIV/AIDS, anaemia and tuberculosis. This research has been used to advise healthcare strategy in Malawi and has also contributed to the worldwide fight against these diseases. • The centre has also trained local doctors and graduates.

161 Nosten F et al. Effects of artesunate-mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study. Lancet 2000;356(9226):297–302.

162 Dondorp A et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

163 Nosten F et al. Effects of Plasmodium vivax malaria in pregnancy. Lancet 1999;354:546–9.

164 **www.kemri-wellcome.org**

165 **www.wellcome.ac.uk/Funding/International/Global-health-research/Major-Overseas-Programmes/Kenya/**

166 Snow RW et al. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature 2005;434(7030):214–7.

167 **www.wellcome.ac.uk/Funding/International/Global-health-research/Major-Overseas-Programmes/Vietnam/**

168 **www.wellcome.ac.uk/Funding/International/Global-health-research/Major-Overseas-Programmes/Malawi/**

169 **www.mlw.medcol.mw/research.html**

Table 8 Overview of malaria-focused collaborations, partnerships and resources where the Wellcome Trust has played a major part

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
Major Overseas Programmes				
Malaria Genome Project	1996	The £18.5m *Plasmodium falciparum* project was funded in the UK by the Wellcome Trust (£8m) and in the USA by the Burroughs-Wellcome Fund (£4.9m), the National Institute of Allergy and Infectious Diseases (£2.2m), and the US Department of Defence (£3.4m).	To determine the sequence of the *P. falciparum* genome	• Completed the genome sequence of the *P. falciparum* parasite, published in *Nature* in 2002.[170] • Responsibility for sequencing the genome was split on a chromosome-by-chromosome basis between three sequencing centres: WTSI (UK), chromosomes 1, 3–9 and 13; TIGR/Naval Medical Institute (USA), chromosomes 2, 10, 11 and 14; and Stanford University (USA), chromosome 12.
The International Anopheles Genome Project	1999	Funded principally by the US National Institute of Allergy and Infectious Diseases and by the French Government, with the World Health Organization/Tropical Disease Research (WHO/TDR, Geneva, Switzerland) programme providing a coordinating role and assisting in database development. The Wellcome Trust supported this project through the annotation of the genome by Ensembl – the latter being a collaboration between the European Bioinformatics Institute and the WTSI.	To determine the sequence of the genome of *Anopheles gambiae*.	• Completion of the genome sequence of *A. gambiae*, published in *Science* in 2002.[171] • In 2007, Sharakhova *et al.* improved the physical map and assembly of the *A. gambiae* genome.[172]
Multilateral Initiative on Malaria (MIM)	1998	The Wellcome Trust helped establish the MIM, an alliance of organisations and individuals concerned with malaria. The Wellcome Trust provided the first Secretariat, for a period of 18 months (1997–1999).[173] An audit of international research activity in malaria was carried out by the Wellcome Trust in 1996 and again in 1999. The Wellcome Trust's International Programmes produced a report, 'Strengthening Health Research in the Developing world: Malaria Research Capacity in Africa', to provide evidence to guide the development of the MIM.[174]	MIM is an alliance of individuals, funding partners, and four autonomous constituents: the MIM/TDR, MIMCom, MR4 and the MIM Secretariat.[175]	• Establishment of the MIM Secretariat. The MIM Secretariat convened the first, second, third, fourth and fifth MIM Pan-African Malaria Conferences in Dakar, Senegal (1997), Durban, South Africa (1999), Arusha, Tanzania (2002), Yaoundé, Cameroon (2005) and Nairobi, Kenya (2009). • The MIM Secretariat is the coordinating arm of the MIM, initially based in London at the Wellcome Trust (1997–1999), then based at Fogarty International Center at NIH, USA (1999–2001), the Karolinska Institutet/ Stockholm University, Stockholm, Sweden (2003–2005), and African Malaria Network Trust (AMANET), Dar es Salaam, Tanzania (2006–2010). On 15 October 2010, the Biotechnology Centre of the University of Yaounde I/ Amsterdam Medical Centre officially became the new host of the MIM Secretariat. • Creation of Malaria Research and Reference Reagent Center (MR4). MR4 is a biological resource centre providing research reagents for free to malaria scientists. The MR4 is located at the American Type Culture Collection (ATCC) in Manassas, Virginia, USA. It has more than 300 reagents, including antibodies, antigens, plasmids, expressed sequence tag (EST) clones, polymerase chain reaction (PCR) primers and genomic/cDNA libraries, and several different species and strains of *Plasmodium* and *Anopheles*. MR4 has supplied reagents for malaria research to 19 African countries. • Creation of MIM Communication Network (MIMCom). MIMCom is based at the National Library of Medicine (NLM) in the USA and comprises telecommunications, information access, and new tools for research, training and evaluation. MIMCom has built fast and reliable internet connections at 27 internet satellite sites in 14 African countries. • Creation of MIM/TDR – embedded in the UNICEF/ UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. • Since its inception, more than 220 graduate-level scientists have been trained in 33 institutions in Africa.

170 Gardner MJ et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 2002;419:498–511.

171 Holt RA et al. The genome sequence of the malaria mosquito Anopheles gambiae. Science 2002;298(5591):129–49.

172 Sharakhova et al. Update of the Anopheles gambiae PEST genome assembly. Genome Biol 2007;8(1):R5.

173 www.mimalaria.org/eng/historyandevolution.asp

174 www.wellcome.ac.uk/stellent/groups/corporatesite/@sitestudioobjects/documents/web_document/wtd003224.pdf

175 www.mimalaria.org/eng/aboutmim.asp

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
Medicines for Malaria Venture (MMV)[176]	1999 (the Wellcome Trust has been a partner since 2002)	Initial MMV funding: US$4 million from the Governments of Switzerland, the UK (Department for International Development, or DFID) and the Netherlands, The World Bank, and the Rockefeller Foundation. In 2003, the Gates Foundation pledged US$40 million over five years. In 2005, the Wellcome Trust and DFID pledged £10 million each over five years and BMGF US$100 million over five years. In 2006, the Irish government donated €9 million over three years. In 2007, the Gates Foundation donated an additional US$37 million over two years and the NIH awarded its first donation of US$5.6 million over five years. In 2008, the Spanish government became MMV's sixth public sector donor with a grant of €3 million. In 2009, MMV received its fifth and largest grant from the Gates Foundation (US$115 million), in addition to new funding from DFID (US$30 million) – both to support MMV over five years.[177] In 2011, the Trust provided a further award of £5m.	MMV's mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating the delivery of new, effective and affordable antimalarial drugs.	• A study by the Ministry of Health and MMV showed that heavily subsidising ACTs by 90 per cent or more results in greater uptake of these life-saving medicines in the private sector. The availability of ACTs at minimal cost led to a rapid increase of ACT stocks and use by children under the age of five, as well as a fall in market share of ineffective antimalarials such as chloroquine.[178] • 2009: Novartis and MMV launched the first high-quality ACT formulated especially for children – Coartem® Dispersible. By June 2011, 72 million treatments of this life-saving medicine had been delivered to 35 countries. • 2010: Guilin Pharmaceutical Artesunate injection received WHO prequalification. The trial, led by Professor Nick White, demonstrated that artesunate reduced the mortality rate by 22.5 per cent. In response to this important data, the WHO updated their guidelines to recommend artesunate injection as the first-line treatment for severe malaria in African children. • 2010: MMV and Shin Poong Pharmaceutical Co Ltd developed a new ACT. Pyramax is a fixed-dose combination of pyronaridine and artesunate that has completed a program of clinical trials demonstrating more than 95 per cent efficacy at day 28. The Pyramax dossier was submitted to the European Medicines Agency (EMA) for regulatory approval at the end of March 2010. • 2011: MMV and partners completed a series of tests to determine which marketed and in-development antimalarials have gametocidal or transmission-blocking capability. The data will be crucial in informing the development of the next-generation antimalarials to eradicate malaria. • 2011: Funding agreed with Anacor Pharmaceuticals and MMV to extend the existing development agreement to fund the clinical development of AN3661, a boron-based drug candidate for the treatment of malaria. • 2011: Two new medicines (Sigma-tau's DHA-piperaquine and artesunate pyronaridine) are currently awaiting regulatory approval, and MMV has 14 innovative novel molecules in the pipeline with the potential to tackle drug resistance. Fifty projects are specifically targeting malaria eradication.[179]
MalariaGEN[180]	2005	MalariaGEN was formally established in 2005 as part of the Grand Challenges in Global Health initiative, with joint funding from the Wellcome Trust and the Gates Foundation through the Foundation for the National Institutes of Health.[181] In 2005, Professor Dominic Kwiatkowski received a Wellcome Trust award (£4.3m) from the Grand Challenges in Global Health initiative to integrate and build on the work of malaria research groups around the world through the formation of MalariaGEN.	To develop cost-effective genome-based technologies that could provide early warning of the emergence and spread of new forms of drug resistance.	• 2009: Published the first genome-wide association study conducted in Africa.[182] • Discovered a method to detect the malaria-protective effect of the sickle variant and also pinpointed the precise spot in the genome where this malaria-protective factor is located. • 2009: Researchers carried out a GWA study in search of genetic variants associated with resistance to fatal forms of malaria.[183]

176 **www.mmv.org/**

177 Poll E, Banerji J (eds). 2009. Medicines for Malaria Ventures: 10th Anniversary. **www.mmv.org/sites/default/files/uploads/docs/publications/MMV_10th_Anniversary.pdf**.

178 **www.mmv.org/achievements-challenges/achievements/making-quality-affordable**

179 **ec.europa.eu/research/horizon2020/pdf/contributions/post/international_organisations/medicines_for_malaria_venture_-_mmv.pdf**

180 **www.malariagen.net/home**

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
The Malaria Atlas Project[184]	2005	Led by Robert Snow and Simon Hay. Robert Snow was supported by the Wellcome Trust through a Senior Research Fellowship (£3.4m), and Simon Hay was also supported through a Senior Research Fellowship (£1.14m). This work was also supported by Wellcome Trust Collaborative grants (£370 000).	To assemble medical intelligence and survey data to provide evidence-based maps on the distribution of malaria risk, human population, disease burdens, mosquito vectors, inherited blood disorders, and malaria financing and control worldwide.	• Produced the first global malaria risk map to be developed in more than 40 years.[185] • Collected information from 3670 communities in 79 countries and represents the single largest repository of contemporary information of malaria risk.[186] • Assembled a unique spatial database of linked information based on medical intelligence and satellite-derived climate data to constrain the limits of malaria transmission and the largest ever archive of community-based estimates of parasite prevalence.[187] • Defined the spatial limits of *P. falciparum* transmission, showing the disease affected 2.37 billion people in 2007.[188] • Showed how funding disparities had achieved varied intervention coverage in Africa by 2007: 90 million African children remained unprotected by an insecticide-treated mosquito net in 2007.[189] • Outlined the implications of population-at-risk for global financing of control and elimination: funding from international and bilateral agencies toward malaria control remains less than $1 per year per person at risk (a shortfall of between 50 per cent and 450 per cent of projected need, depending on the country).[190] • Showed that strategies to combat disease are likely to have a much greater effect on the distribution of malaria than climate change.[191] • Showed the intensity of transmission within these margins of risk, revealing three-quarters of the global population live in areas of low risk and suggesting elimination is feasible in many areas outside of Africa. [192] • Developed a map of malaria risk for Kenya in 2009.[193] The Malaria Atlas Project has shown that there could have been between 349 and 552 million clinical cases of *P. falciparum* malaria worldwide in 2007.[194] • Developed an Atlas of Malaria-Eliminating Countries in 2011, with the Global Health Group at the University of California, San Francisco. • Developed a global map of *P. falciparum* malaria for the year 2010.[195] • Developed a global map of vivax malaria endemicity in 2012.[196]
Malaria Drug research at The Novartis Institute for Tropical Diseases (NITD)	2007	The Wellcome Trust, the Singapore Economic Development Board and MMV pledged more than £10m in funding, and NITD manage the programme and conduct research jointly with several institutions, including the Genomics Institute of the Novartis Research Foundation and the Swiss Tropical Institute.	To achieve the ambitious goal of producing a robust pipeline of drug candidates to treat dengue, tuberculosis and malaria. Aim by 2012 to have at least two drug candidates in patient trials.[197]	• Research at NITD focuses on the identification of compounds that can be used to produce a single-dose cure for *P. falciparum* and a cure for *P. vivax*.[198] • A high-throughput cell-based screen of 1.7 million compounds identified 6000 able to inhibit the growth of *P. falciparum* in red blood cells.[199] • 2006: A Wellcome Trust grant of £6.4m awarded to Professor Alex Matter for a programme of drug discovery research in malaria.[200]

181 **www.malariagen.net/about/funding**

182 Malaria Genomics Epidemiology Network. A global network for investigating the genomic epidemiology of malaria. Nature 2008;456:732–7.

183 Jallow et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. Nat Genet 2009;41:657–65.

184 **www.map.ox.ac.uk/**

185 Hay SI et al. A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 2009;6:e48.

186 **www.map.ox.ac.uk/**

187 **www.map.ox.ac.uk/milestones/**

188 Guerra et al. The limits and intensity of Plasmodium falciparum transmission: implications for malaria control and elimination worldwide. PLoS Med 2005;5(2):300–11.

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
The Human Heredity and Health in Africa (H3Africa)[201]	2010	Over the next five years, H3 Africa will receive at least £8m from the Wellcome Trust and £3.4m a year from the NIH. The NIH also provided US$750 000 to fund the initial project start-up.	To facilitate a contemporary research approach to the study of genomics and environmental determinants of common, non-communicable disorders such as heart disease and cancer, as well as infectious diseases such as malaria. The overall aim is to improve the health of African populations.[202]	• Researchers funded under H3 Africa will establish or enhance local research facilities in their home country. This will enable them to use genome-wide scanning and sequencing technologies to identify genetic changes that contribute to the diseases and disorders selected for study.
PATH Malaria Vaccine Initiative (MVI)	1999	Established after a grant from the Bill and Melinda Gates Foundation. The trials were funded by PATH MVI, but the facilities at the KEMRI–Wellcome Trust Research Programme were used for the phase II RTS,S trials and are still being used for the ongoing phase III trials.	To accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. MVI have a multi-pronged approach to developing a next-generation vaccine by 2025.	• 2011: GlaxoSmithKline Biologicals candidate malaria vaccine RTS,S was in large multi-centre phase III trials. This is the leading malaria vaccine, which has shown promising efficacy. The first results from the ongoing phase III trial showed that RTS,S reduces the risk of malaria by half in African children aged 5 to 17 months.[203] • 2008/2009: Two phase II studies published online in the *New England Journal of Medicine* demonstrated that the RTS,S vaccine candidate provides both infants and young children with significant protection against infection and clinical disease caused by *P. falciparum*. This research, conducted at the KEMRI–Wellcome Trust Research Programme in Kenya and Tanzania, brought RTS,S closer to phase III clinical trials. • In 2009, MVI and GSK launched a large-scale phase III efficacy trial of RTS,S in 11 sites in seven African countries. The target enrolment of more than 15 000 children and infants was reached at the end of January 2011, making this the largest malaria vaccine trial to date. The KEMRI–Wellcome Trust Research Programme is participating in these ongoing phase III trials. • If the required public health information, including safety and efficacy data from the phase III programme, is deemed satisfactory, the WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015.

189 Noor et al. Insecticide-treated net coverage in Africa: mapping progress in 2000-07. Lancet 2009;373(9657):58–67.

190 Snow et al. International funding for malaria control in relation to populations at risk of stable Plasmodium falciparum transmission. PLoS Med 2008;5(7):1068–78.

191 Gething et al. Climate change and the global malaria recession. Nature 2010;465:342–5.

192 Hay et al. A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 2009;6(3):286–302.

193 Noor AM et al. The risks of malaria infection in Kenya in 2009. BMC Infect Dis 2009;9:180.

194 Hay et al. Estimating the global clinical burden of Plasmodium falciparum malaria in 2007. PLoS Med 2010;7(6):1–14.

195 Gething PW et al. A new world malaria map: Plasmodium falciparum endemicity in 2010. Malar J 2011;10:378.

196 **www.map.ox.ac.uk/**

197 **www.nibr.com/research/developing_world/NITD/our-mission.shtml**

198 **www.nibr.com/research/developing_world/NITD/malaria-faqs.shtml**

199 Plouffe D et al. In silico activity profiling reveals the mechanism of action of antimalarials discovered in a high-throughput screen. Proc Natl Acad Sci USA 2008;105(26):9059–64. Zhou Y et al. Evidence-based annotation of the malaria parasite's genome using comparative expression profiling. PLoS ONE 2008;3(2):e1570.

200 Wellcome Trust Annual Review 2006.

201 H3Africa is not included in the malaria portfolio review funding analysis. Wellcome Trust grant data are 'committed' between Wellcome Trust financial years 1989/1990 and 2007/2008.

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
The Malaria Capacity Development Consortium (MCDC)	2008	Led by Professor Brian Greenwood at LSHTM, the MCDC is funded by a £7.3m Wellcome Trust Strategic Award. The consortium has also received an award of US$5m from BMGF, which will allow it to sustain investment in the investigators who were previously trained through the Gates Malaria Partnership (GMP).[204]	Designed to help able and motivated African scientists undertake high-quality research that will enhance the research capacity of their home institutions.	In 2009: • the MCDC recruited 18 PhD scholars • twenty-one students benefitted from a Research Methodology Course hosted by the College of Medicine (COM), University of Malawi, Blantyre • a Re-entry Grant was awarded to an MCDC investigator previously supported by the GMP • three Investigator Programme Initiative Awards were awarded to MCDC investigators previously supported by the GMP • the MCDC inaugural meeting took place at the KEMRI–Wellcome Trust Programme in Kilifi • two Senior Postdoctoral Fellowships were awarded. In 2010: • two new students joined the MCDC PhD Programme, making a total of 20 PhD students • a Re-entry Grant was awarded to an Investigator previously supported by the GMP • an MCDC researcher was awarded a Senior Research Fellowship R&D grant • four Investigator Programme Initiative Awards were awarded to MCDC Investigators previously supported by the GMP • a two-day workshop to support the supervisors and advisors of the MCDC PhD students was held in Kumasi • a web-based supervisor forum used to facilitate communication within the MCDC Community website was launched. In 2011: • five Investigator Programme Initiative Awards were awarded to MCDC Investigators previously supported by the GMP • the MCDC postdoctoral mentoring programme was launched.
MalariaGEN (see Table 7)				
WTSI malaria-focused tools and resources				
Pathogen Sequencing Unit (renamed the Pathogen Genomics Program)	1996	The Wellcome Trust committed £14.5m in 1996–97 to fund the work of Dr Bart Barrell and his colleagues.	To collaborate internationally with other organisations in sequencing up to 50 pathogenic bacteria and five parasites.	• In 1996, sequencing of chromosome 1 of *P. falciparum* was identified as a pilot project. • Bart Barrell and his colleagues at the Sanger Centre demonstrated that the assembly of the malaria sequence was possible from small clones of chromosome 1 – the proof of principle needed for large-scale sequencing to begin. • In 1996, the malaria sequencing consortium launched the whole-genome sequencing effort of *P. falciparum*. • In 2002, the complete genome sequence of *P. falciparum* was published in *Nature*.[205]
Ensembl genome browser	2000	European Bioinformatics Institute and WTSI		• Enables genomic science by providing high-quality, integrated annotation on chordate and selected eukaryotic genomes within a consistent and accessible infrastructure.[206]

202 **h3africa.org/**

203 The RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863–75.

204 **www.mcdconsortium.org/about-mcdc/how-we-are-funded.php**

205 Gardner MJ et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 2002;419:498–511.

206 Flicek et al. Ensembl 2011. Nucleic Acids Res 2011;39:D800–6.

207 Rutherford K et al. Artemis: sequence visualization and annotation. B Bioinformatics 2000;16(10):944–5.

Title	Established	Funding/support	Aim	Key malaria-focused accomplishments
Artemis/ Artemis Comparison Tool	2000	The development of Artemis and Artemis[207] Comparison Tool[208] is funded by the Wellcome Trust, through its support of the Pathogen Genomics Group[209] at the WTSI.	To provide researchers with free software tools to annotate and compare two or more pathogen genomes.	• Enables the comparative analysis of genomic sequences of bacteria and parasites, which is fundamental to medical research. • The open source software enables the malaria community to access, analyse and compare sequence data made available by other research groups. • Developed training courses in Artemis and Artemis Comparison Tool, which are held in frontline countries. • The freely available software is downloaded extensively. In 2007, the paper describing Artemis Comparison Tool[210] was referred to as a 'Hot Paper' in the field of Computer Science by the ISI Essential Science Indicators™.[211]
LookSeq	2009	LookSeq was funded by the Wellcome Trust, through its support of the Pathogen Genomics Group[212] at the WTSI, the Bill and Melinda Gates Foundation, and the Medical Research Council.		• Provides a web-based application for alignment visualization, browsing and analysis of genome sequence data.[213] By enabling seamless browsing and fast zooming, the LookSeq program helps the user to assimilate information at different levels of resolution – from an overview of a genomic region to fine details, such as heterogeneity within the sample.[214]
Mapseq/pf	2009	Primarily funded by the Wellcome UK Medical Research Council and the Foundation for the National Institutes of Health in the USA.		• MapSeq/pf is a database of genome variation in the malaria parasite *P. falciparum* in populations around the world. The database contains data on 347 samples (at the time of writing) and is growing. It provides the ability to browse data for a geographical location or for a genomic region.[215]

208 Carver TJ et al. ACT: the Artemis Comparison Tool. Bioinformatics 2005;21(16):3422–3.

209 The Pathogen Genomics Group, formerly known as the Pathogen Sequencing Unit, was established in 1995 by the Wellcome Trust. It was funded initially through individual grants and later through the Wellcome Trust Beowulf Genomics Panel. The Beowulf Panel no longer operates, and the Pathogen Genomics Group is now funded through Sanger Institute Wellcome Trust envelope funding.

210 Carver TJ et al. ACT: the Artemis Comparison Tool. Bioinformatics 2005;21(16):3422–3.

211 ISI Essential Science Indicators from ISI lists highly cited papers in 22 broad fields of science. These papers comprise the top 1 per cent of papers in each field and each year from 1991 to the present day. The 'Hot Papers' rankings are based on total citations and may change slightly from one bimonthly update to the next as new citations are added to each paper's total. (**esi-topics.com/**)

212 The Pathogen Genomics Group, formerly known as the Pathogen Sequencing Unit, was established in 1995 by the Wellcome Trust. It was initially funded through individual grants and later through the Wellcome Trust Beowulf Genomics Panel. The Beowulf panel no longer operates, and the Pathogen Genomics Group is now funded through the Sanger Institute Wellcome Trust envelope funding.

213 **www.sanger.ac.uk/resources/software/lookseq/**

214 Manske HM, Kwiatkowski DP. LookSeq: a browser-based viewer for deep sequencing data, Genome Res 2009;19(11):2125–32.

215 **www.sanger.ac.uk/MapSeq/**

Annex D: Wellcome Trust bibliometric analysis for malaria: 1989–2008

24. Bibliometric analysis was conducted by Evidence Ltd, part of Thomson Reuters (Scientific UK). The final dataset contained 34 197 malaria-linked papers published over the period 1989–2008. See Annex B: Methodology for a detailed description of the methods used.

Table 1 Number of malaria papers published in five-year periods by country (selected 20*)

Country (ranked by output over 20-year period)	Number of articles and reviews, 1989–93	Number of articles and reviews, 1994–98	Number of articles and reviews, 1999–2003	Number of articles and reviews, 2004–08
USA	1524	2128	3006	4880
UK	725	1322	1802	2657
France	462	664	916	1358
Germany	174	326	678	1041
Australia	252	439	543	829
Switzerland	255	358	467	778
India	185	258	418	844
Thailand	200	289	425	588
Kenya	129	229	372	674
Japan	107	208	447	561
Netherlands	167	291	336	497
Brazil	127	186	301	535
Italy	100	156	248	360
Canada	75	161	243	360
Sweden	121	143	199	368
Tanzania	55	129	160	346
South Africa	49	85	179	347
Denmark	53	95	182	274
Belgium	37	117	136	287
Malawi (ranked 32nd)	22	60	88	124

*The top 20 countries have been modified to include Malawi (ranked 32nd), because the Wellcome Trust is interested in outputs linked to the Wellcome Trust Research Programme in Malawi, and exclude Nigeria (ranked 20th with 572 research articles and reviews since 1989). The significant increase in research papers from China over the past decade, as evidenced in the human genetics 1990–2009 portfolio review using this method, has yet to be demonstrated in malaria-related research.

Table 2 Countries showing the fastest growth in malaria-focused papers (top 20*)

Country	Number of publications				
	1994–98	Change[a]	2004–08	Change[b]	Change[c]
Belgium	117	216%	287	111%	676%
South Africa	85	73%	347	94%	608%
Tanzania	129	135%	346	116%	529%
Germany	326	87%	1041	54%	498%
Malawi	60	173%	124	41%	464%
Japan	208	94%	561	26%	424%
Kenya	229	78%	674	81%	422%
Denmark	95	79%	274	51%	417%
Canada	161	115%	360	48%	380%
India	258	39%	844	102%	356%
Brazil	186	46%	535	78%	321%
UK	1322	82%	2657	47%	266%
Italy	156	56%	360	45%	260%
Australia	439	74%	829	53%	229%
USA	2128	40%	4880	62%	220%
Switzerland	358	40%	778	67%	205%
Sweden	143	18%	368	85%	204%
Netherlands	291	74%	497	48%	198%
Thailand	289	45%	588	38%	194%
France	664	44%	1358	48%	194%

* The top 20 countries have been modified to include Malawi (ranked 32nd) and exclude Nigeria (ranked 20th) because the Wellcome Trust is interested in outputs linked to the Wellcome Trust Research Programme in Malawi.

[a] Percentage change between 1989–93 and 1994–98 (ten years).

[b] Percentage change between 1999–03 and 2004–08 (ten years).

[c] Percentage change between 1989–1993 and 2004–08 (20 years).

Source: Thomson Reuters 2009. Analysis: Evidence, Thomson Reuters (Scientific UK).

Table 3 Subjects showing the fastest growth in malaria-focused papers

Subject field	Number of publications				
	1994–98	Change[a]	2004–08	Change[b]	Change[c]
Chemistry, medicinal	76	111%	425	235%	1081%
Biotech and applied microbiology	79	182%	277	186%	889%
Biochemistry and molecular biology	292	97%	899	50%	507%
Microbiology	134	26%	597	104%	463%
Infectious diseases	341	121%	814	35%	429%
Paediatrics	57	104%	138	29%	393%
Pharmacology and pharmacy	308	132%	644	42%	384%
Biophysics	85	70%	216	35%	332%
Chemistry, multidisciplinary	58	57%	154	75%	316%
Genetics and heredity	129	72%	312	51%	316%
Entomology	309	78%	718	61%	313%
Biology	62	32%	185	55%	294%
Research/experimental medicine	94	42%	173	42%	162%
Veterinary sciences	266	46%	477	20%	162%
Public health	167	–10%	481	148%	159%
Parasitology	1055	42%	1692	39%	128%
Tropical medicine	1309	38%	1973	42%	107%
General medicine	390	27%	585	22%	91%
Haematology	109	14%	152	1%	58%
Immunology	424	6%	431	12%	8%

[a] Percentage change between 1989–93 and 1994–98 (ten years).

[b] Percentage change between 1999–03 and 2004–08 (ten years).

[c] Percentage change between 1989–1993 and 2004–08 (20 years).

Source: Thomson Reuters 2009. Analysis: Evidence, Thomson Reuters (Scientific UK).

Table 4 Organisations linked to the most highly cited malaria research papers[a] worldwide, 1989–2008

World organisation (ranked by highly cited papers over 20-year period)	Highly cited papers			
	1989–93	1994–98	1999–2003	2004–08
University of Oxford, UK	20	33	47	94
London School of Hygiene and Tropical Medicine, UK	19	27	27	97
KEMRI, Kenya	16	25	39	61
Mahidol University, Thailand	20	18	22	43
US National Institute of Allergy and Infectious Diseases, USA	17	24	24	28
University of Liverpool, UK	5	12	26	49
CDC, USA	14	19	21	36
John Radcliffe Hospital, UK	15	31	22	17
Walter Reed Army Institute of Research, Australia	26	12	14	26
Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia	11	19	15	26
WHO (worldwide)	2	7	19	42
Imperial College London, UK	4	14	19	32
Swiss Tropical Institute, Basel, Switzerland	3	9	8	48
Johns Hopkins University, USA	6	9	11	41
Institut Pasteur, France	12	17	11	26
MRC (UK), Gambia	22	14	5	14
University of Edinburgh, UK	9	11	16	14
Harvard University, USA	9	4	7	24
IRD (Inst Recherche Dev), France	1	17	6	18
University of Washington, Seattle, USA	2	0	7	31

[a] 'Highly cited papers' refers to those papers with an average rebased impact of at least four (i.e. they received at least four times as many citations as the average paper published in that year in the same subject area).

Base: 20 organisations linked to the most highly cited malaria research papers in the 1989–2008 period.

Table 5 Authors of highly cited malaria research papers worldwide, 1989–2008

Author	Number of highly cited papers
Nick White	69
Brian Greenwood	58
Kevin Marsh	50
Bob Snow	50
Adrian Hill	44
François Nosten	38
Alan Cowman	30
Chris Newbold	30
Louis Miller	28
Marcel Tanner	28
Stephen Hoffman	27
Dominic Kwiatkowski	25
Pedro Alonso	24
Richard Price	21
Jean-François Trape	21
Thomas Wellems	21
Frank Collins	20
W Ripley Ballou	19
Joe Cohen	19
Sarah Gilbert	19
Philip Rosenthal	19

Base: 21 authors producing the most highly cited papers in malaria in the 1989–2008 period.

Annex E: Malaria research timeline

25. The Timeline sets out the key scientific, policy and funding developments that have influenced the field of malaria research in recent history. In the most recent 20 years, the emphasis is on the contribution of the Wellcome Trust – where the Wellcome Trust has played a key part or a contributory part alongside others in the field.

Timeline Key landmarks in malaria research (Wellcome Trust-associated post-1990 shaded)

Date	Key	Summary	Description	People and place
2700 BCE	Scientific advance and knowledge	Oldest reference to malaria	The oldest reference to periodic fever believed to be malaria was found in China and dates from approximately 2700 BCE.	
1500 BCE	Scientific advance and knowledge	High prevalence in ancient Egypt	Modern molecular methods have confirmed the high prevalence of *P. falciparum* malaria in ancient Egyptian mummies.	
400 BCE	Scientific advance and knowledge	Symptoms of malaria described by Hippocrates	Hippocrates described the symptoms of malaria and observed that the illness seems to be related to the time of year and the proximity of marshy areas.	
100 BCE	Scientific advance and knowledge	Romans drain malarial marshes	The Romans found that draining marshes reduces the risk of the illness.	
340 CE	Scientific advance and knowledge	First record of the antimalarial properties of qinghao	The fever-reducing properties of the herb *Artemisia annua* (qinghao) were first recorded.	China
1600s	Scientific advance and knowledge	Cinchona bark brought to Europe	Jesuits brought to Europe the first effective treatment for malaria: the bark of the Peruvian cinchona tree, which contains quinine.	
1630s	Scientific advance and knowledge	The *Schedula Romana*, instructions on dosage for cinchona bark	Sydenham's contributions were also important.	
1712	Scientific advance and knowledge	Torti clearly distinguishes fevers that can be treated by cinchona from those that cannot		
1820s	Scientific advance and knowledge	Quinine extracted from cinchona bark	Two French chemists isolated and extracted the active ingredient (quinine) from cinchona bark.	Joseph Pelletier and Jean Bienaimé Caventou
1850s	Scientific advance and knowledge	Large-scale use of quinine began		
1880	Scientific advance and knowledge	Parasites observed in erythrocytes of malaria sufferers	A French army doctor observed parasites inside red blood cells in malaria sufferers for the first time and was awarded the Nobel Prize in 1907.	Charles Louis Alphonse Laveran
1880	Policy development	Marked reduction in the price of quinine	The extensive cultivation of *Cinchona ledgeriana* in the Dutch East Indies led to a marked reduction in the price of quinine. In 1880, it became an affordable medicine for the first time.	
1890	Scientific advance and knowledge	The pathology of malaria and therapeutic action of quinine described		Marchiafava and Bignami
1891	Scientific advance and knowledge	First description of the antimalarial properties of a synthetic, methylene blue		Guttman and Ehrlich
1898	Scientific advance and knowledge	Proof that malaria is transmitted by mosquitoes	Sir Ronald Ross, an English army doctor, proved that malaria is transmitted by mosquitoes and was awarded the Nobel Prize in 1902.	Ronald Ross, India
1898–1899	Scientific advance and knowledge	Transmission of the human malaria parasites *Plasmodium* discovered		Giovanni Batista Grassi, Italy
1901	Scientific advance and knowledge	Pyrethrum first used	During the US military occupation of Cuba, a campaign against yellow fever and malaria commenced at Havana early in 1901. Under the leadership of the Assistant Surgeon General William Crawford Gorgas of the United States Army, the anti-mosquito measures used produced very marked results. Pyrethrum, a natural insecticide derived from the chrysanthemum flower, was first used here, where it was burned inside sealed dwellings. Spreading kerosene on mosquito breeding sites was also among the first strategies adopted by early malaria control programmes.	William Gorgas, Cuba
1904	Scientific advance and knowledge	Larvivorous fish used in the control of malaria vectors	In India, as far back as 1904, larvivorous fishes were used in Mumbai City for the control of the malaria vector *An. stephensi*. The larvivorous fishes *Poecilia reticulata* (the guppy, a native of South America) and *Gambusia affinis* (the gambusia, a native of Texas) were exported to India in 1908 and 1928, respectively, for the control of malaria vectors.	
1905–07	Scientific advance and knowledge	Mosquito control prevents malaria and yellow fever and allows the building of the Panama canal		William Gorgas
1917	Scientific advance and knowledge	Fever therapy and, ultimately, the malaria therapy of neurosyphilis developed (Nobel Prize 1927)		Wagner-Jauregg
1920s	Scientific advance and knowledge	Pamaquine developed	The first synthetic antimalarial drug (pamaquine, more widely known as plasmoquine) was developed.	IG Farben, part of the Bayer group, Germany
1921–24	Scientific advance and knowledge	Long latency in *P. vivax* is proven and anophelism without malaria in the Netherlands by *Anopheles* speciation is described		Kortweg, van Thiel, Swellengrebel and de Buck
1922	Policy development	Opening of the Mott clinic, Horton		Horton Hospital, Epsom, Surrey
1923	Scientific advance and knowledge	Isolation of the Madagascar strain (*P. vivax*)		
1925	Policy development	Foundation of the malaria reference laboratory, LSHTM		LSHTM
1925	Scientific advance and knowledge	Appreciation that sexual-stage antimalarial activity in *P. falciparum* differed from asexual-stage activity		
1930s	Scientific advance and knowledge	Organophosphates experimented with as insecticides	A German chemist began to experiment with organophosphates as insecticides. Early examples included the potent systemic insecticide schradan in 1941 and tetraethyl pyrophosphate, which was the first marked organophosphate insecticide. Organophosphate compounds are the most widely used group of insecticides in the world.	Gerhard Schrader, IG Farben, part of the Bayer group, Germany
1932	Scientific advance and knowledge	Mepacrine introduced	Mepacrine is introduced as an antimalarial drug.	IG Farben, part of the Bayer group, Germany
1933	Policy development	The Malaria Commission of the League of Nations recommends that treatment with quinine should not exceed one week		League of Nations, Geneva, Switzerland

Date	Key	Summary	Description	People and place
1934	Scientific advance and knowledge	Chloroquine discovered	The antimalarial drug chloroquine was initially rejected as "too toxic", and methylchloroquine was developed instead. Chloroquine was not widely used until after World War II.	IG Farben, part of the Bayer group, Germany
1939	Scientific advance and knowledge	Insecticidal action of DDT discovered	DDT was discovered, leading to the Nobel Prize in 1948.	Paul Hermann Müller
1941	Scientific advance and knowledge	First evidence that irradiated sporozoites can prime the immune system, preventing erythrocyte infection		
1942–44	Scientific advance and knowledge	DDT used as an anti-mosquito spray	In 1942, DDT was used as an anti-mosquito spray in army camps in the USA and the UK. In 1944, it was used at Volturno in Italy in civilian areas.	
1944	Scientific advance and knowledge	The first antifol antimalarial, proguanil (chloroguanide), was discovered		Curd, Davey and Rose, ICI
1944–48	Scientific advance and knowledge	A classic series of therapeutics studies (published in *JCI* in 1948), which established dosing for the cinchona alkaloids and the aminoquinolines based on pharmacokinetics and pharmacodynamics		James Shannon
1945	Scientific advance and knowledge	Cyclodiene compounds introduced	Several cyclodiene compounds were introduced after 1945. These insecticides include aldrin, chlordane, dieldrin, heptachlor, endrin and endosulphan. After DDT, dieldrin has been the most extensively used in malaria control programmes.	
1946	Scientific advance and knowledge	Chloroquine introduced	Chloroquine was introduced and soon became the preferred treatment for malaria.	IG Farben, part of the Bayer group, Germany
1946	Scientific advance and knowledge	DDT resistance reported	Resistance to DDT was reported as early as 1946 (in house flies).	
1946	Policy development	US CDC founded	The US Centers for Disease Control (CDC) was founded to limit the impact of malaria.	USA
1947	Policy development	First Expert Committee on Malaria established	The First Expert Committee on Malaria was established by the Interim Commission of the WHO.	WHO, Geneva, Switzerland
1948	Scientific advance and knowledge	Discovery of the pre-erythrocytic stage of malaria	It was discovered that after injection, sporozoites undergo a period of multiplication in the liver – the pre-erythrocytic stage.	Garnham and Shortt
1949	Scientific advance and knowledge	Proguanil resistance in *P. falciparum* and *P. vivax* confirmed in Malaysia		Malaysia
1949	Scientific advance and knowledge	USA declared free of malaria	The USA was declared free of malaria as a significant public health problem.	USA
1949	Funding development	Wellcome Trust Research Laboratories established	Wellcome Trust Research Laboratories were established in Nairobi.	Henry Foy, Kenya
1950s	Scientific advance and knowledge	Carbamates introduced	Carbamates were first discovered by the Geigy company in Switzerland in 1947. The first carbamate, carbaryl, was introduced in 1956.	Geigy, Swizerland
1950	Scientific advance and knowledge	Malathion introduced	Malathion, an organophosphate, was first introduced as an insecticide.	

Date	Key	Summary	Description	People and place
1951	Scientific advance and knowledge	Development of pyrimethamine	Development of pyrimethamine for treatment of malaria – targeting the parasite's unique folic acid pathway. Produced under the name of Daraprim by Burroughs Wellcome & Co.	Falco et al.
1954	Scientific advance and knowledge	Discovery of protective effect of sickle cell trait in heterozygotes	It was discovered that the sickle cell trait in heterozygotes protects children against malaria.	Anthony Allison
1955	Policy development	WHO launches Global Malaria Eradication Campaign	The 8th World Health Assembly launched the Global Malaria Eradication Campaign; the campaign excluded sub-Saharan Africa and was eventually abandoned.	WHO, Geneva, Switzerland
1959	Scientific advance and knowledge	DDT-resistant mosquitoes detected	DDT-resistant mosquitoes were first detected in India in 1959.	India
1959	Scientific advance and knowledge	First reports of chloroquine resistance	The first reports of chloroquine resistance in *P. falciparum* emerged in countries such as Thailand and Colombia.	South-east Asia
1961	Scientific advance and knowledge	Demonstration of the role of antibodies in acquired immunity to human malaria	Establishment of the role of γ-globulin, an antibody, in acquired immunity to malaria.	Cohen S et al.
1962	Scientific advance and knowledge	Link between pesticides and negative ecological effects suggested	A scientist published *Silent Spring,* which detailed the links between the use of pesticides (including DDT) and the deaths and decreasing populations of animals.	Rachel Carson
1963	Scientific advance and knowledge	Burkitt's lymphoma related to the endemicity of malaria		
1967	Scientific advance and knowledge	Pyrethroids, synthetic pyrethrum, discovered		Dr Michael Elliott, UK
1969	Policy development	World Health Assembly revises global malaria eradication strategy	The World Health Assembly revised its global malaria eradication strategy, focusing on control where eradication is not possible.	World Health Assembly, Geneva, Switzerland
1971	Scientific advance and knowledge	Artesunate isolated	After an appeal by Ho Chi Minh during the Vietnam war, Chinese scientists finally isolated the active ingredient of *A. annua* – artesunate. Low-temperature ethyl ether extract of qinghao (*A. annua*) yields qinghaosu, later named 'artemisinin'.	China
1972	Policy development	DDT banned	DDT was banned in the USA.	USA
1976	Scientific advance and knowledge	Malaria parasite first grown in culture in a lab	The malaria parasite was first grown in culture in a lab, opening the way for drug discovery and vaccine research.	Dr William Trager and Dr J B Jensen, USA
1977	Funding development	Rockefeller Foundation launches its 'Great Neglected Diseases of Mankind' Programme	The Rockefeller Foundation coined the term 'neglected diseases' inaugurating its 'Great Neglected Diseases of Mankind' Programme, which includes malaria.	The Rockefeller Foundation, New York, USA
1978	Scientific advance and knowledge	Thirty-seven countries declared free from malaria		
1978	Scientific advance and knowledge	First chloroquine resistance reports from Africa	The first chloroquine resistance reports came from Africa. By the 1980s, most malaria-endemic areas in Asia and South America were affected by chloroquine resistance, and it is spreading in Africa.	Africa
1979	Scientific advance and knowledge	Clinical trials of artemisinin published	The results from human trials of artemisinin were published in the *Chinese Medical Journal*, allowing those outside China to access information about the drug.	
1979	Funding development	Wellcome Trust–Mahidol University of Oxford Tropical Medicine Research Unit established	The Wellcome Trust-funded cerebral malaria research unit was formed as a collaboration between the Faculty of Tropical Medicine, Mahidol University, Bangkok and The Centre for Tropical Diseases, Nuffield Department of Medicine, John Radcliffe Hospital, University of Oxford.	Mahidol University, Bangkok, Thailand, University of Oxford, UK

Date	Key	Summary	Description	People and place
1980	Scientific advance and knowledge	Identification of the circumsporozoite protein (CSP) as a protective antigen	Research leading up to the development of the malaria vaccine, RTS,S was based on the identification of CSP as a protective antigen.	Potocnjak et al.
1981	Scientific advance and knowledge	Demonstration that a single protein could be used to vaccinate against blood-stage malaria		Holder AA and Freeman RR
1982	Scientific advance and knowledge	Discovery of the hypnozoite	The dormant pre-erythrocytic stage of *P. vivax*, the hypnozoite, was discovered.	Krotoski et al.
1983	Scientific advance and knowledge	Hypoglycaemia in falciparum malaria demonstrated		White et al.
1983	Scientific advance and knowledge	Quinine loading dose treatment of severe malaria	Loading dose of quinine increased four- to eight-fold compared with WHO recommendations in the 1970s.	White et al.
1984	Scientific advance and knowledge	Mefloquine sulfadoxine–pyrimethamine introduced	The combination of sulfadoxine–pyrimethamine and mefloquine, known as Fansimef®, was introduced to limit the development of resistance to both sulfadoxine–pyrimethamine and mefloquine in Thailand.	Thailand
1984	Policy development	WHO says parenteral chloroquine "should no longer be used"		WHO, Geneva, Switzerland
1985	Scientific advance and knowledge	First large-scale trials of insecticide-treated bednets		Snow et al., the Gambia
1986	Policy development	WHO says intramuscular quinine "should not be used"		WHO, Geneva, Switzerland
1986	Policy development	WHO guidelines for the management of severe falciparum malaria		WHO, Geneva, Switzerland
1986	Funding development	Shoklo Malaria Research Unit predecessor founded	A Wellcome Trust-funded malaria research unit – now the Shoklo Malaria Research Unit – was established in Shoklo. The Shoklo Malaria Research Unit is now based in Mae Sot.	François Nosten, Mae Sot, Thailand
1987	Scientific advance and knowledge	SPf66 vaccine undergoes field trials	SPf66 became the first vaccine to undergo field trials.	Manuel Patarroyo, Colombia
1988	Scientific advance and knowledge	Antimalarial prophylaxis reduces mortality of children aged 1–4 by 25 per cent in the Gambia		The Gambia
1989	Scientific advance and knowledge	Blantyre Coma score developed	The Blantyre Coma score is a system that helps monitor children in malaria-induced coma.	Molyneux and Taylor, Blantyre, Malawi
1989	Funding development	Joint KEMRI–Wellcome Trust Research Programme on severe malaria in childhood begins	Work begins at Kilifi, Kenya, in a joint KEMRI–Wellcome Trust Research Programme on severe malaria in childhood. The Programme was formally established in 1989 as a partnership between KEMRI, Oxford University and the Wellcome Trust.	KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya
1990s	Scientific advance and knowledge	First clinical studies to test the efficacy of artemisinin in treating malaria outside China		Tran Tinh Hien et al.
1991	Scientific advance and knowledge	Insecticide-treated bednets shown to reduce child mortality in the Gambia		The Gambia
1991	Scientific advance and knowledge	Mefloquine resistance first reported		Nosten et al., Thailand
1991	Funding development	The Vietnam Research Programme and Oxford University Clinical Research Unit established	The Vietnam Research Programme and Oxford University Clinical Research Unit was established in Ho Chi Minh City in 1991 and in Hanoi in 2006.	

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1992	Policy development	WHO Global Malaria Control Strategy 1993–2000 developed	A dramatic increase in the malaria burden led to WHO devising a Global Malaria Control Strategy 1993–2000.	WHO, Geneva, Switzerland
1992	Scientific advance and knowledge	RTS,S vaccine candidate enters clinical trials	The vaccine candidate was initially tested in healthy adults in the USA and Belgium.	GlaxoSmithKline, United States Walter Reed Army Institute of Research
1994	Scientific advance and knowledge	Three-day ACT regimen (artesunate–mefloquine) first deployed on the Thai–Burmese border		Nosten et al., Thailand
1995	Scientific advance and knowledge	Rapid diagnostic tests for malaria introduced		
1995	Scientific advance and knowledge	Introduction of Malarone	Malarone was introduced for the treatment of malaria	GlaxoSmithKline
1997	Scientific advance and knowledge	PCR parasite genotyping allows clinical trials to be conducted and interpreted correctly in malaria-endemic areas		Brockman et al.
1997	Policy development	MIM established	The MIM was established in 1997 to maximise the impact of global activities against malaria in Africa. MIM has the objectives of developing research capacity in Africa, increasing international cooperation for malaria research and facilitating relevant communication at all levels.	CDC, NIH, EC, Wellcome Trust, Malaria Foundation International, MRC, NLM, WHO,WHO/TDR, AU, UNESCO, Walter Reed Army Institute of Research, USAID, SHARED, GTZ, HealthNet and World Bank
1997	Policy development	First MIM Pan-African Conference on Malaria	An International Conference on Malaria in Africa was held in Dakar, Senegal, 6–9 January 1997 (African Malaria Vaccine Testing Network 1997, unpublished, and Malaria Foundation International 1997, unpublished). This conference was a watershed for the MIM.	Dakar, Senegal
1998	Policy development	Roll Back Malaria Partnership (RBM) launched	RBM was launched. Now a global initiative made up of more than 500 partners, its high-level aim is to halve the burden of malaria by 2010 and to reduce global malaria deaths to near zero preventable deaths in 2015.	WHO, UNICEF, UNDP and the World Bank
1998	Policy development	European Malaria Vaccine Initiative (EMVI) established	The EMVI, which addresses structural deficiencies in public-funded malaria vaccine development, was established by the European Commission and interested European member states.	European Commission
1999	Funding development	Medicines for Malaria Venture (MMV) founded	MMV, a public–private partnership funded by foundations and bilateral agencies with the high-level aim of securing the registration of one new antimalarial drug every five years, was founded.	Governments of the Netherlands and Switzerland, the World Bank, the Rockefeller Foundation and UK DFID
1999	Policy development	Wellcome Trust Nairobi and Kilifi units are integrated into a single unit	The Wellcome Trust Nairobi and Kilifi units were integrated into a single unit under the directorship of Professor Kevin Marsh.	Kenya
1999	Policy development	PATH Malaria Vaccine Initiative (MVI) established	The PATH MVI, a global programme of the international non-profit organisation PATH, was established through a grant from the Bill and Melinda Gates Foundation.	The Bill and Melinda Gates Foundation

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2000	Policy development	UN declares 2001–2010 the 'Decade to Roll Back Malaria'	The UN declared 2001–2010 the 'Decade to Roll Back Malaria', meaning that by 2010 it aimed to have rolled back malaria and fulfilled the UN Millennium Development Goals (MDGs).	UN
2000	Policy development	Abuja Declaration	African leaders affirmed their commitment to halve malaria mortality by 2010.	RBM, Abuja, Nigeria
2000	Policy development	MDGs agreed	MDGs were agreed by every UN member state, including the aim of halting and reversing malaria by 2015.	UN
2002	Funding development	The Global Fund established	The Global Fund to Fight AIDS, TB and Malaria, a public–private partnership and the world's largest funder of these diseases, was created.	Geneva, Switzerland
2002	Scientific advance and knowledge	Genome sequences of *P. falciparum* and *An. gambiae* completed	Genome sequencing of *P. falciparum* was completed. The £18.5m *P. falciparum* project was funded in the UK by the Wellcome Trust (£8m) and in the USA by the Burroughs-Wellcome Fund (£4.9m), the US National Institute of Allergy and Infectious Diseases (£2.2m), and the US Department of Defense (£3.4m). In addition, the sequence of *A. gambiae* was released by the International Anopheles Genome Project.	Wellcome Trust, UK, Burroughs Wellcome Fund, USA, US Department of Defense, US National Institute of Allergy and Infectious Disease, and International Anopheles Genome Project
2002	Scientific advance and knowledge	Scientists create genetically modified (GM) mosquito incapable of transmitting malaria to humans	Scientists created a GM mosquito that is almost incapable of transmitting malaria to humans. The development could lead to the release of GM mosquitoes into malaria-endemic regions to prevent the transmission of the disease.	
2003	Policy development	WHO recommendations on intermittent prevention of malaria in pregnancy introduced	WHO introduces recommendations for the prevention and management of malaria during pregnancy by using ITNs, intermittent preventive treatment and effective case management.	WHO, Geneva, Switzerland
2003	Scientific advance and knowledge	Placental malaria infection link to HIV	Placental malaria infection during pregnancy was found to significantly increase the risk of mother-to-child transmission of HIV.	
2004	Scientific advance and knowledge	Demonstration that 25 per cent of the patients who satisfy the standard clinical case definition of cerebral malaria die for reasons unrelated to malaria	The link to malaria retinopathy is first described here.	Taylor TE et al., Malawi
2004	Policy development	Malaria R&D Alliance established	A group of malaria R&D organisations jointly advocating for global commitment for increased and sustained resources for malaria R&D established the Malaria R&D Alliance in 2004.	
2004	Scientific advance and knowledge	Trials show RTS,S efficacious in children	The results of a phase II trial demonstrating the feasibility of administering RTS,S in children were published. RTS,S was efficacious for at least 18 months in reducing clinical malaria by 35 per cent and severe malaria by 49 per cent.	Alonso et al., Mozambique
2004	Policy development	UK All Party Parliamentary Group on Malaria and Neglected Tropical Diseases established	The UK All Party Parliamentary Group on Malaria and Neglected Tropical Diseases was set up to raise awareness of malaria among Parliamentarians. ACT introduced for the treatment of *P. falciparum*.	UK
2004	Scientific advance and knowledge	*P. knowlesi* is recognised as the fifth malaria species infecting humans		Singh B et al.
2005	Scientific advance and knowledge	SEAQUAMAT, the 'South East Asian Quinine Artesunate Malaria Trial'	The largest clinical trial ever conducted into the treatment of severe malaria in adults found that using artesunate reduced the number of deaths by more than a third when compared with quinine, the most commonly used treatment. The trial was funded by the Wellcome Trust.	Dondorp A et al.
2005	Policy development	World Health Assembly adopts insecticide-treated bednets target	The World Health Assembly adopted the target of 80 per cent worldwide coverage of insecticide nets and ACTs by 2010.	World Health Assembly, Geneva, Switzerland
2005	Funding development	President's Malaria Initiative launched	The President's Malaria Initiative was launched by former President George Bush, with the targeted goal of halving malaria deaths in 15 of the worst hit countries. The Initiative is led by USAID.	USAID, CDC and the US Department of Health and Human Services, USA
2005	Policy development	World Bank's Malaria Booster Program launched	The World Bank's Malaria Booster Program was established to help countries in sub-Saharan Africa reduce illness and death from malaria by 2015.	The World Bank, Washington DC, USA
2005	Funding development	MalariaGEN established	The MalariaGEN genomic epidemiology network was established with funding from the Wellcome Trust and the Bill and Melinda Gates Foundation as part of the Grand Challenges in Global Health initiative.	Wellcome Trust and The Bill and Melinda Gates Foundation
2005	Scientific advance and knowledge	Study of malaria prevalence in African children	A study of children in Africa estimated that 80 per cent of all new malaria infections are concentrated in one-fifth of the population.	Smith DL et al., NIH Fogarty International Centre, Washington and Princeton University, New Jersey, and Wellcome Trust-funded scientists working at the University of Oxford and in Kenya
2005	Funding development	KEMRI–Wellcome Trust Research Programme renewed	The KEMRI–Wellcome Trust Research Programme was renewed for a further five years, and Professor Kevin Marsh was appointed Unit Director.	Kenya
2006	Scientific advance and knowledge	Retinopathy as a proxy for cerebral malaria		Beare NA et al.
2006	Policy development	ACTs developed	ACTs are developed and recommended by WHO as the first-line malaria treatment.	WHO, Geneva, Switzerland
2007	Policy development	Gates Malaria Forum launched	The Gates Malaria Forum was launched, calling once more for the eradication of malaria and marking a return to earlier approaches to prevent the disease.	
2007	Policy development	New guidelines on insecticide-treated mosquito nets issued by WHO	WHO issued new guidelines on insecticide-treated mosquito nets, recommending for the first time that nets be long lasting, either free or highly subsidised, and used by all community members. The policy was informed by research examining the positive impact of distributing free bednets.	Killeen, Noor et al., Kenya, WHO, Geneva, Switzerland
2007	Policy development	Malaria Elimination Group (MEG) is established	The Malaria Elimination Group (MEG) was established as a group of 45 international experts convened by the Global Health Group at the University of California to elaborate the scientific, technical, operational, economic and programmatic issues that countries need to consider when pursuing malaria elimination.	Global Health Group, University of California, San Francisco, USA
2007	Policy development	World Malaria Day instituted	World Malaria Day was instituted by the World Health Assembly at its 60th session. The First World Malaria Day was adopted by the UN in 2008.	World Health Assembly, Geneva, Switzerland

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2007	Funding development	£10m pledged to the Novartis Institute for Tropical Diseases (NITD): Malaria Drug Discovery	Over £10m pledged to NITD: Malaria Drug Discovery, a five-year partnership dedicated to identifying a preclinical small molecule to provide a single-dose cure for malaria caused by *P. falciparum* and identifying treatments for *P. vivax*.	The Wellcome Trust, the Singapore Economic Development Board and MMV
2008	Scientific advance and knowledge	Genome of *P. knowlesi* decoded, revealing extended host range	The genome of *P. knowlesi* was decoded, revealing a host range from monkeys to man. This potentially fatal species of malaria was previously commonly misdiagnosed in humans as a more benign form of malaria.	Pain, Cox-Singh et al., Malaysia (Sarawak)
2008	Scientific advance and knowledge	Eight new proteins that transport PfEMP1 discovered	An international collaboration of scientists identified eight new proteins that transport the *P. falciparum* parasite's PfEMP1 to the surface of the infected red blood cells. Removing just one of these proteins prevents the infected red blood cells from sticking to the walls of the blood vessels.	Cowman A et al., Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia
2008	Policy development	Universal coverage by 2010 called for by UN Secretary General	The UN Secretary-General called for universal coverage by 2010 to halt the death rate from malaria. Ray Chambers was appointed as the UN Secretary-General's Special Envoy for Malaria.	UN
2008	Scientific advance and knowledge	Efficacy of rectal artesunate demonstrated in children	Rectal artesunate was proven to reduce mortality and illness among young children with severe malaria.	Gomes et al., Ghana, Tanzania and Bangladesh
2008	Policy development	Elimination becomes the main goal for most organisations	Elimination has become the main aim for most organisations. RBM launched its Global Malaria Action Plan 2005–2015 for a malaria-free world – reaching near zero deaths by 2015. The Plan recommends a mixed approach to malaria, where the effective delivery of current treatments is carried out alongside basic research and drug and vaccine development.	
2008	Scientific advance and knowledge	ACTs adopted as the first-line treatment for *P. falciparum* throughout the world	All except four countries and territories worldwide (Cape Verde, Dominican Republic, French Guyana and Swaziland) had adopted ACTs as the first-line treatment for *P. falciparum*.	
2008	Funding development	Affordable Medicines Facility for Malaria endorsed	The Affordable Medicines Facility for Malaria (AMFm) was endorsed by the Board of the Global Fund. AMFm is an innovative financing mechanism, hosted by the Global Fund, designed to expand access to affordable ACTs through the public, private and nongovernmental organisation sectors.	The Global Fund
2008	Scientific advance and knowledge	Operation discovers fake ACT drugs in southern China	Operation Jupiter – a unique 'forensic pharmacological' collaboration between INTERPOL, the WHO Western Pacific Office and the Wellcome Trust–University of Oxford South-east Asian Tropical Medicine Research Programme – led to the arrest by the Chinese authorities of alleged traders of fake ACT drugs in southern China and the seizure of a large quantity of drugs.	Newton et al., South-east Asia
2008	Scientific advance and knowledge	Phase II trials of RTS,S	Two phase II studies published online in the *New England Journal of Medicine* demonstrated that the RTS,S vaccine candidate provides both infants and young children with significant protection against malaria.	Bejon P et al., Abdulla S et al., KEMRI–Wellcome Trust programme in Kilifi, Kenya, and Tanzania
2008	Funding development	The Mahosot Hospital–Wellcome Trust–University of Oxford Infectious Disease Centre established	The first ever centre dedicated to the diagnosis and treatment of infectious diseases in Laos is established with funding from the Wellcome Trust.	Vientiane, Laos

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2008	Scientific advance and knowledge	Dynamic alterations in microcirculatory flow and visualisation of microvascular obstruction demonstrated in buccal and rectal mucosa		Dondorp et al.
2009	Scientific advance and knowledge	DHA–piperaquine introduced		MMV and pharmaceutical company Sigma-Tau
2009	Scientific advance and knowledge	Coartem® Dispersible launched	First-ever high-quality paediatric formulation of an ACT, Coartem® Dispersible, launched	Novartis and MMV
2009	Policy development	G-FINDER study published	The first G-FINDER study is published by The George Institute, tracking R&D funding towards new products for neglected diseases. $468.4m was allocated to malaria R&D in 2008; more than a quarter of this came from the Bill and Melinda Gates Foundation.	Policy Cures
2009	Scientific advance and knowledge	Global map of *P. falciparum* endemicity in 2007 published	The most detailed map created of malaria risk worldwide.	Hay SI et al, MAP, KEMRI, Kenya, University of Oxford, UK
2009	Scientific advance and knowledge	Genome-wide association studies pinpoint the malaria-protective effect of the sickle cell variant	Through genome-wide association studies, the malaria-protective effect of the sickle cell variant was pinpointed in the genome of African populations.	Kwiatkowski et al., Gambia
2009	Policy development	African Leaders Malaria Alliance launched	The leaders of 20 African nations, meeting in New York during the UN General Assembly, launched ALMA, the African Leaders Malaria Alliance, to achieve a united approach in efforts to meet the MDGs on malaria.	New York, USA
2009	Scientific advance and knowledge	Research shows children aged 5–19 least protected	Research showed that older children, aged 5–19 years, are the least well protected by insecticide-treated bednets in Africa.	Noor AM et al., KEMRI–Wellcome Trust Research Programme and the University of Oxford
2009	Scientific advance and knowledge	*var* gene expression shown to be modified by host immunity	Research showed that *P. falciparum var* gene expression is modified by host immunity.	Warimwe G et al., KEMRI–Wellcome Trust Programme and the Sanger Institute
2009	Scientific advance and knowledge	Artemisinin resistance found in Cambodia	Research showed that malaria parasites in western Cambodia have become resistant to artemisinin-based therapies. The study was funded by the Wellcome Trust, the Li Ka Shing Foundation and the Global Malaria Programme of the WHO through grants from the Bill and Melinda Gates Foundation and the Western Pacific Regional Office.	Dondorp et al., South-east Asia
2009	Funding development	Trust-funded malaria researchers are among most cited authors	An analysis of papers from 1996 to 2007 by the online journal *Lab Times* shows that Trust-funded researchers make up more than three-quarters of the top 30 most cited authors in the field of parasitology, including the top seven.	Publication analysis 1996–2007: parasitology. Lab Times 2009;3:3840.
2010	Funding development	Award to use advanced genetics to create strains of sterile mosquitoes	Wellcome Trust Translation award to Oxford-based company Oxitec Ltd to use advanced genetics (RIDL) to create strains of sterile mosquitoes, to help combat mosquito-borne diseases.	Oxitec Ltd, Oxford, UK
2010	Policy development	malERA Zenith Week	The Malaria Eradication Research Agenda (malERA) culminated in 'Zenith Week', where an output White Paper was published proposing how current malaria R&D should change with the goal of global eradication. MalERA was launched in 2008 and aims to identify current knowledge gaps and new tools needed for malaria eradication.	Washington DC, USA

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2010	Policy development	GSK launches 'Open Innovation' strategy	As part of its 'Open Innovation' strategy, GSK announced that it will make 13 500 malaria compounds, including the chemical structures and associated assay data, freely available to the public and pledged to create a sustainable pricing model for its RTS,S vaccine candidate.	GlaxoSmithKline
2010	Policy development	WHO issues revised malaria guidelines	WHO published the second edition of its *Guidelines for the Treatment of Malaria*. Main features include an emphasis on testing before treating, using quality-assured rapid diagnostic tests, and the addition of a fifth ACT (dihydroartemisinin plus piperaquine) to the previous list of recommended medicines.	WHO, Geneva, Switzerland
2010	Scientific advance and knowledge	AQUAMAT, the 'African quinine versus artesunate malaria trial'	The largest ever study in severe malaria showed that artesunate reduces the mortality of severe malaria in African children by 22 per cent compared with quinine and is highly cost-effective.	Dondorp et al., Mahidol Oxford Tropical Medicine Research Unit, Thailand
2011	Scientific advance and knowledge	*Atlas of Malaria-Eliminating Countries* is launched.	The *Atlas* displays the geographic distribution of malaria in the 36 countries that are closest to eliminating the disease.	MAP and University of California,San Francisco (UCSF) Global Health Group
2011	Scientific advance and knowledge	Demonstration that albumin infusion is harmful in children with severe infection		Maitland K et al, KEMRI–Wellcome Trust Programme, Kilifi, Kenya
2011	Scientific advance and knowledge	First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children shows that RTS,S reduces the risk of malaria by half in African children aged 5 to 17 months		The RTS,S Clinical Trials Partnership. N Engl J Med 2011
2011	Scientific advance and knowledge	Identification of the basigin receptor	A crucial malaria protein essential for erythrocyte invasion by *P. falciparum.*	Crosnier et al., WTSI, Cambridge, UK
2011	Scientific advance and knowledge	Eurartesim® approved	Eurartesim®, an artemisinin combination therapy, has been approved by the European Commission for the treatment of uncomplicated malaria caused by the parasite *P. falciparum*.	MMV and pharmaceutical company Sigma-Tau; Hospital for Tropical Diseases and the Wellcome Trust Major Overseas Programme in Vietnam; Shoklo Malaria Research Unit, Mae Sot, Bangkok, Thailand; Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
2011	Scientific advance and knowledge	Demonstration that the blood-stage malaria antigen PfRH5 is susceptible to vaccine-inducible cross-strain neutralizing antibody		Douglas AD et al., University of Oxford, UK
2011	Scientific advance and knowledge	A global map of *P. falciparum* malaria for the year 2010 is launched	This map builds on the *Atlas of Malaria-Eliminating Countries*.	Gething PW et al., MAP, University of Oxford, UK
2012	Scientific advance and knowledge	Global map of vivax malaria endemicity is launched		MAP, University of Oxford, UK

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