

Global Forum
for Health Research
HELPING CORRECT THE 10|90 GAP



Global Forum for Health Research
1-5 route des Morillons
PO Box 2100
1211 Geneva 2
Switzerland

Tel +41 22 791 4260
Fax +41 22 791 4394
info@globalforumhealth.org

www.globalforumhealth.org

Global Forum
for Health Research

HELPING CORRECT THE 10|90 GAP



GLOBAL FORUM FOR HEALTH RESEARCH

MONITORING FINANCIAL FLOWS 2005
www.globalforumhealth.org

Monitoring Financial Flows for Health Research 2005 Behind the Global Numbers

2005

Foundation Council of the Global Forum for Health Research

Chair : Pramilla Senanayake

Monitoring Financial Flows for Health Research 2005: Behind the Global Numbers

© Global Forum for Health Research 2006
Published by the Global Forum for Health Research, February 2006
ISBN 2-940286-39-6

The reproduction of this document is regulated in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights are reserved by the Global Forum for Health Research. The report may be freely reviewed and abstracted, with the usual acknowledgement of source, but not for sale or for use in conjunction with commercial purposes. Requests for permission to reproduce or translate the report, in part or in full, should be addressed to the Secretariat where information on any translations or reprints is centralized (see address below).

The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the Secretariat of the Global Forum for Health Research concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

With the exception of Chapter 1, the views expressed in this document are not necessarily those of the Global Forum for Health Research.

Suggested citation: Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2005*

Additional copies of *Monitoring Financial Flows for Health Research 2005* can be ordered (at no charge) via the website www.globalforumhealth.org or from

Global Forum for Health Research
1-5 route des Morillons
PO Box 2100
1211 Geneva 2, Switzerland

T + 41 22 791 4260 F + 41 22 791 4394
E-mail info@globalforumhealth.org

Jie Chen
Fudan University, China

Mahmoud Fathalla
Assiut University, Egypt

María G. Guzmán
Institute of Tropical Medicine, Cuba

Richard Horton
The Lancet

Carel B. IJsselmuiden
Council on Health Research for Development
(COHRED)

Marian Jacobs
University of Cape Town, South Africa

Alejandra Lopez-Gomez
Development Alternatives with Women
for a New Era (DAWN)

Adolfo Martinez-Palomo
Center for Research and Advanced
Studies, Mexico

Daniel Mäusezahl
Swiss Agency for Development
and Cooperation

Carlos Morel
FIOCRUZ, Brazil

Ravi Narayan
Society for Community Health Awareness, Research
and Action

Berit Olsson
Swedish International Development Cooperation
Agency

Ok Pannenberg
World Bank

Robert Ridley
Special Programme for Research and Training in
Tropical Diseases (TDR)

Gill Samuels
International Federation of Pharmaceutical
Manufacturers and Associations

Nelson Sewankambo
Makerere University, Uganda

Nahid Toubia
RAINBO

Ragna Valen
Research Council of Norway

Judith A. Whitworth
WHO Advisory Committee on Health Research
(ACHR)

Christina Zarowsky
International Development Research Centre, Canada

The Global Forum for Health Research is an international independent foundation based in Geneva, Switzerland.

The Global Forum is supported by the Rockefeller Foundation, World Bank, World Health Organization and the governments of Canada, India, Ireland, Mexico, Norway, Sweden and Switzerland.

Monitoring Financial Flows for Health Research 2005

Behind the Global Numbers

Edited by Mary Anne Burke and Andrés de Francisco

Acknowledgements

The work of the Monitoring Financial Flows for Health Research Project presented in this report adds to the body of work presented in the 2001 and 2004 volumes, examining several aspects of the overall picture behind the global numbers on health R&D expenditure. Mary Anne Burke and Andrés de Francisco have main editorial responsibility for the report and authored Chapter 1.

Other contributors to the report are as follows: Chapter 2, Mary Moran and Javier Guzman; Chapter 3, Donald W. Light with commentary provided by Adrian Towse; Chapter 4, Reinaldo Guimarães, José de Rocha Carvalheiro and Wim Degrave; Chapter 5, The Malaria Research and Development Alliance; Chapter 6, Gabrielle Lamourelle, Polly Harrison, Jane Rowley and Mitchell Warren.

We would like to thank Stephen Matlin for his helpful comments on all chapters.

Mary Anne Burke
Health Analyst/Statistician
Global Forum for Health Research

Andrés de Francisco
Deputy Executive Director
Global Forum for Health Research

Contents

Acknowledgements	ii
List of figures	v
List of tables	vi
Introduction <i>by Stephen Matlin</i>	vii
Chapter 1 Towards the building of robust, sustainable systems of data collection and reporting on expenditures for research for health	1
<i>Mary Anne Burke and Andrés de Francisco</i>	
Why measure?	3
Efforts to date in tracking financial flows for health research in LMICs	3
Efforts to date in tracking global financial flows for health research	9
Building sustainable systems for national reporting on health research expenditures	10
New understanding of national health research systems needed	11
Wider variety of players	13
Conclusions	13
Chapter 2 Drug R&D for neglected diseases by public-private partnerships: are public funds appropriately distributed?	15
<i>Mary Moran and Javier Guzman</i>	
Past PPP expenditure by disease	17
Factors associated with different levels of R&D expenditure by PPPs	19
Future funding needs	21
Total PPP budgets as a reflection of global drug R&D expenditure on neglected diseases	22
Are any of these diseases underfunded, and what is the "right" amount of drug R&D funding among PPPs	23
Conclusions	24
Chapter 3 Basic research funds to discover important new drugs: who contributes how much?	27
<i>Donald Light</i>	
The role of basic research	30
What matters is significant therapeutic gain	30
Global shares of basic research	31
Industry contribution to basic pharmaceutical research	31
Net industry contributions	33
Government contributions to basic research	35
Foundations	35

	Summing up	35
	Redirecting basic pharmaceutical research to greatest need	36
	The new landscape of basic pharmaceutical research	38
	Redirecting public funds to maximize new drugs	39
	Complementing research with guaranteed purchasing	41
	Commentary by Adrian Towse	44
Chapter 4	Health technology and innovation: a Brazilian experience	47
	<i>Reinaldo Guimarães, José da Rocha Carneiro and Wim Degraeve</i>	
	The Oswaldo Cruz Foundation (Fiocruz)	50
	Vaccines and sera	51
	Medicines and drugs	52
	Reagents and diagnostic kits	53
	Public-private partnerships	53
	Conclusions	56
Chapter 5	Malaria research and development: an assessment of global investment	57
	<i>Malaria R&D Alliance</i>	
	Introduction	59
	Surveys findings: malaria R&D investment	60
	Who received funding?	63
	How was the funding allocated?	66
	Malaria R&D investment in context	69
	Conclusions: Global commitment to combating malaria	72
Chapter 6	New prevention technologies: trends in resource flows for HIV vaccines and microbicides	75
	<i>HIV Vaccines and Microbicides Resource Tracking Working Group</i>	
	Introduction	77
	Methods: estimating resource flows for HIV vaccines and microbicides	77
	Estimating investments for HIV vaccines and microbicides	77
	Estimating annual expenditures	80
	Results	80
	Investments in preventive HIV vaccine R&D	80
	Expenditures on preventive HIV vaccine R&D	83
	Resource flows for microbicide R&D	84
	Discussion	86
	Research approach	86
	Enhancing resource tracking	87
	Trends in R&D investments	89
	Conclusion	89

List of figures

Chapter 1

- 1 Country studies (1997-98): systematic mapping of institutions linking sources and users of funds
- 2 Government health R&D resources as a percentage of government budget, health budget and gross domestic product (GDP)
- 3 Health R&D expenditure by type of R&D activity
- 4 Health R&D expenditures as a proportion of total non-defence expenditures, USA and India
- 5 Distribution of federal expenditures in S&T, Brazil 2002
- 6 South African government non-defence R&D expenditure 2003

Chapter 2

- 1 Number of drug R&D projects carried out by drug development PPPs since their creation, sorted by disease
- 2 Total PPP budgets by disease from 2000 to 2004
- 3 Distribution of total PPP budgets by disease since their creation
- 4 Projected PPP budgets by disease in the next five years
- 5 Past budgets and projected PPP needs per DALY lost per year

Chapter 5

- 1 Funds flow of donor 2004 malaria R&D investment
- 2 2004 funding by type of research entity
- 3 Investment by sector
- 4 Government investment by region
- 5 Allocation of 2004 funding by R&D category
- 6 Categorization of 2004 intramural investment
- 7 Categorization of 2004 extramural investment

Chapter 6

- 1 Sources of funding for preventive HIV vaccine R&D, 2004
- 2 Annual investment in preventive HIV vaccine R&D by the public and philanthropic sectors between 2000 and 2005
- 3 Annual public sector investment in preventive HIV vaccine R&D, 2000 to 2005
- 4 Breakdown of HIV vaccine expenditures, 2004
- 5 Annual investment in microbicide R&D by the public and philanthropic sectors between 2000 and 2005
- 6 Annual public sector investment in microbicide R&D, 2000 to 2005

List of tables

Chapter 3

- 1 Global R&D funds, 2001
- 2 Contrasting models of Advanced Purchase Commitments

Chapter 4

- 1 Mean annual expenditures with health R&D activities, Brazil 2000-2002

Chapter 5

- 1 2004 malaria R&D investment by largest funders
- 2 2004 malaria R&D investment by other significant donors
- 3 Funding managers and 2004 funding received
- 4 Comparison of total health R&D and malaria R&D funding by sector
- 5 Disease burden and funding comparison, 2001-2002 data
- 6 New chemical entities (NCEs) approved between 1975 and 1999 by therapeutic area, disease burden and sales

Chapter 6

- 1 Public, philanthropic and commercial sector primary funders
- 2 Annual investment in preventive HIV vaccine R&D by the public and philanthropic sectors between 2000 and 2005
- 3 National public sector investment in preventive HIV vaccine R&D by country in 2004
- 4 Annual investment in preventive HIV vaccines by the commercial sector in 2004
- 5 Annual investment in microbicide R&D by the public and philanthropic sectors between 2000 and 2005
- 6 National public sector investment in microbicide R&D by country in 2004

Boxes

Chapter 6

- 1 Process followed to estimate annual HIV vaccines and microbicides investments

Introduction

The new knowledge and technologies that health research has created have made important contributions to the rapid improvements in average life expectancy and health status that the world has seen during the last century. But these improvements have not been evenly spread and behind the averages there are growing disparities between and within populations. In particular, those who live in poorer countries or communities and those who are marginalized on the basis of ability, caste, class, ethnicity, gender, race or religion have much worse health and lower life expectancies than their richer and more privileged neighbours.

Mirroring these inequities, in health research itself there is an imbalance globally in how resources are applied. The 1990 Commission on Health Research for Development¹ estimated that less than 10% of the world's resources for health research (which totalled US\$ 30 billion in 1986) were being applied to the health problems of developing countries, where 90% of the avoidable burden of ill-health was to be found. Since then, the expression '10/90 gap' has become a symbol of inequity in global expenditures on health research and, while global health research spending has more than tripled, a large imbalance remains.

As part of its contribution to closing the '10/90 gap', the Global Forum for Health Research conducts studies of the flows of financial resources for health research and the extent to which these do, or do not, address the health needs of the poor and marginalized. Two earlier studies of global resource flows^{2,3} traced the substantial increases that have taken place in investments in health R&D (US\$ 85 billion in 1998, rising to almost US\$ 106 billion in 2001) and highlighted the mismatch that persists between how research resources are used and the burdens of disease affecting less developed countries.

The 'bottom line' of the accounting sheet does not tell the whole story, however. These global totals of research expenditure are composed of many sub-components derived from the public and private sectors in high-income, middle-income and low-income countries. Where exactly does the money come from? How much does each source provide, where does the money go and how well are the allocations aligned with health research priorities at global and local levels? The answers to these questions are not merely of academic interest. The information can be immensely valuable in the identification of gaps that require filling and in supporting evidence-based policies on the magnitude and direction of future health research efforts.

This new volume of *Monitoring Financial Flows for Health Research* looks behind the global totals and examines several facets of the overall picture, including health research funding by low- and middle-income country governments and the private sector, as well as with the financing of research on some major neglected diseases.

Well over 90% of global health research finances in the public sector are derived from high-income countries.³ However, the 1990 Commission on Health Research for Development¹ recommended that developing countries should themselves allocate at least 2% of their national health budgets to essential health research and research capacity strengthening. As delineated in

the 2004 report,³ very few countries have so far reached this target; more seriously, few countries have made the effort to track health research resources and none has established a comprehensive and reliable statistical system for the routine gathering, analysis and use of such data. The first chapter in this volume, by Mary Anne Burke and Andrés de Francisco of the Global Forum, summarizes the efforts that have been made and that are ongoing in this field. It also highlights the evolution of a much broader and more holistic definition of health and the need for a wider and more multisectoral approach to understanding the determinants of health. This points to the challenge of defining ‘health research’ – indeed, of re-conceptualizing it as ‘research for health’ – and of developing tracking systems that identify relevant sources and applications of research resources that lie beyond the health sector.

During the last decade, there has been an explosive growth in the number of public-private partnerships (PPPs) in the health field, some of which are engaged in the development of new drugs for neglected diseases. This changing landscape is surveyed by Mary Moran of the Pharmaceutical R&D Policy Project at the London School of Economics, who highlights the considerable progress that the PPPs have already achieved in creating a steady pipeline of potential new drugs moving into clinical trials. She also draws attention to two key roles that governments must now play if the pipeline is not to run dry in the near future: first, to recognize that existing funding mechanisms and proposed new ones, such as Advanced Purchase Agreements, may not be the best way to support and stimulate the new model of drug development and may even harmfully distort the priorities of commercial partners; and second, that it is time for governments to play a more direct role in the financing of key PPPs if they are to complete clinical trials with their candidate drugs.

Data from the pharmaceutical industry itself³ indicates that, globally, it makes the largest contribution of any sector to health R&D, amounting to more than US\$ 50 billion dollars annually. However, little is known about the exact components of this total – including how much is spent on basic research as opposed to applied R&D for the later stages of drug development, testing, introduction and monitoring. The Global Forum is pleased to provide a platform in this publication for a critical assessment by Donald Light, Professor of Comparative Health Care Systems at the University of Medicine and Dentistry of New Jersey, of the real costs to industry of the basic research it conducts. The results – suggesting that these costs are far less than industry has claimed – will doubtless provoke intense debate. We welcome the reactions of other analysts and especially of industry itself. The potential for dispute in this area serves to highlight the fact that extremely little data is available to the public. The debate may encourage industry to develop more transparency about its funding of research while preserving the confidentiality of commercially sensitive information. The following chapter, contributed by Reinaldo Guimarães from FIOCRUZ, Brazil, provides an example of the tracking of research resources in a middle-income country that has become a leader in innovation in recent years.

HIV/AIDS and malaria are among the leading causes of death in a number of developing countries, especially in sub-Saharan Africa but increasingly in other regions as well. The two diseases are given specific attention in the Millennium Development Goals. There is little evidence that at present rates, the goals will be met, with both the ‘3x5 Initiative’ and the ‘Roll Back Malaria’ campaign failing to meet their targets so far. For both diseases, the tools available are limited and

increasingly the available drugs are being compromised by problems of resistance. New knowledge and technologies (drugs, vaccines, diagnostics and, in the case of HIV/AIDS, microbicides) are required. More research is necessary on upstream interventions needed to keep people healthy and prevent infection in the first place. Downstream interventions aimed at treatment are much more costly, and with increasing rates of infection, they represent a potentially bottomless pit for funding. Also needed is access to information on how resources are currently being spent to discover these new technologies. Donald Light's findings in the previous chapter draw attention to the difficulty that exists in obtaining information on R&D spending from industry. There is an urgent need to collect and use this information, while publishing only aggregate (non-threatening, non-competition-sensitive) data. The final two chapters of this volume, contributed by the Malaria R&D Alliance and the HIV Vaccines and Microbicides Resource Tracking Working Group, summarize the available information on the flows of financial resources for research in these vital areas. In both cases, while some welcome increases in resources have been seen in recent years and the creation of specific PPPs has attracted greater investments, it is clear that major gaps remain and much greater effort is required if these major scourges are to be beaten.

The Global Forum is extremely grateful to the authors and organizations that have contributed to this compendium of studies of resource flows for health research. We hope that the information and views they have provided – sometimes surprising new data, sometimes provocative opinions – will stimulate more debate and more action that will lead, ultimately, to enhanced resources for health research to focus on the neglected health challenges that the world faces. For the millions of people whose deaths and burden of ill-health are avoidable every year, this is the bottom line that counts.

Professor Stephen Matlin
Executive Director
Global Forum for Health Research

-
1. Commission on Health Research for Development. *Health Research: Essential Link to Equity in Development*. New York: Oxford University Press, 1990.
 2. *Monitoring Financial Flows for Health Research 2001*. Global Forum for Health Research, Geneva, 2001.
 3. *Monitoring Financial Flows for Health Research 2004*. Global Forum for Health Research, Geneva, 2004.

Chapter 1

Towards the building of robust, sustainable systems of data collection and reporting on expenditures for research for health

by Mary Anne Burke and Andrés de Francisco

Mary Anne Burke is the Health Analyst/Statistician for the Global Forum for Health Research. Previous positions include Director of Research, The Roeher Institute, Toronto, Coordinator of the Gender-based Analysis (GBA) Initiative and Senior Policy Analyst with Health Canada, and Social Statistician with Statistics Canada and UNICEF. She has published widely in the areas of public policy, social conditions and human rights and undertaken pioneering work to develop analytic frameworks for health policies and programmes.

Andrés de Francisco, Deputy Executive Director of the Global Forum for Health Research, is a medical doctor with post-graduate training in public health and extensive experience in the interface between research findings and health policies. He has worked on the design, implementation, and evaluation of health interventions, and the subsequent development of research knowledge into policies for health and population programmes in South America, Africa and Asia.

Chapter 1

Why measure?

Research for health is essential for continued improvements in health and for reductions in health inequities within and among countries. Knowing how much money is spent on research for health, by whom, for what and where the gaps are is critical for reducing the '10/90 gap'. This has been the focus of the work of the Global Forum for Health Research.^{1,2}

Tracking expenditures on research for health is required to:

- monitor current levels of effort and describe trends
- identify gaps where more effort is needed
- assess the impact of public policies aimed at increasing investment in R&D for health
- use this information for advocacy purposes
- promote a debate at the policy level.

Tracking of resource flows for R&D for health at the global level is essential to inform funding and policy-making decisions of the international community, governments of high-income countries (HICs) and the private sector so that the continuing under-investment in health research for the needs of low- and middle-income countries (LMICs) can be addressed.

Additionally, tracking of national expenditures on research for health by LMICs is essential for countries a) to assess how well their investments are meeting research objectives and national priorities for research for health and addressing national health problems; and b) to inform national funding and policy decisions to best direct national research towards national health needs. As well, data on health research expenditures are therefore an

essential element in the process of identifying and setting national health research priorities and increasing the responsiveness of research efforts. They can also provide valuable evidence to inform the monitoring and evaluation of national health research systems and improve accountability.

In addition, this information can be used to develop funding strategies that make best use of national resources and opportunities provided by international sources, to target local health research priorities. It can strengthen arguments for more funding for research and inform decisions to ensure that it is spent more wisely. It demonstrates the national commitment to health research, and a strong commitment can be a powerful tool in negotiations with foreign donors.³

Efforts to date in tracking financial flows for health research in LMICs

The Council on Health Research for Development (COHRED) carried out some of the early work to measure and monitor investments in health research in LMICs. Information from three country studies undertaken by COHRED in Malaysia, Philippines, and Thailand in 1997 and 1998 was presented in the Global Forum's first publication on financial flows for health research: *Monitoring Financial Flows for Health Research 2001*.⁴

The three country studies were an important contribution to the field. They served to stimulate the development and piloting of a methodology to collect information at the country level from both users and funders of health research investments. The results of the

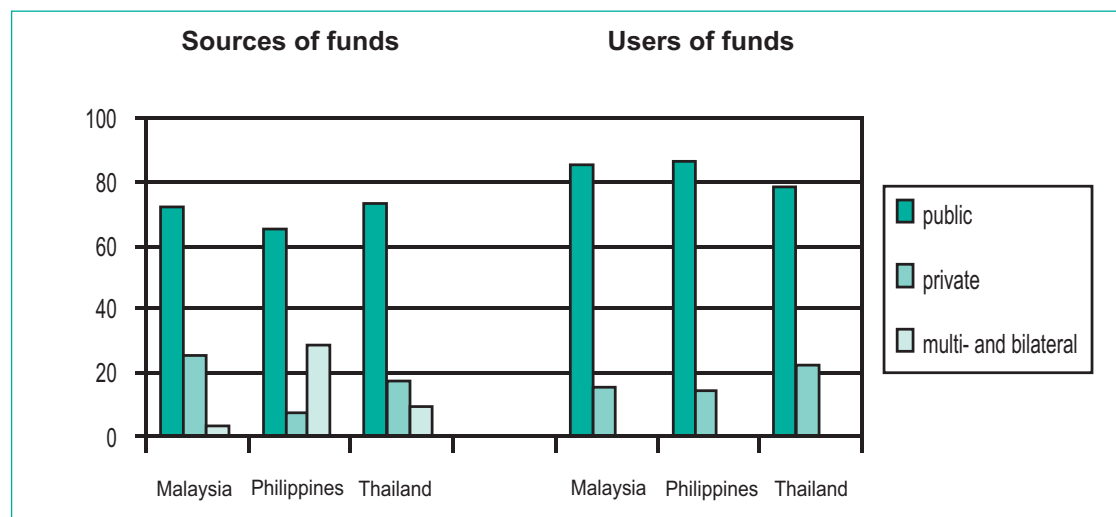
studies provided very useful information for the countries themselves and for the global monitoring of financial flows for health research. While mapping users and producers of health research (see Figure 1), these studies also showed the feasibility of collecting data in LMICs using a standardized format. They served as inputs to a comparative report and for a manual for tracking health R&D funds, published in 2000.⁵

Subsequently, COHRED, WHO and the Global Forum initiated a study to obtain resource flows information from other LMICs. A workshop supported by COHRED and the Global Forum was undertaken in Geneva in April 2002 for this purpose. The workshop aimed to standardize the methodology, train

the investigators and identify users and funders of health research for each country. The objective of the new studies was to present a comparative picture of resource flows for health R&D across countries. Principal investigators from seven countries were invited to participate. These included: Brazil, Burkina Faso, Cameroon, Cuba, Hungary, Kazakhstan and Uzbekistan.

The seven country studies were funded by COHRED. Brazil had changes in administration and the study was delayed. The studies followed an ‘accounting framework’ model in which information from funding sources and funding users was related. The strategy included the following steps for each country:

Figure 1: Country studies (1997-98)
Systematic mapping of institutions linking sources and users of funds



Source: Alano & Almeria, 2000⁵

1. Undertake desk research on health research
2. Conduct key informant interviews for priority setting process
 - identify agencies
 - identify interviewees
 - design interview schedule.
3. Conduct interviews
 - develop findings
4. Conduct survey for the database
 - develop the respondent base
 - design the survey instrument
 - conduct the survey
 - process the data
 - format the tables
5. Integrate findings into final report.

1. Information on funding for health research as a proportion of Government Budget, Health Budget and GNP to estimate the recommendations made by the 1990 Commission on Health Research for Development (Figure 2, includes some of the earlier studies).
2. Health R&D investments by type of activity by country (Figure 3).
3. Relation between national health R&D expenditure and identified national health research priorities in Cuba.

The results of these studies were presented in a paper by Bing Alano and Andrew Kennedy at Forum 6 (the Global Forum’s 2002 annual meeting in Arusha, Tanzania). Selected results from the integrated study included the following:

These findings can help to inform country policy-making. Figure 2, for example, shows the proportion of health research investments as a proportion of health investments, and depicts that none of the countries have reached the 2% recommended by the Commission on Health Research for Development in 1990.⁶ Figure 3 shows interesting contrasts of type of health research expenditures between countries.

Figure 2: Government health R&D resources as a percentage of government budget, health budget and gross domestic product (GDP)

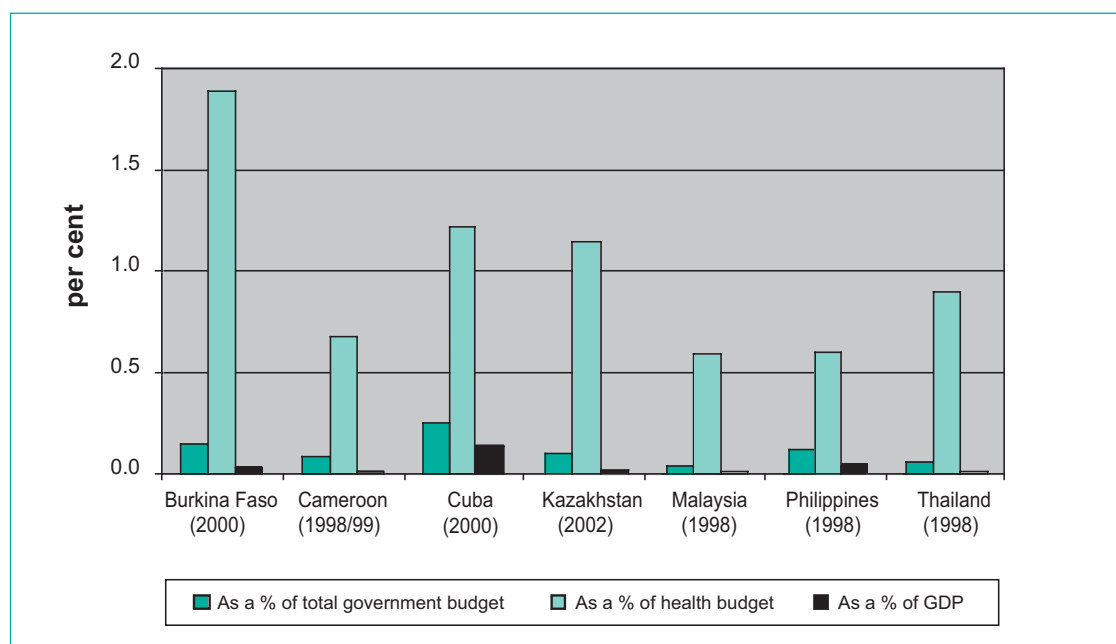
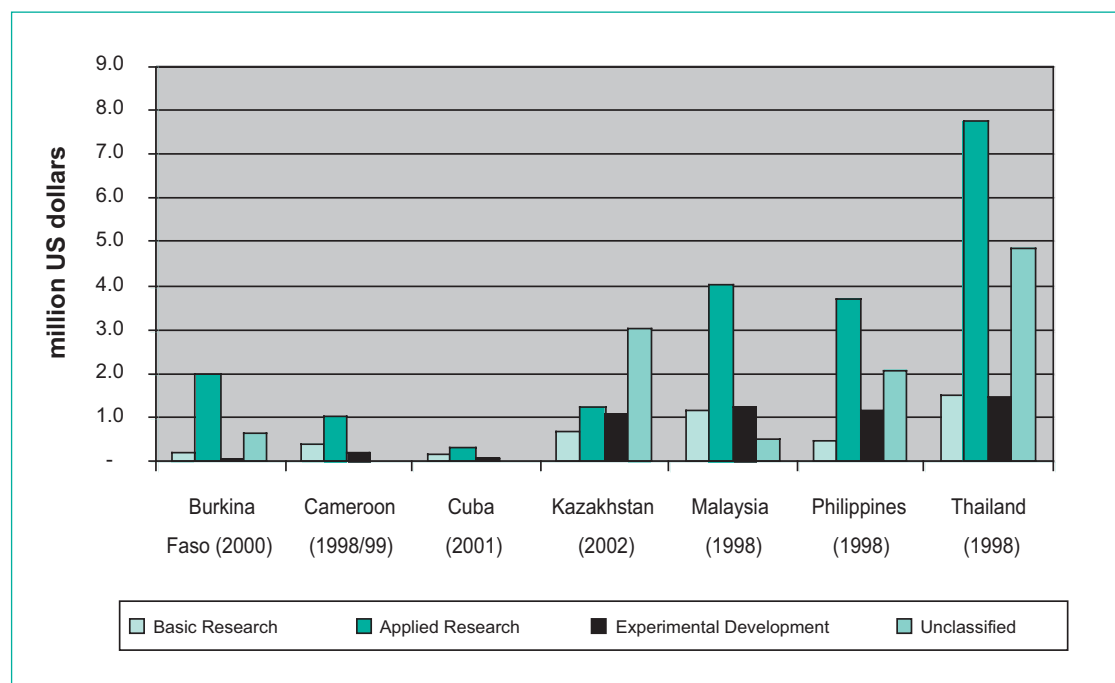


Figure 3: Health R&D expenditure by type of R&D activity



The study intended to collect information from the private and public sectors. One additional important finding was the reluctance of some private-sector institutions to divulge financial information to the study investigators. This low level of transparency reflected a fear that divulging such information could lead to a reduction in government assistance for R&D to private-sector institutions.⁷

A key objective of the study was to create capacity in countries to undertake studies on financial flows on an ongoing basis. Another key objective was to generate information about investments in health R&D that could be used to inform policy (on health systems reform and disease burden), to monitor practice (priority setting and progress with essential national health research) and to mobilize national and international resources for health research and its monitoring.

The workshops and subsequent follow up of the project management served to transfer knowledge and skills related to tracking financial flows for health R&D to those conducting the studies in the countries involved. The studies were also useful to these countries for immediate advocacy purposes. They also assisted other countries (through dissemination of findings and pitfalls) to create awareness of health research and its financing (through the results) and to set the base for future studies and activities in this field.

Nonetheless, the studies did not result in sustained capacity to measure and monitor investments in health R&D on an ongoing basis. There has been no follow up to these studies, and the countries involved did not establish programmes to continue tracking their investments. While some knowledge transfer did take place in the countries involved, some

of the selected investigators left their positions and the institutional memory of the know-how to undertake these studies was lost. A more long-term, sustainable approach to collect resource flows data is needed.

The original financial flows studies used an accounting framework and data were gathered through interviews, desk work and a few one-off studies among a few countries. The data generated through these methodologies was useful to flesh out the overall picture and for advocacy for increased investments in health research.

A similar exercise conducted in India generated data that were presented in a simple figure successfully used to advocate for increased investments in health research (see Figure 4). The figure was a powerful yet simple instrument to demonstrate under-investment in health relative to other sectors of the economy in India.

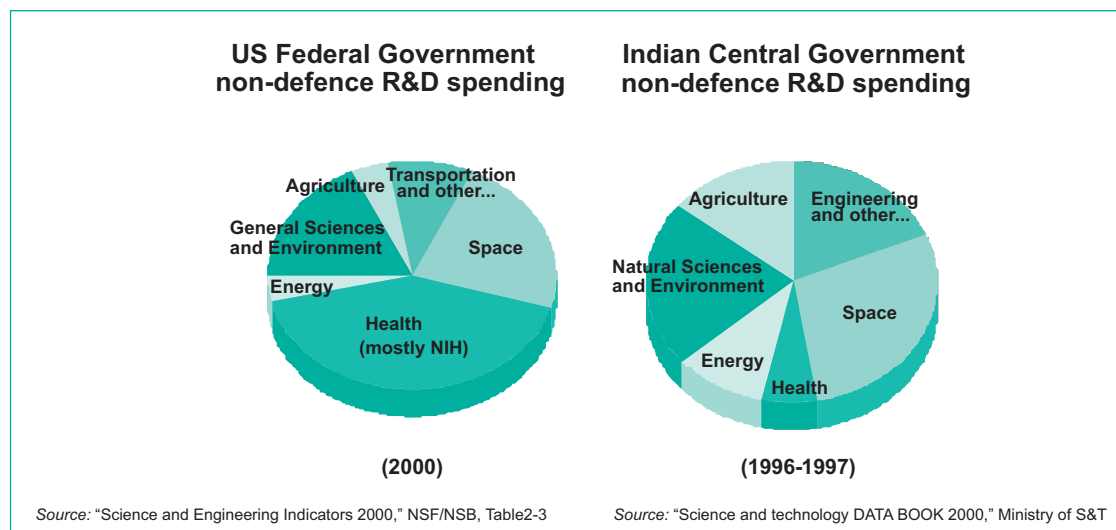
With funding from the Rockefeller Foundation, the Global Forum for Health Research, in

collaboration with COHRED and with inputs from WHO, launched a project in early 2005, in three “innovative developing countries”⁹: Brazil, India and South Africa. One objective of the project was to produce figures similar to Figure 4 that could be used for advocacy purposes. “The intent is to generate data on health R&D expenditures in relation to expenditures on all other types of non-defence R&D and to national health priorities that can be used for advocacy for increased domestic (and international) expenditures on health research in each of the countries, with the goal of reducing inequities in health and health research and improving the overall health of their populations.”¹⁰

India is in the process of producing the data needed to update Figure 4. Brazil and South Africa were able to produce similar figures with data drawn from their recent science and technology and R&D surveys, respectively: see Figures 5 and 6.

Figure 5 shows federal investments in science and technology (S&T) in Brazil by the source

Figure 4: Health R&D expenditures as a proportion of total non-defence expenditures, USA and India⁸



of funding. It demonstrates the complexity of funding for S&T from multiple sources. It also demonstrates the difficulty in apportioning funding for health R&D from overall S&T expenditures. It is likely that each of the ministries funds health R&D as part of the S&T activities to some extent, while most of what the Ministry of Health funds could be considered to be health research.

Figure 6 shows South Africa's investment in health R&D relative to investments in other sectors of its economy. It may suggest the need

for relatively larger investments in health, especially given the health needs of the country.

Such information clearly has the potential to be used in determining priorities for investment in research, including research for health. The data produced, however, are only very rough estimates and do not lend themselves to the sophisticated analysis needed for informed policy-making for addressing inequities in health and in the conduct and financing of health research.

Figure 5: Distribution of federal expenditures in S&T, Brazil, 2002 (BRL thousands)

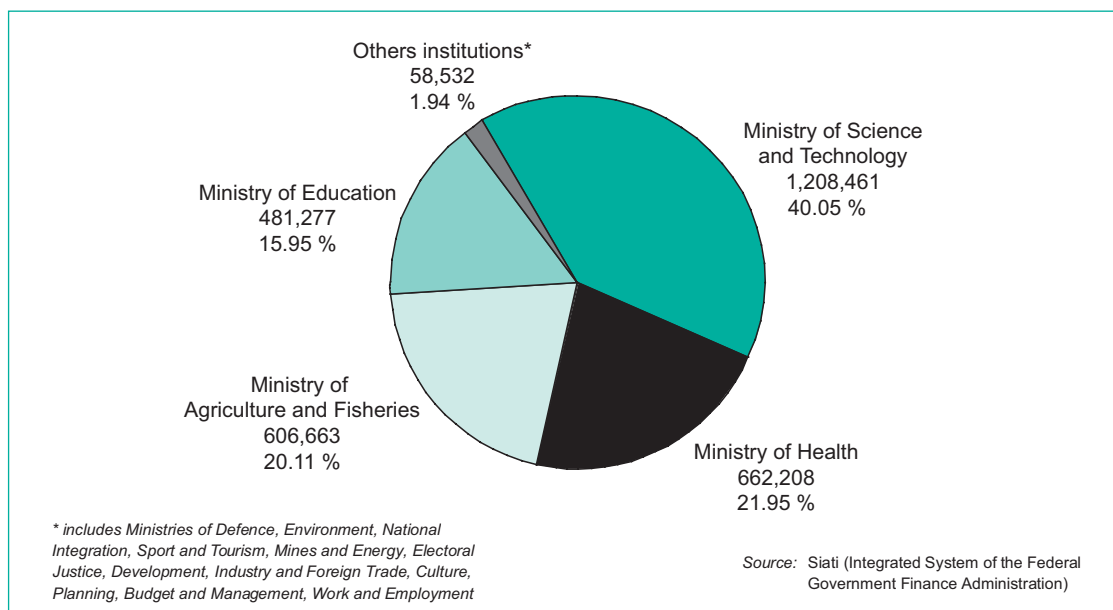
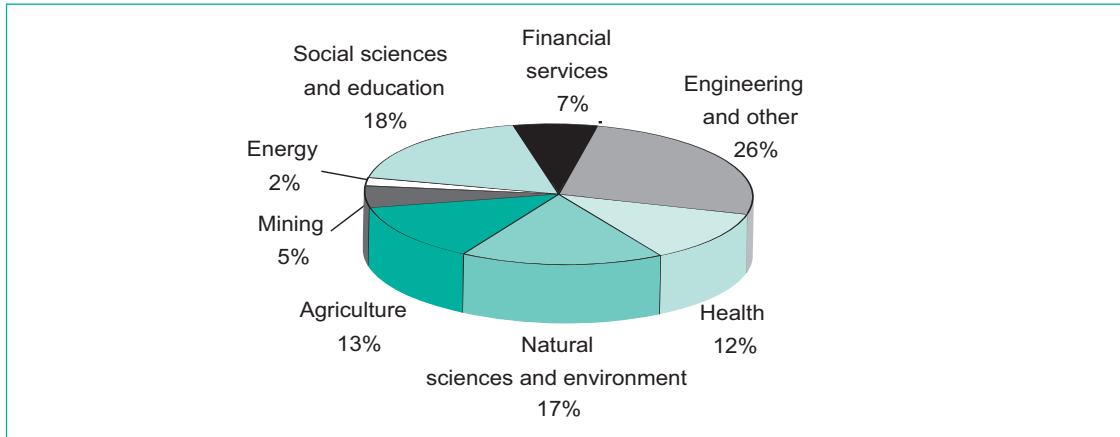


Figure 6: South African government non-defence R&D expenditure, 2003



Source: 2003/04 South African R&D Survey, Department of Science and Technology, South Africa, 2005.

Efforts to date in tracking global financial flows for health research

If gathering data on national health research and health research expenditures has been a very onerous and labour-intensive exercise to date, so too has been the effort to produce estimates of total global investments in research for health. The 1990 Commission on Health Research for Development made the first estimates of global spending on health R&D (US\$ 30 billion in 1986). This rough estimate was updated in 1996 by the WHO Ad Hoc Committee to US\$ 55.8 billion for the year 1992.

Given the complexity and importance of the task, the Commission recommended a mechanism for monitoring and analysing global funding for health research. This led to the establishment of the Global Forum for Health Research in 1998, and to its first global estimate of US\$ 73.5 billion in expenditures on health research for the year 1998, published in *Monitoring Financial Flows for Health Research 2001*.

This estimate was arrived at by bringing together data from multiple sources so that as complete a picture as possible could be given.

It involved the development of a sophisticated estimation methodology¹¹ to extract information about health R&D expenditures by countries who report to the Organization for Economic Cooperation and Development (OECD) and to the Network on Science and Technology Indicators – Ibero-American and Inter-American (RICYT).

Improvements in the estimation methodology and the inclusion of data from more countries resulted in a revision of this estimate to US\$ 84.8 billion for 1998. More recent work has led to an estimate that global health R&D expenditures further increased to US\$ 105.9 billion, by 2001 as published in *Monitoring Financial Flows for Health Research 2004*.

Nonetheless, these figures are still very rough estimates of global expenditures by the largest players in the field, assembled through complicated estimation methodologies aimed at assigning to the health field a proportion of total R&D expenditures reported by countries to the OECD and RICYT. The data account for the largest public expenditures on health R&D globally; however, data on expenditures on R&D for health by many of the LMICs and by

the private, for-profit sector from many of those countries is largely not accounted for. In many countries, R&D surveys are isolated exercises, and in many low- and middle-income countries are not administered at all. Furthermore, data are reported at an aggregate level, making it impossible to examine disaggregated investments in specific health research areas.

Indeed, there is no systematic and sustainable system in place for collection and reporting on health research or health research expenditure data in any country. **Routine, comprehensive statistics on expenditures on research for health simply do not exist for any country in the world.**

Additionally, the estimates do not permit us to break the data down into finer levels of detail to really understand which areas of health are receiving attention and where the big gaps remain. The estimation methodology also probably favours the identification of expenditures on biomedical over social science research – research that is very much needed to fully explore how the determinants of health play out in the lives of individuals and communities.

Better national statistical systems that report on expenditures on health R&D are urgently needed to:

- track investments in health and health R&D in a more accurate way
- disaggregate R&D investments by the nature and kind of research being conducted
- track financial flows within and among countries.

Work is needed at two levels: 1) building the capacity in countries to develop viable, robust and sustainable national statistical systems, and 2) developing good quality data and mechanisms for its analysis, communication and use by policy-makers leading to better

prioritized and resourced health research that ultimately improves health status and health equity in the population.

At issue are lack of commitment and funding by governments in low- and middle-income countries to invest in building and sustaining robust national statistical systems, lack of technical expertise, and lack of infrastructure to support and sustain data collection, analysis and dissemination. Also at issue is the very fragmented international statistical system, with different international organizations collecting different sets of global health data, and each employing different concepts, definitions and methodologies all designed to suit their own data collection needs for various programmatic purposes.

Building sustainable systems for national reporting on health research expenditures

Clearly better systems are needed for tracking expenditures on research for health both among LMIC and globally. It is evident that sustainable ongoing national systems to collect and report on data on national R&D expenditures for health are urgently needed. COHRED, WHO and the Global Forum have begun work in this area, building collaboratively on and learning from efforts to date.

Better national systems require work at two levels. First, efforts must be made to build viable infrastructures within countries to support a sustainable and ongoing system for statistical collection and reporting on health research expenditures. Second, there is an urgent need for the elaboration of an internationally accepted classification system of health research to underpin data collection and reporting activities on expenditures.

The 2005 project in Brazil, India and South Africa aimed to address these needs, as do other efforts of COHRED and WHO. The draft health R&D classification framework developed jointly by COHRED, WHO and the Global Forum was appealing to the various stakeholders in the 2005 project. There was considerable interest in having the data described by the framework available to the level of disaggregation and detail anticipated in the classifications system. Many participants recognized that having such data would very much enhance their policy-making for health and health research and would permit them to address some of the persistent health inequities in their societies.

Several areas for work were identified. First, existing R&D surveys are not designed to fully capture national statistics on research for health. Typically any health R&D data that are captured tend to focus on expenditures on research related to diseases and biomedical health issues. Considerable work would be needed to design an instrument to capture the full spectrum of expenditures on national health research systems. Secondly, given the complexity of the task and sheer scope of the research system, investments would be needed to build the required capacity to undertake this kind of work.

New understanding of national health research systems needed

The need to broaden the scope of what is considered within a national health research system is prompted by new understanding about health and health inequities. One of the key findings of the Global Forum's *Monitoring Financial Flows for Health Research 2004* report was that, given the nature of the available data and the complexity of research for health, an exact measurement of the '10/90 gap' at the global

level was not only an impossible task, but also that a single global aggregate figure might "obscure or distract attention not only from the real health needs of many populations (given the diversity of health problems in different populations and sub-groups in countries and regions) but from the more complex determinants of health such as poverty, inequities, gender, violence and abuse, access to education, and opportunities to participate and be part of decision-making processes".

The 2004 *Financial Flows* report thus signalled a new approach to health and health research, being taken not only by the Global Forum for Health Research, but by a growing constituency of thinkers, including within WHO and its newly constituted Commission on Social Determinants of Health. Indeed, the 2005 Bangkok Charter for Health Promotion situates health within a human rights framework, calling for solidarity in efforts to achieve democracy, equity and social justice as the cornerstones of health. In this paradigm, health is no longer seen as a means to achieve economic growth and national wealth. Indeed, health is viewed as the end and the primary responsibility of governments, international organizations and corporate and civil society alike. Ensuring economic and social development is the pathway to health, and, as such, research for health must expand beyond biomedical and health care systems' 'downstream' responses to diseases and ill-health.

Research is needed to understand what people, especially those experiencing inequities in health, need to be healthy. Research is also needed to understand how biases that derive from social hierarchies play out in access to health, in the health care system and in access to and delivery of a wide range of supports, services and programmes that create and sustain conditions for health.

“Historically, women, disabled persons and others belonging to certain classes or ethnic, racial, linguistic or religious groups have tended to be disadvantaged relative to men, ‘non-disabled’ and other dominant groups in their society... These pervasive inequalities have negative health consequences and contribute substantially to global health inequities and the ‘10/90 gap’ in health research.”¹²

Likewise, people with low incomes, low education and low social and occupational status experience poorer health than their higher status peers.¹³ Research is also needed to understand this social gradient in health – what are “the causes of the causes” of the poor health experienced by people positioned towards the bottom of the gradients of various social hierarchies? How do social exclusion, lack of control over decisions affecting one’s life and feeling vulnerable, stereotyped, objectified and treated without dignity affect the health and well-being of individuals?

There are many different pathways into poverty and social exclusion, and research is needed to understand not only these pathways, but also the differential effect of the diverse pathways on the health of the affected people. At the same time, research is needed to explore why some people are able to obtain and sustain health despite the inequities they face. Research is needed to understand the intricate set of individual, family, community and societal factors at work in the lives of these people and how they play out across the physical, mental, spiritual and social domains of well-being to create and sustain health.

Research for health then must be understood in much broader terms, encompassing research on:

- health planning
- public health
- safety, quality, availability, affordability, accessibility, inclusivity of:
 - ◆ water, food, housing, sanitation
 - ◆ natural environments
 - ◆ built environments
 - ◆ social environments

- health promotion
- health education
 - ◆ health knowledge, attitudes and practices
- health research systems
 - ◆ health classifications systems, measures and indicators
- health status & human functioning
- health equity
- rehabilitation
- social determinants of health
- safety, quality, accessibility, affordability, inclusivity, efficiency, effectiveness, impact of
 - ◆ public policies, programmes, systems and services *outside the health sector*
 - ◆ *health* policies, programmes, systems and services
 - ◆ *health-care* policies, programmes, systems and services
 - training of health-care workers
 - human resources
 - scale-up
- disease monitoring and surveillance
- disease prevention and treatment
 - ◆ risk factors for ill-health and disease
 - ◆ specific diseases or conditions
 - ◆ disease outcomes and impacts

This research reaches across all sectors of the public and private sector. It ranges from biomedical research on drugs, vaccines, diagnostics and appliances to research in the chemical, biological, physical, agricultural, human and social sciences, encompassing policy and systems research, operational research and behavioural research.

Wider variety of players

This enlarged scope of research for health has obvious implications for work to map out who funds and who uses funds for research for health. Much more research is needed to identify this full set of players, what kind of research they fund, who sets the priorities for research funding, who governs it, who conducts it, who uses it and where there are inequities and gaps in research and research expenditures.

One of the key issues to emerge from the discussions of the 2005 6th Global Conference on Health Promotion in Bangkok, Thailand was the importance of engaging individuals and communities experiencing health inequalities as equal and active participants in research for health. This stems from a fundamental understanding that health belongs to individuals

Conclusions

Resource flows indicate the level of support provided to specific areas of research, and analyses and comparisons of these flows can point to inequities and gaps in the funding and conduct of research. It is critical information for improvements in health research at country level, for improving the allocation of funding to redress inequities and address the major health issues facing low- and middle-income countries and populations coping with persistent inequalities in health and for advocacy towards these ends nationally and internationally.

Having reliable, good quality and trustworthy data on health research and health research expenditures is essential for democracy, a right of citizenship and fundamental to the development, implementation, monitoring and evaluation of policies, programmes and interventions aimed at reducing inequities in health and health research.

and communities and that they not only define what health means for themselves, but are the most knowledgeable about what they need to create and sustain health for themselves. Civil society, including global networks of NGOs, social and health movements, professionals and academics, labour organizations and employers must also be engaged with public- and private-sector researchers as full and equal participants. This will contribute to a fuller understanding of the issues and more informed and responsive research.

The inclusion of this broader range of actors in the scope of what is defined as “health research”^a or “research for health” poses substantial challenges for the development of national systems for tracking research resources. Considerable further work will be required to develop, test and operationalize systems that can meet the requirements.

There is an urgent need for governments in low- and middle-income countries to commit to and invest in building and sustaining robust national statistical systems that can support the collection of and reporting on health research and health research expenditure statistics. It is important that the international community support these countries towards this end, to bolster the technical expertise and infrastructure required to support strong and sustainable national systems and to work towards the standardization of concepts, definitions and methodologies for collecting and reporting on these data, within an agreed-upon international classification system for health research. This will necessarily involve a number of key stakeholders responsible for undertaking this kind of work.¹⁴

WHO, COHRED and the Global Forum are continuing to work with countries and within the international system, to refine the

classification framework to incorporate the wider understanding of health called for by the Bangkok Charter, among others, and to support the development of sustainable national

infrastructures for the collection and reporting of expenditures on national systems of health research.

- ¹. Global Forum for Health Research. *The 10/90 Report on Health Research 2003-2004*. Geneva: Global Forum for Health Research, 2004.
- ². Global Forum for Health Research. *Monitoring Financial Flows for Health Research 2004*. Geneva: Global Forum for Health Research, 2004.
- ³. COHRED. *Health research expenditures: essential information for rational decision-making*. Policy Brief No 2004.2. Geneva: COHRED, 2004. See www.cohred.org, accessed 29.11.2005.
- ⁴. Global Forum for Health Research. *Monitoring Financial Flows for Health Research*. Geneva: Global Forum for Health Research, 2001.
- ⁵. Alano BP, Almario ES. *A Comparative Report on Malaysia, the Philippines, and Thailand, with a Manual on Tracking Country Resource Flows for Health Research and Development*. Geneva: COHRED, 2000.
- ⁶. Commission on Health Research for Development. *Health Research: Essential Link to Equity in Development*. New York: Oxford University Press, 1990.
- ⁷. Alano BP & Almario ES. Tracking Funds Flow for Health R&D: Comparative Results from Burkina Faso, Cameroon, Cuba, Kazakhstan, Malaysia, Philippines, and Thailand. Paper presented at Forum 7, the Global Forum for Health Research's 2003 annual meeting in Geneva, 2-5 December 2003.
- ⁸. Figures courtesy of Charles Gardner, Rockefeller Foundation
- ⁹. Morel CM et al. Health Innovation Networks to Help Developing Countries Address Neglected Diseases. *Science*, 2005; 309:401-404. See www.sciencemag.org
- ¹⁰. Global Forum for Health Research, forthcoming. *Financial Flows Study in Brazil, India and South Africa*. Project Proposal Number: 13 /2004.
- ¹¹. See Chapters by Alison Young and Andrew Kennedy in *Monitoring Financial Flows for Health Research: Work in progress for discussion and feedback on the occasion of Forum 7*. Geneva: Global Forum for Health Research, 2003.
- ¹². Eichler, Margrit and Mary Anne Burke, forthcoming. *The BIAS FREE Framework: A practical tool for identifying and eliminating social biases*. Geneva: Global Forum for Health Research.
- ¹³. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, White I, Brunner E, Feeney A. Health inequalities among British civil servants: the Whitehall II study. *Lancet*, 1991; Jul 6, 338(8758):58-9.
- ¹⁴. International classifications systems currently exist in a number of areas, including for health, disability and disease.

Chapter 2

Drug R&D for neglected diseases by public-private partnerships: are public funds appropriately distributed?

by Mary Moran and Javier Guzman

Mary Moran trained as a medical doctor and spent thirteen years working in Emergency Medicine. A post-graduate degree in international relations and politics at University of NSW and later Monash University (1995) led her into a diplomatic career with the Australian Department of Foreign Affairs & Trade, followed by three years with Médecins Sans Frontières, working on the Access to Essential Medicines Campaign. In 2004, she founded the Pharmaceutical R&D Policy Project (PRPP) at the London School of Economics & Political Science. The PRPP transferred to the George Institute, Sydney, in 2006, where Dr Moran continues as Director.

Javier Guzman trained as a medical doctor and worked in the planning and implementation of primary health care projects in the Colombian countryside for several years. Javier moved to the UK in 2002, where he worked as a Post Graduate Clinical Fellow in Paediatrics at the Royal London Hospital. In 2004, he obtained his MSc in Health Policy, Planning and Financing from the LSE and the London School of Hygiene and Tropical Medicine. Previous work also includes early detection and treatment programmes of endemic infectious diseases such as Tuberculosis and Chagas disease.

Chapter 2

The landscape of neglected disease drug development has improved dramatically over the past five years.¹ This renewed activity is evidenced by the more than 60 R&D projects underway at the end of 2004, including twenty new neglected disease products in clinical trials or at the registration stage.² Although different initiatives have been associated with what has been described as “a new era of hope for these forgotten diseases,”³ the major impetus for this change has been the creation of four new public-private partnerships (PPPs) for neglected disease drug development.⁴ These new PPPs, in addition to the UNICEF/UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR), conducted nearly 75% (47 out of 63) of neglected disease drug development projects identified at the end of 2004; and, based on standard attrition rates, their portfolios would be expected to deliver six to seven new neglected disease drugs within five years.

We define PPPs as public-health-driven, not-for-profit organizations which drive neglected disease drug development in conjunction with industry groups. Using these criteria, five neglected diseases drug development PPPs are identified:

- one for malaria: Medicines for Malaria Venture (MMV) founded in late 1999
- one for tuberculosis: Global Alliance for TB Drug Development (TB Alliance), founded in late 2000
- one with a first focus on the kinetoplastid diseases:⁵ Drugs for Neglected Diseases initiative (DNDi), founded in mid-2003
- Institute for OneWorld Health (iOWH), founded in 2000, which addresses a range of diseases from malaria to diarrhoea, and

works not just on drugs, but also on vaccines and technologies

- TDR, which has operated as a de-facto PPP since the mid-1970s.

Earlier papers have focused on the R&D cost structures and financial flows of these PPPs, including quantification of their past and future funding needs.^{6,7} However, we focus here on financial flows to PPPs by disease, in order to provide policy-makers with at least an early indication of how and where they are prioritizing their funding. (A mechanism to allow such information to be routinely collated is suggested elsewhere).⁸ This paper will describe past PPP expenditure and future budget projections by disease, identifying possible limitations within this approach. It will also try to illustrate factors associated with the different levels of funding found.

Past PPP expenditure by disease⁹

The creation in late 1999 of MMV, the first new drug development PPP, was followed by increased R&D neglected disease activity under the partnership approach. This is evidenced not just by the entry of further new PPPs, with the consequent increase in the number of projects conducted, but also by the growth in individual PPP R&D expenditure since 2000. For instance, in 2004, these new PPPs (excluding TDR) had an aggregated portfolio of 41 projects compared to 33 in 2003. Furthermore, their R&D expenditure nearly doubled from US\$ 23 million to US\$ 44 million in the same period.

This burst of activity has, however, not been even across diseases (Figures 1 and 2). For instance, in 2004 nearly 60% of PPP projects in the preclinical stages (17 out of 29) and 82%

(9 out of 11) in clinical stages were dedicated to malaria. Moreover, 75% of total PPP budgets were used to cover expenditure on these malaria projects in that year (Figure 3).

In the next sections the reasons behind these different levels of funding, and the future

distribution of PPP funding, will be reviewed. We will also examine whether these figures are a reliable indicator of global drug R&D expenditure on these neglected diseases and, if so, whether the current distribution is appropriate to global public health needs.

Figure 1: Number of drug R&D projects carried out by drug development PPPs since their creation, sorted by disease

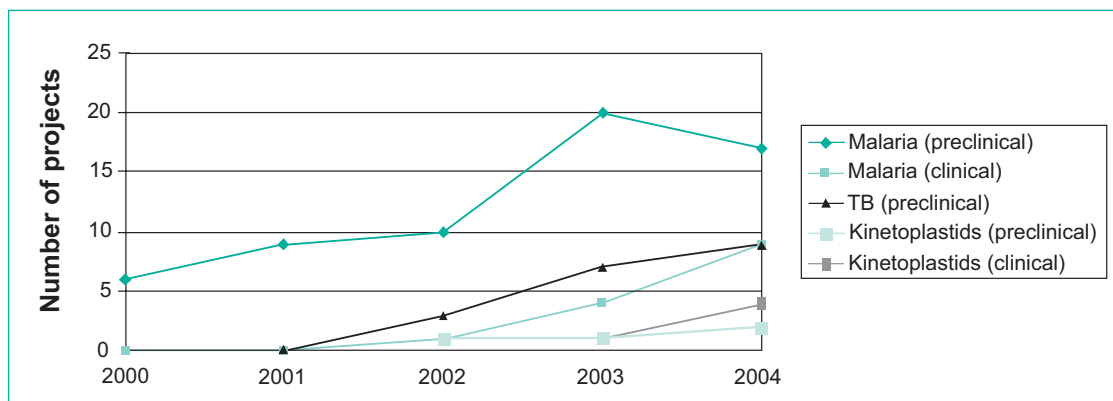


Figure 2: Total PPP budgets by disease from 2000 to 2004*

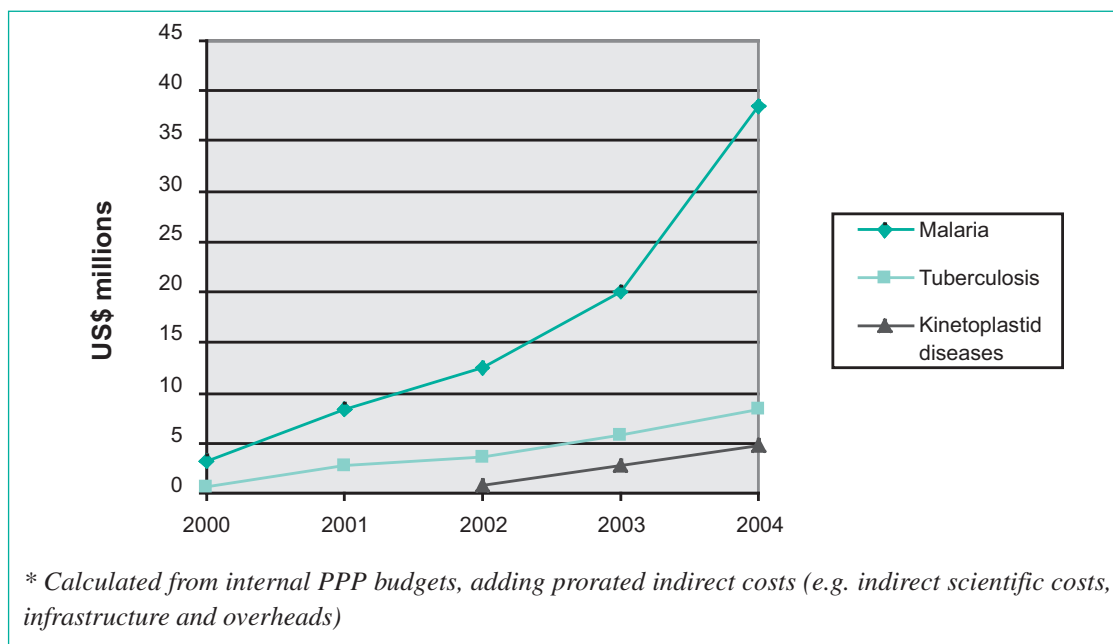
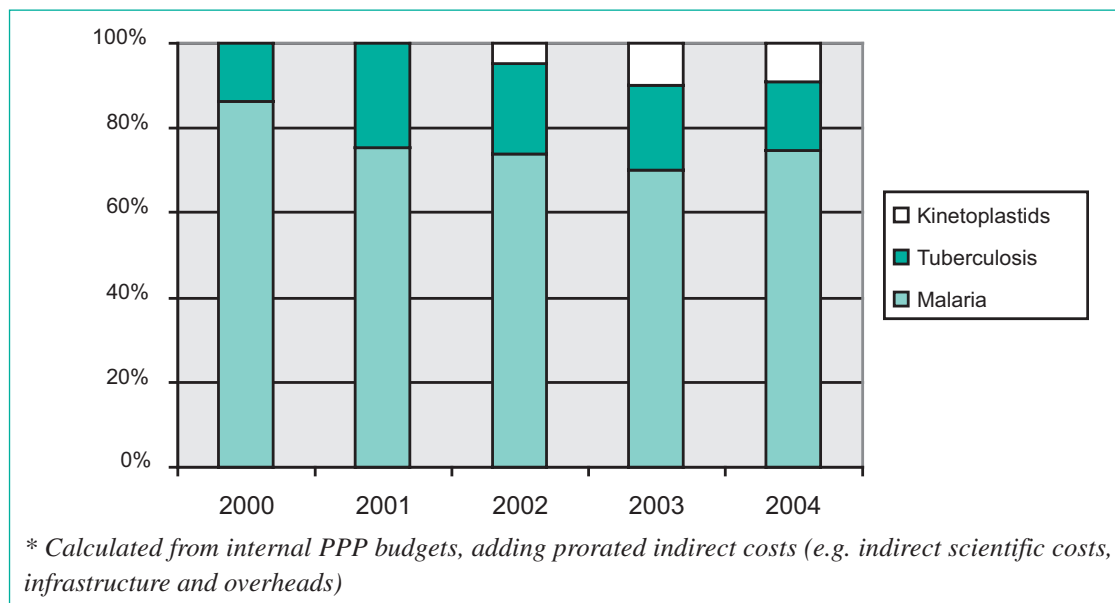


Figure 3: Distribution of total PPP budgets by disease since their creation*



Factors associated with different levels of R&D expenditure by PPPs

Over the past five years, malaria has dominated R&D expenditure by drug development PPPs. The reasons behind this trend are several – some structural, others related to the respective organizations (e.g. the way each PPP operates and the distribution of their portfolios in the pipeline); while yet others are disease specific (e.g. scientific and functional aspects).

Structural factors

The establishment of new drug development PPPs began in 1999 with the creation of MMV for malaria and continued up to 2003 when a PPP focused on kinetoplastids diseases was set up (DNDi). Funding and expenditure are difficult to compare between mature PPPs and relatively young PPPs, however we note that growth rates are similar among PPPs in their first years.

Furthermore, although PPPs tend to focus on specific diseases, three out of the four PPPs analysed conducted malaria projects even though for two of them malaria is not the main disease target. For instance, DNDi’s Fixed-dose Artesunate Combination Therapy (FACT) projects (artesunate/amodiaquine and artesunate/mefloquine) accounted for 45% of their total R&D budget for 2003 and 2004. This trend is not likely to continue, at least for DNDi which has already made clear that it will not conduct further malaria projects in the future.

PPP also differ in their secondary goals. Some have a sole focus on neglected disease drug development while others also aim to foster technology transfer, academic skills, regional integration or capacity-building. These variations have an impact on the number of projects PPPs are able to manage efficiently and also on the strategic and operational choices they take.

Size and distribution of a PPP portfolio has a very substantial impact on its expenditure. In particular, the relationship between discovery and development projects represents the most important variable to take into account. For instance, the TB Alliance portfolio has focused on preclinical work (and now increasingly on early stage projects), but until recently it had not moved a drug into the most expensive clinical trial stages,¹⁰ which are calculated to represent nearly 70% of total R&D costs.¹¹

The level of PPP funding is also related to the efficiency of the PPP. Efficient PPPs have pipelines that move more rapidly and effectively, and therefore have projects that enter clinical trials earlier. For instance, MMV's synthetic peroxide project progressed from drug discovery, through lead identification, optimization and preclinical to phase I in 4.5 years. This efficiency attracts high levels of funding from donors which in turn allows PPPs to conduct studies in parallel rather than sequentially, thereby matching or even exceeding standard industry development timelines. Although advocacy skills clearly also play a significant role in the funding levels received by PPPs, efficiency is highly valued by donors who routinely examine PPP project reports, R&D budgets per project and funding projections.

Specific factors

Although neglected diseases have many characteristics in common, such as the lack of effective, affordable or easy to use drug treatments, each disease has important particularities that affect the R&D process. Differences in the pathogen or in the epidemiology of the disease (for instance, the increased link between HIV and TB and visceral leishmaniasis) as well as in the science base, historic policy approaches and previous public investments on early research are just some of the factors that affect the current state

of the pipeline and which, in turn, influence PPP funding needs and budgets.

The nature of the pathogen is important. For instance, the slow growth of *M. tuberculosis* requires lengthier infection models,¹² while patients enrolled in TB trials require a long treatment period (six months for the comparator treatment) and up to a two-year follow-up to identify treatment relapses.¹³ By contrast, patients are followed for 28 days in malaria studies or six months in studies for visceral leishmaniasis.

The science base also plays an important role in opening up R&D opportunities. Important scientific advances such as genome sequencing have the potential to benefit R&D for neglected diseases; however, the applicability of these developments and the science base among diseases vary considerably. For instance, although genetic tools for manipulating *M. tuberculosis* have been developed and have led to the identification of many potential new drug targets, few drug candidates have emerged to date.

Past health policy approaches have also impacted the current state of neglected disease pipelines. For instance, WHO's recommendation of DOTS as the optimal TB treatment in the early 1990s and its aggressive promotion of DOTS as the solution to TB control¹⁴ had a marked dampening effect on R&D for TB, as it was assumed that the regimen would lead to steady elimination of the disease as a public health threat and therefore minimize the need for new TB drugs.¹⁵ As a result, the TB Alliance has not benefited as much as other PPPs from a short-to medium-term R&D approach based on capturing "low-hanging fruits" and has identified as critical the identification of new leads and the establishment of properly resourced optimization programmes if it is to meet its goals. By comparison, the iOWH was

able to complete registration of an almost finished drug for visceral leishmaniasis (paromomycin) while MMV has acknowledged that part of its success is due to the fact that there were “more low-hanging fruit projects than originally envisaged”.¹⁶

Although all neglected diseases affect mainly the poor and disadvantaged, the commercial value of different diseases, and therefore the R&D activity found within them, varies. For instance, a number of small pharmaceutical (“biotech”) companies are currently pursuing TB drug R&D programmes for a market that was calculated to be between US\$ 412.5 million and US\$ 470.5 million in 2000.¹⁷ The fact that the TB drug market was larger than first thought, that it is growing and that there is a significant private market component makes it even more attractive. Hence, the TB Alliance has sometimes had difficulties finalizing deals with companies interested in TB. For instance, the PPP could not pursue the development of analogues of ethambutol since a small pharmaceutical firm (Sequella) refused to sign the deal on the grounds that the PPP’s

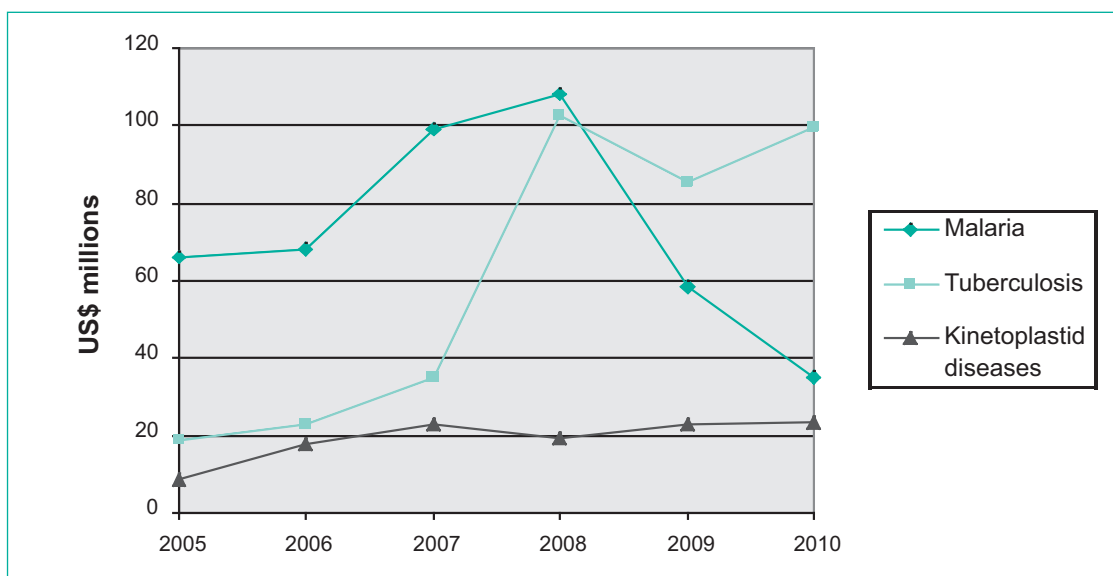
pricing, production and/or distribution terms were incompatible with the company’s commercial model.

Future funding needs

Total PPP expenditure on R&D for neglected diseases is expected to increase heavily in the coming years (see Figure 4). This can be explained by the fact that the number of projects in young PPP portfolios is increasing, but also because established projects will begin to reach clinical trials. For instance, the TB Alliance’s budget is expected to nearly triple between 2007 and 2008 when two of their projects enter phase III trials (PA-824 and the recently announced moxifloxacin project).

It is also evident from Figure 4 that malaria expenditure is expected to fall after 2008. This is mainly because as MMV moves forward, its portfolio will increase its share of discovery projects, which have much smaller costs, to fuel its future pipeline.

Figure 4: Projected PPP budgets by disease in the next five years



These future funding projections by disease were calculated based on data provided by the four new drug development PPPs. We note, however, that they are not precise. For instance, MMV's and the TB Alliance's projected expenditure until 2010 assume that all drugs in their current portfolio will succeed (i.e. no attrition rate has been applied). On the other hand, neither includes provision for funding new projects, which they assume will be covered by the funding unspent on failed projects. In the long run this formula may be more likely to apply for MMV than for the TB Alliance since the former's portfolio has reached its target size (around 25 projects) as opposed to the latter, which is still maturing.

Moreover, there are limitations inherent in the process of drug development itself, as well as limitations associated with the evolving state of science and the ability of new drug PPPs to deal with downstream issues they have not faced yet. For instance, it is not clear to what extent PPPs will participate in the delivery of developed products post-registration (e.g. supporting manufacturing, launch and marketing, including phase IV trials) nor whether PPPs will be able to keep feeding their pipeline to maintain their target portfolio size. Inclusion of these additional roles would significantly increase costs.

Total PPP budgets as a reflection of global drug R&D expenditure on neglected diseases

Although PPPs are the main driver behind the burst of activity evidenced in the past five years, their total budgets cannot be taken as a full representation of drug R&D expenditure on neglected diseases for several reasons.

Firstly, industry R&D spending is not fully included. On the one hand, this stems from the PPP practice of leveraging substantial in-kind

inputs from multinational company partners and public groups. For instance, MMV estimated the industry pro bono contribution to their projects in the order of 1:1¹⁸ which would substantially increase the figures given above. On the other hand, some multinational pharmaceutical companies still conduct in-house neglected disease R&D programmes (albeit increasingly with a view to partnering) but this expenditure is not always publicly disclosed.¹⁹ For example, Novartis has an active dengue R&D programme in Singapore and Sanofi-Aventis has a malaria R&D portfolio under their Impact Malaria programme.

Secondly, although these figures include small pharmaceutical company R&D within PPPs (most of which is paid on a commercial basis), they do not include independent small company activity, which is again not publicly disclosed. For example, TB drug R&D programmes are currently being pursued by small companies such as Sequella, while Immtech has an R&D programme for Human African trypanosomiasis (HAT).

Thirdly, upstream R&D, including broader public/academic basic and exploratory research, is not included in these PPP figures although it constitutes the basis of later discovery and development programmes. This expenditure is considerable for some diseases. For instance, after the resurgence of TB in the United States in the 1980s and 1990s, funding for TB research increased and the National Institutes of Health (NIH) spent approximately US\$ 60 million in TB research carried out in their own institutes in 1999.²⁰

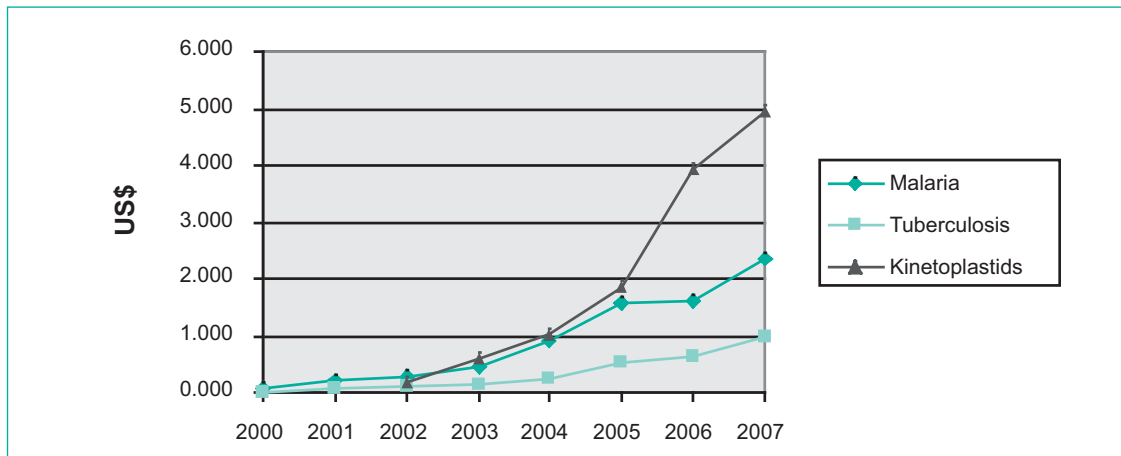
Finally, TDR, although operating as a de-facto PPP, is not included in our figures since it could not provide clear R&D budgetary information. The questions of whether funds to PPPs have been distributed appropriately to date and how much total funding is needed are difficult but important.

Are any of these diseases underfunded, and what is the “right” amount of drug R&D funding among PPPs?

Ideally, PPP budgets and projections would reflect drug R&D driven by global public health needs. In the absence of a formula to link burden of disease with R&D funding needs (even high-income countries), analysts

generally fall back on other approaches, for instance the calculation of R&D spend per DALY lost.²¹ Using this approach, TB ranks lowest on R&D funding (see Figure 5). Figure 5 also highlights that, although PPP expenditure on malaria drug R&D was the highest in absolute terms, more dollars per DALY lost have been spent, and will be needed, by PPPs on R&D for kinetoplastid diseases than for any other neglected disease. (This is partly because fixed R&D costs are spread over a smaller number of patients.)

Figure 5: Past budgets and projected PPP needs per DALY lost per year



Before going further, we wish to emphasize that the DALY approach has clear limitations and should be used with caution as a tool to allocate R&D spending particularly to PPPs. For instance, there are deviations caused by the mechanism itself (e.g. it favours diseases like malaria that affect mainly children since the younger the age of death, the more DALYs lost). The share of drug R&D carried out by PPPs also differs across neglected diseases, being higher for kinetoplastid diseases where the main player is DNDi than for tuberculosis where there is greater R&D activity outside the PPP framework, for example in small pharmaceutical companies and some multinationals (e.g. AstraZeneca).

Most importantly, the DALY approach does not shed light on the “correct” level of R&D investment. Most tropical disease doctors would immediately recognize that the “high” PPP spend on kinetoplastids using the DALY approach is nonsense, given the dangerously suboptimal nature of most current kinetoplastid treatments compared to the superior range and quality of antimalarials available for developing world use. In other words, the DALY measure can only indicate how governments are spreading their current limited levels of funding, but not the total level of funding needed.

Nevertheless, the DALY approach can at least begin to help policy-makers compare their R&D funding among diseases and PPPs and therefore provide an indication of whether they are allocating funds according to health needs and priorities. For instance, it highlights the lack of public funding for TB drug R&D.

In order to move forward, the DALY approach needs to be supplemented by further research

into the total funding needed to guarantee development of acceptable treatments for all neglected diseases; the public and private contributions towards this; the optimal number of new neglected disease products; and the optimal delivery time for these, given patterns of resistance and the ability of developing country health systems to absorb new products.

Conclusions

A clear burst of activity is evidenced in the drug R&D neglected disease panorama, with this being largely due to the establishment of public-private partnerships over the past five years. PPP budgets have increased steadily over this period in an uneven manner, with malaria being the disease that has received the most funding so far. There are structural factors (related to how PPPs have been set up and how they work) and disease-related factors that explain this trend.

However, there are no clear mechanisms to assess whether PPP expenditure on particular diseases has been appropriate, nor what the appropriate total levels of funding should be. Tools should be developed and tested to find correct levels of funding to appropriately address global public health needs.

-
- ¹ Neglected diseases are understood in this article as the ten diseases listed by the Special Programme for Research and Training in Tropical Diseases (TDR). These are leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, malaria, leprosy, Human African trypanosomiasis (HAT), tuberculosis and dengue.
 - ² Moran M, Ropars AL, Guzman J, Diaz J and Garrison C. *The new landscape of neglected disease drug development*. The Wellcome Trust, September 2005.
 - ³ PLoS Medicine Editors. A new era of hope for the world's most neglected diseases. *PLoS Med*, 2005, 2(9):e323.
 - ⁴ Pink R, Hudson A, Mouries MA and Bending M. Opportunities and challenges in antiparasitic drug discovery. *Nature Reviews Drug Discovery*, 2005, 4:727-740.
 - ⁵ The kinetoplastids are a group of parasites that cause a family of diseases including leishmaniasis, Human African trypanosomiasis (HAT) and Chagas disease.
 - ⁶ Moran M, Guzman J. Neglected disease drug development: How big is the gap? Paper presented at Forum 9, the Global Forum for Health Research's 2005 annual meeting in Mumbai, India, 12-16 September 2005. See www.globalforumhealth.org

7. Kettler H, Towse A. The role of public-private partnerships in the provision of R&D for new medicines. Commission on Macroeconomics and Health (CMH), World Health Organization, 2001.
8. See above Moran et al. (note 2), pp. 64-71.
9. TDR is excluded from the economic analysis since, unlike other PPPs, it could not provide full information on their total R&D budgets or how these funds were spent.
10. The TB Alliance is now moving two drugs into clinical studies (PA-824 and moxifloxacin).
11. Global Alliance for TB Drug Development. *The economics of TB drug development*. Global Alliance for TB Drug Development, October 2001. See www.tballiance.org
12. Duncan K. Progress in TB drug development and what is still needed. *Tuberculosis*, 2003, 83:201-207.
13. Hopewell P, Cynamon M, Starke J, Iseman M, O'Brien R. Evaluation of new anti-infective drugs for the treatment and prevention of tuberculosis. Infectious Diseases Society of America and the Food and Drug Administration, *Clin Infect Dis*, 1992, 15 Suppl 1:S282-295.
14. Ogden J, Walt G, Lush L. The politics of 'branding' in policy transfer: the case of DOTS for tuberculosis control *Social Science and Medicine*, 2003, 57, 1:163-172.
15. See above Moran et al. (note 2).
16. Medicines for Malaria Venture (MMV). *Annual Report 2004*, p. 4.
17. See above Kettler and Towse (note 7).
18. MMV. *Annual Report 2002*, p. 5.
19. We note that companies have recently produced information on their malaria R&D expenditure for a study on global R&D (the assessment of global investment on malaria R&D study carried out by The Malaria Research and Development Alliance – see chapter 5 and www.malariaalliance.org). However, the study will only disclose an aggregate figure of private malaria R&D expenditure.
20. Centers for Disease Control and Prevention. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). *Morbidity and Mortality*, 1999, weekly report, 48 (RR-9):1-13.
21. The DALY (disability-adjusted life year) is an indicator of the time lived with a disability and the time lost due to premature mortality and has become a common unit of disease burden measurement in the public health community.

Chapter 3

Basic research funds to discover important new drugs: who contributes how much?

by Donald W. Light

Donald Light is a professor of comparative health care systems at the University of Medicine and Dentistry of New Jersey. He is a fellow at the Leonard Davis Institute of Health Economics at the University of Pennsylvania and at its Center for Bioethics. Light is a member of the Business Advisory Council of the Republican Party and a member of the President's Business Commission.

Chapter 3

The 10/90 Report on Health Research 2003-4¹ and Monitoring Financial Flows for Health Research 2004 both highlight that “there are still major gaps in our knowledge and in the adequacy of the tools available to improve health and reduce inequities – gaps that are themselves reflections of past failures of health research to adequately address the health problems of a large proportion of the world’s population.”^{2,3} Fifteen years ago, the Commission on Health Research for Development estimated that less than 10% of the world’s resources for health research (which totalled US\$ 30 billion in 1986) were being applied to the health problems of developing countries, where 90% of the avoidable burden of ill-health was to be found.⁴ Since then, global expenditure on health research has more than tripled, but a large imbalance remains in how it is applied and the closure of the ‘10/90 gap’ has been the focus of the work of the Global Forum for Health Research since its foundation in 1998.

Three themes are developed in the Global Forum reports concerning the pharmaceutical industry. First, the industry “funds almost half of global health R&D,” and consolidation into fewer global giants raises “concerns that drugs that are largely needed for [low- and middle-income country] LMIC ‘markets’ will simply not be developed.”⁵ Second, research on diseases in high-income countries will have a “trickle-down effect on LMICs, but often these outputs do not address the most pressing health issues in low- and middle-income countries...” Third, the private for-profit sector claims to be

the largest investor in R&D globally, and the biggest actors are the multinational pharmaceutical companies. It follows that policy leaders must find ways to induce the multinationals to do more research and development for diseases prevalent in LMICs to rectify the prevailing imbalance. This is the central focus of such new tools as advanced purchase commitments (APC) proposed for getting multinational companies to do research to discover new vaccines.^{6,7}

This report focuses on basic research to lay the groundwork and discover new, effective drugs and vaccines. Equally important are applied, translational research to turn a discovery into an appropriate drug for human consumption, and development through trials to establish with greater confidence the safety and efficacy of a drug-candidate. All three elements together constitute one, albeit substantial, part of the larger landscape concerning research for health. This report uses information from a number of sources including industry critics to offer evidence that governments and the public provide the lion’s share of funds for basic research to discover new drugs and vaccines. Realizing the public’s role opens the door to new ways of thinking about how to close the ‘10/90 gap’. If most funds for basic research to discover new drugs come from the public sector, then programmes and incentives can be developed to focus more on global diseases that now are largely neglected. Certainly the goal for high-income countries (HICs) to allocate at least 5% of their health Official Development Assistance to research, as

The support of the Global Forum for Health Research is gratefully acknowledged. I would also like to thank Adrian Towse for his helpful comments published at the end of this chapter. For their detailed review of this paper and suggestions for its improvement, I am grateful to Stephen Matlin and Mary Anne Burke.

recommended by the 1990 Commission on Health Research, is still important, but how best to use those funds can be rethought. The report ends with some recommendations for moving from current policy initiatives based on incomplete information about basic research to designing a new set of strategies.

The role of basic research

The interest and goal of biomedical research is the R part of R&D: to discover important new drugs. Even in high-income countries, policy-makers are most concerned about the decreased number of important new drugs, even though many new variations of existing molecules and new molecules within well-populated drug classes provide physicians and patients with more choices and improved health. The industry also emphasizes that it devotes a substantial proportion of its profits to funding research to find breakthrough drugs and its leaders speak about the promise of new cures for major illnesses and improving people's lives. The slogan "Today's medicines pay for tomorrow's miracles" captures the essential theme of the pharmaceutical industry for the past 50 years. Most biomedical R&D is for applied research and development, a term that stands for several stages in drug development, including animal testing and human trials. In this paper we focus on the earlier stage "basic research" which generates the scientific knowledge to enable this applied R&D (translational research and development) to take place.

What matters is significant therapeutic gain

The common measure of significant innovation is new molecular entities (NMEs). Yet NMEs do not measure significant new drugs well,

because many efforts to develop a variant of a widely used molecule involve creating a related molecule that is therapeutically similar. The Food and Drug Administration (FDA) used to make an assessment of new drug candidates (not just NMEs) and judged that only 2-3% of new drug candidates (not just NMEs) offered important therapeutic gains. Another 8-10% offered modest therapeutic gains. For example, in one review of 1,816 new drug candidates (not just NMEs), the FDA judged 2.1% as offering important therapeutic gains and another 8.6% as offering modest therapeutic gains, a total of 10.7%.⁸ This figure of 1 in 9 new drugs (not just NMEs) offering a modest or significant therapeutic gain in the 1970s and 1980s, is right in line with a famous industry assessment of all internationally marketed drugs from 1975 to 1989.⁹ This assessment is also close to the findings by Prescrire in more recent years, which rates the therapeutic gain of all new drugs (not just NMEs) *after* they are being used by patients, as distinct from when they are about to be tested. Of the 2,693 new drugs and variations evaluated from 1981 to 2002, 3% were judged by Prescrire to provide significant therapeutic gain and another 7.9% offered advantages over existing drugs, a total of 10.9%.¹⁰ Their twenty-two year analysis does not show a recent drop in new drugs with significant benefits.

In the current period, the FDA uses a two-part assessment of the therapeutic promise of drug candidates, as they begin their clinical trials: standard and priority. A priority rating indicates a "significant improvement compared to marketed products in the prevention of a disease."¹¹ For the decade of 1994-2004, 39.5% of all new NME candidates received priority standing, and 14.1% of all new formulations, much higher than before. In all, 22.5% of all new candidates (not just NMEs) for the decade received a priority score, about twice the earlier percentage.

Whether one goes with the assessment by the clinicians and pharmacists of Prescrire or with the FDA's current process, the data show that discovering a therapeutically important new drug is very difficult, even for diseases where substantial research already exists. Merrill Goozner provides several examples of the 20-30 year struggle – blind alleys, dead ends, hunches and above all a determination not to give up – that ultimately leads to an effective, therapeutically important new drug.¹² Some pharmaceutical companies have steadfastly funded years of such basic research in pursuit of an important breakthrough; but with the pressure of financial quarterly returns, it is difficult to do this, and increasingly companies are leaving the high-risk basic research to others.

A focus on pioneering research needs to be complemented by an appreciation of the benefits of new formulations, administrations and new molecules that are developed in applied research to find drugs to replace or improve on existing molecules. These efforts lead to more convenient ways to take drugs, which increases the proportion of patients who actually take their medicine. They also offer different profiles of side effects that work better for some patients. That is to say, patients vary greatly in how they respond to drugs in a class; so the more choice of profiles, the more likely a physician is to find the best one for a given patient. Finally, these applied research projects to develop related drugs within a class may contribute to research that will later result in a major discovery. Still, bottom-line profiles of results over large samples of new drugs conclude that from 11 to 23% provide a significant therapeutic improvement.

If national and global leaders wish more basic and applied research for neglected diseases, they should fund it directly and also create greater incentives for doing it. Current IP protections apply equally to breakthrough new

molecules as to many other patentable products or features of products. Long-term patents, “territorial patents”, and “patent thickets” are widely discussed as obstacles to innovation, even in the business community.^{13,14}

Global shares of basic research

Monitoring Financial Flows 2004 gathers together the best estimates of R&D contributions for health. In various passages, it indicates that a very large proportion of the total expenditure is for pharmaceutical research, one of whose central goals is discovering more effective drugs for major neglected diseases. Precisely how much of total R&D is devoted to pharmaceuticals is not clear; so for want of exact figures, the total figures for all research given in *Monitoring Financial Flows* will be used. Total R&D for pharmaceuticals includes, as explained below, research in genetics, cell biology, molecular biology, and related basic sciences and some engineering that is devoted to understand the basic mechanisms, systems, dynamics and organs of the body, its pathologies and its diseases.

Industry contribution to basic pharmaceutical research

Let us begin with the breakdown of the industry's R&D. The National Science Foundation (NSF) has been conducting a survey of basic and applied research by industry for over 50 years. It is the most objective source of information gathered by the most experienced staff independent of any industry, and it has developed the most reliable measures. For this reason, and because no one can know what costs are included by companies in the R&D estimates that they send to their trade associations, NSF figures should be used in reports on R&D as a percentage of sales. In its most recent assessment, it concluded that pharmaceutical

firms with American offices devote about 12% of gross domestic sales to research and development, and about 18% of their R&D budget to basic research for discovering what the industry calls “breakthrough drugs,” like first in class.^{15,16} In the UK, where government incentives reward more basic research, both figures are higher.

If one looks at the breakdown by cost area in the more detailed report from the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2002, 9.3% of companies’ confidential, self-reported R&D budgets was attributed to synthesis and extraction.¹⁷ This is clearly part of basic research, but builds on basic research funded by government. The industry emphasizes that such research is only “background” to their real discovery of drugs, but a more accurate picture begins with appreciating how critical it is to understand how a given disease works, including at a molecular biological level. Scientists in basic research projects also develop novel, critical new techniques for tracing, measuring and isolating potentially active agents that pharmaceutical companies and others then employ. A key step is identifying good targets of vulnerability in the defences of a disease. Large companies can then turn to their huge libraries of molecules and rapidly screen them to identify which will work or look as if they might.^{18,19} Without the targets, companies would be helpless – like someone with a huge ring of keys in the dark but not knowing where the keyhole is. Once it is illuminated, he can start to identify which keys look as if they might work and then find the one that does. There are many cases in which most of the research costs for major drugs, and sometimes the development costs, are not paid by the company that owns the patent.^{20,21,22}

The next category in the PhRMA list of R&D functions is biological screening and pharmacological testing, which accounted for

an additional 12.1% of total R&D expenditures in 2000. This can be reasonably counted as part of applied research, after discovery, as can toxicology and safety testing, dosage, formulating and stability testing, animal testing and clinical testing.²³ By this account, basic research takes up even less of total R&D than reported to the NSF by research officers of pharmaceutical companies. Given that a lot of synthesis and extraction appears to be aimed at discovering or developing a new or altered molecule to replace an older one or compete with a similar one, the 9.3% would be still lower. If we take the higher number, 18%, then US\$ 9.2 billion of the global pharmaceutical R&D budget is devoted to basic research to discover important new drugs. If we take the lower number, 9.3%, then the basic research budget of the industry is US\$ 4.7 billion.

Both of these figures are probably high. Since the 1993 study by the US Office of Technology Assessment (OTA),²⁴ investigative reporters and reviewers have speculated that self-reported R&D budgets may include such expenses as:

- the executive costs in finding and negotiating with other firms for new products
- the rapidly rising budgets for “seeding” trials and trials to develop off-label uses
- costs for medical writers and public relations to develop stories and market demand for products in trials as they progress
- support for scientific journals and supplementary issues in which the results of industry-supported research get published
- lectures and courses to inform physicians about current research
- legal fees devoted largely to patents and research-related issues
- land and costs for buildings in which some research is done
- company-wide technical upgrades, like software or computers.

The Canadian Patented Medicine Prices Review Board reported that companies included in R&D administrative overhead major equipment, the cost of land and buildings used substantially for research or development, and all the costs of their contracting related to R&D with biotech companies, contract research organizations (CROs) and other research-related organizations.²⁵ If, for example, one allowed only itemized line items that reasonably pertain to R&D and excluded phase IV trials not required by the FDA or European Agency for the Evaluation of Medicinal Products (EMA) and the line item called “Other”, they together account for 32% of the R&D budget in the PhRMA report cited above. If these proportions are applied to the total industry’s R&D budget of US\$ 51.2 billion that the Global Forum reports for 2001, it would drop to US\$ 34.8 billion, and 18% for basic research would drop to US\$ 6.3 billion rather than US\$ 9.2 billion.

Net industry contributions

Total or gross R&D costs benefit from provisions that reduce taxes. The comprehensive review by the US OTA stated, “The net cost of every dollar spent on research must be reduced by the amount of tax avoided by that expenditure.”²⁶ Some argue that taxes are on profits, not expenses, but such a view misses the central goal of the corporations, which is to reduce by various means the amount that gets counted as taxable profits. To hold that taxes are on profits and not on expenses misses the point. The fact that R&D is treated as a business expense (at least in US law) and is fully deducted each year, is one argument used for the view that R&D is not like a capital investment but is a business expense. The corollary argument is that research-based companies must do research to survive.²⁷ Regardless of what one thinks of such arguments, taxpayers are in effect partners in developing every drug, because their elected

representatives have chosen to provide various tax deductions and credits to pharmaceutical companies that in effect mean that other taxpayers make up for what drug companies do not pay or receive as credits. Reports on the large corporate R&D budgets read as if it is all company money, when in fact companies in other industrial sectors and citizens help subsidize pharmaceutical research. One might think of them as partners in funding corporate research for new drugs. This implies that research to discover new drugs should be rewarded in proportion to the impact of each on the global burden of disease, a proposal of moral philosophy and law developed by Thomas Pogge at Columbia University.²⁸

How much is reasonable to deduct from gross R&D to get a net cost figure? The amount of tax deductions, credits, and other indirect supports from government, such as paying for the graduate and advanced training of researchers over many years and funding the laboratories in which they learn, varies from country to country according to their laws and practices. Here, the United States will be used as an example. When the top marginal tax rate was 46%, the OTA conducted the most comprehensive review of pharmaceutical research costs and estimated that tax savings and credits reduced R&D costs by nearly 50%.²⁹ The top marginal tax rate is now 35%.³⁰ One should adjust for the four-percentage-point average difference between nominal and effective corporate tax rates, as reported by Grabowski et al.,³¹ for a period average tax rate of 31%. This may be conservative, however, as another detailed analysis concluded that effective tax rates for US pharmaceuticals, including state taxes and credits were 39-41%.³²

Effective tax subsidies for R&D can be higher than tax savings for other expenditures because of deferrals and credits, such as the 20% R&D tax credit and manufacturing tax credits for

plants in selected foreign tax havens. The OTA reported that the latter were worth more than 14 times the value of research tax credits. They are applied to the R&D investments that generated them. For example, tax exemptions for foreign profits, which have recently been “repatriated” at 5.25% tax rate, save companies 29.75% on profits in locations with no local tax (for years, Puerto Rico) or less in locations with a small local tax.^{33,34} Pfizer had foreign profits of US\$ 38 billion, Merck US\$ 18 billion, Johnson and Johnson US\$ 14.8 billion and Eli Lilly US\$ 9.5 billion. Thus pharmaceutical companies save up to US\$ 3 billion for every US\$ 10 billion of accumulated foreign profits they repatriate. If this were credited against R&D expenditures over the same period, or with a time lag, net R&D costs would be considerably lower than the estimates used in this report.

To get a feeling for how much, let us take the profits of a major pharmaceutical company’s report to the Securities and Exchange Commission for the year 2000, which were US\$ 6.8 billion. If it could shelter half of these profits abroad by leaving much of the profits on US sales in off-shore manufacturing facilities or by licensing patents cheaply and then buying back finished products at a high price, it could accumulate such profits for several years until Congress declares a “tax holiday” in order to repatriate them as described above. The savings for this company for 2000 would therefore be US\$ 922 million. If these savings were applied to its R&D budget 10 years earlier of US\$ 850 million (a time lag reflecting past R&D investments for present drugs sold), these tax savings for one year would completely pay for all gross R&D (before deducting tax savings and other provisions), with US\$ 72 million left over. If the time lag of five years were used, the tax savings in this case would cover 69% of gross R&D investments, which for this company were US\$ 1.33 billion in 1995.

A more sophisticated time lag model could be constructed using data over a long period, but this simple illustration allows one to appreciate why the comprehensive OTA analysis of pharmaceutical R&D regarded tax savings from tax havens as worth 14 times more than direct R&D tax deductions and credits. Sheltering profits overseas has been rising sharply.³⁵ Perhaps when all tax provisions are taken together on rapidly rising sales, they cover most or all of past and trailing R&D expenditures. To summarize, the huge R&D investments which the industry continuously emphasizes in pressing the EU for more market protections and arrangements to increase prices and revenues, certainly cost companies much less than is claimed, for example US\$ 1 billion per new drug, and may cost them very little net of tax savings applied to those investments.

Conducting a comprehensive tax analysis would be complex and would require a separate project. Funds received by pharmaceutical companies as income from the National Institutes of Health (NIH), the military and other government agencies would have to be taken into account. The orphan drug act grants a 50% tax credit for the costs of testing drugs with a presumably small number of eligible patients. Limited public money is also provided to companies for research costs for many orphan drug candidates and also to cover some clinical trials. Companies have learned to qualify more and more drugs that subsequently get sold to large markets as “orphan”, and the number of drugs that enjoy these tax and government subsidies has increased substantially.³⁶

If one applies the 31% figure to the US\$ 51.2 billion that pharmaceutical firms contributed to global R&D funds, their net cost or contribution was US\$ 35.3 billion, and other taxpayers covered US\$ 15.9 billion in tax savings to the companies. Turning to the basic research budget of US\$ 9.2 billion, other

taxpayers covered US\$ 2.9 billion and the companies contributed US\$ 6.3 billion net. Given the lower estimates with other methods described above, these figures may overstate both gross and net contributions to global basic research and understate taxpayers' contributions. These estimates and calculations are necessarily crude, because the industry does not provide verifiable figures and details about its R&D budget.

Government contributions to basic research

Now let us turn to the US\$ 46.6 billion contributed by governments and public programmes. How much of this sum goes to basic research as defined and discussed above? To answer that question worldwide would take a separate project, and given its central importance to the Global Forum's purposes, this project should be done. In the case of the NIH, it reports that in 2004 it spent US\$ 2.361 billion on R&D contracts, which are largely applied research. The NIH pays for all or part of several thousand clinical trials every year. It also contracts with pharmaceutical companies on specific research projects, and some company research teams win NIH grants. The NIH also reports having spent US\$ 134 million in construction and another US\$ 49 million in other awards. The rest went to basic research grants (US\$ 19.6 billion), research training grants (US\$ 0.64 billion) and fellowships for advanced research training (US\$ 0.11 billion). These three categories of basic research accounted for 88.9% of the total NIH budget. An analysis of the past 10 years shows that these proportions have not changed much. In 1994, for example, these three accounted for 88.5% of the total budget. To round off to two places, we calculate that 89% of government and public programmes in research are directed at basic research activities. From what is known about the British, German, Japanese, and

Swedish government research programmes, a similar percentage would seem to apply, but detailed analysis may find this is incorrect. Thus, based on the 89% figure, government and public programmes contribute US\$ 41.5 billion to the global budget for basic research.

Foundations

Foundations that contribute to pharmaceutical R&D, like the Hughes and Gates foundations, focus primarily on basic research. Others do much less. Just what proportion is beyond the scope of this study. If we assume that 25% goes to basic research, then they contribute US\$ 2 billion to the global total (see Table 1).

Summing up

All these figures are summarized in Table 1. It shows that, based on the highest estimate of the methods described above, the global estimate for basic research to discover important new pharmaceutical products is US\$ 52.7 billion for 2001. This equals 54% of the total US\$ 105.9 billion global estimate on all health research. Governments and the public contribute 84.2% of the world's basic research budget for health, industry contributes 12%, and private non-profit sources contribute 3.8%. If taxpayers' subsidies to industry are actually higher for the reasons explained, the public's share would be still greater. In conclusion, while it is true as *Monitoring Financial Flows* states that "The private for-profit sector is the largest investor globally", the public sector is by far the largest investor globally in basic research to discover important new drugs and vaccines.

Table 1**Global R&D Funds, 2001**

In US 2004 dollars; for assumptions, see text

	Total R&D ¹	Basic research funds for breakthrough drugs	Per cent basic research funds by source
Governmental & public programmes	46.6 billion	41.5 billion ⁴	78.7
Foundation & non-profit sources	8.1 billion	2.0 billion ⁴	3.8
Pharmaceutical & biotech corporations:			
Gross reported ²	51.2 billion	9.2 billion	17.5
Taxpayers' subsidies ³	15.9 billion	2.9 billion ⁵	5.5
Net corporate funds	35.3 billion	6.3 billion ⁵	12.0
Totals	105.9 billion	52.7 billion	84.2 public 12.0 industry 3.8 foundations

Notes:

1. Based on 2004 Global Forum for Health Research report, Monitoring Financial Flows for Health Research.
2. Unverified but believed by reviewers to include substantial costs not normally considered to be part of research and development, as explained in the text.
3. Based on 31% average for tax deductions and credits. May be low. Does not include large overseas US profits taxed at 41% instead of 35%.
4. Based on 89% for basic research in public contributions and 25% in foundation & non-profit contributions.
5. Based on NSF data showing 18% of pharmaceutical R&D used for basic research. Other estimates suggest higher and lower percentages.

Source: Donald Light (2005)

Redirecting basic pharmaceutical research to greatest need

That the public finances most basic research can be regarded as no news at all. As one seasoned reviewer said, "That's what you would expect and what you would want, for government to fund basic research and for industry to develop drugs and bring them to market." But for less seasoned readers and policy-makers who believe the industry's

emphasis on their dominant role in research is to discover important new drugs, it is news.

For example, the currently advocated model of advance purchase commitments (APCs) as the way that governments should spend billions to induce major firms to unleash their researchers' potential to discover breakthrough vaccines or drugs for neglected diseases is based on the necessity to match the entire income that major companies gain from widely used drugs while

under patent protection.^{37,38} An underlying premise is that corporate researchers are much more innovative than research teams at universities and government centres like the National Institutes of Health. Another premise is that advance purchases of several billion dollars or euros will induce basic research, though a review of the evidence cited found that it was unlikely.³⁹ APCs also encourage secrecy rather than sharing among researchers and in other ways are likely to slow down research – all because they are based on the premise that most of the basic research takes place in the major pharmaceutical firms.^{40,41,42}

If APCs induce basic research, they will tie up several billion euros of government donations to make a one-time large purchase of future vaccines for one disease. If they do not do this, they are failing to achieve their purpose. Advocates emphasize APCs will spawn a plethora of new research at no cost until products are fully developed or tested, on the assumption that a promise of billions that are not put in escrow will be considered independent enough for investors to spend large sums of their real money year after year, for a hoped-for bonanza. For far less, government donations could procure existing and effective vaccines or drugs that can lift the burden of disease in LMICs now. A detailed report on the many new projects to discover and develop new medicines for neglected diseases describes point by point how the current APC model for funding by governments would be irrelevant and is “seriously out of kilter with the current industry neglected disease drug landscape”. APCs are likely to commercialize the large firms’ involvements in half of the new projects in an unsustainable way.⁴³ But public funding and political help that meet the needs of current projects are vital for their success.

Public funds for basic research, despite the dominance of NIH, come from many nations. While the United States accounts overall for

49% of all R&D funds, that is largely because it is much larger than other countries. Given that the United States is so large and accounts for about 60% of all pharmaceutical R&D expenditures, it should be contributing more to basic research.⁴⁴ Charts 2.8 and 2.9 of *Monitoring Financial Flows* measure different ways in which several other countries contribute proportionately more than the United States. The US ranks ninth in health R&D as a percentage of health expenditures and sixth in health R&D as a percentage of total R&D.⁴⁵ In newer NBIC technologies (nanotechnology, biology and medicine, information sciences, and cognitive sciences), government investments are by far the highest in Japan, proportionate to its size; Western Europe is keeping up with the United States, and the governments of other countries have increased their investments the most from 1997 to 2004. It appears that they too, as a group, exceed the US in proportion to their size.

If global funding for basic research to understand how the body and diseases work and to find the targets, strategies and sometimes products to prevent or cure them is largely public, then what *Monitoring Financial Flows* describes as “the implicit understanding that health research will generate global public goods”⁴⁶ can be realized. Research funding and programmes could be (as they are in some cases) directed at the diseases that account for the greatest burden and/or the most premature deaths. Incentives could reward discoveries for these diseases. Various patent exemptions or licensing arrangements could facilitate sale and distribution in LMICs, especially if the net cost of R&D for companies to create new drugs and bring them to market is actually much lower than claimed. The figure of US\$ 802 million for average R&D costs in 2000, or about US\$ 1 billion in 2005, is based on the only authoritative study done on the subject.⁴⁷ But the study used a non-random sample of only the most costly fifth (US\$ 400 million) of new

drug approvals; so the average for all new drug approvals is less than half that amount. Further, half or less of the US\$ 400 million is composed of estimated profits foregone, which are multiplied at a high compounding rate. When more impartial rates recommended by the government are used, the estimated R&D costs decline further, and when tax savings are taken into account, one gets down to a net average cost of R&D of about one-tenth the amount widely claimed. Thus new thinking about how to foster research on neglected diseases can be more flexible.

The costs of clinical trials can also be a fraction of the costs reported in the DiMasi study, which attributes the far higher cost of R&D in 2003 than in their 1991 study to the already huge and rapidly rising costs of clinical trials. Consider, for example, other studies of how much clinical trials cost. The Government Accounting Office examined how much government-sponsored trials cost at cancer centres. It found that trials averaged only US\$ 681 more than the cost of the medical treatment they were receiving anyway.⁴⁸ That is to say, almost all the seeming costs of clinical trials on such seriously ill patients consisted of their medical care. This raises a common misunderstanding about the costs of doing trials with seriously ill patients. Moreover, these “captive” patients are easier to identify, eager to participate in anything that might help them, and easy to monitor. In another study, Goozner compiled data on the cost of government-sponsored trials for AIDS drugs from 1992 to 2001, and found that the additional costs of testing averaged slightly more than US\$ 1,500 each, and their costs rose only 11% over the decade, much less than general inflation. These observations raise questions about why the confidential, self-reported costs of trials for unnamed drugs that constitute the sample of the DiMasi study, collected at one of the industry’s principal policy research centres, were so high and rose so rapidly, questions that

cannot be answered or investigated because the underlying data have not been released.

In conclusion, the aforementioned as well as other studies also suggest that R&D costs are, or can be, much lower than widely circulated estimates. The cost of trials for neglected diseases can be much less expensive because recruitment costs are very low, trial sizes can be smaller, retention is higher and duration shorter.⁴⁹

The new landscape of basic pharmaceutical research

Concrete possibilities are documented in an important new study of every known research project done on a neglected disease from 1975 to 2004 by the Pharmaceutical R&D Project at the London School of Economics.⁵⁰ It documents the need to discard as wasteful and inaccurate the prevailing belief that one needs “to stimulate neglected disease R&D activity by making it profitable enough to attract the interest of big companies.”⁵¹ The LSE study, headed by Dr Mary Moran, found that five of the 12 major firms do not – and say they will not – conduct research on neglected diseases at any price, but they would like to help others. The other seven were devoting a small but meaningful proportion of their R&D budgets to discovering new drugs for neglected diseases and focusing on early-stage basic research. Moran reports that they want to make a meaningful social contribution, repair their damaged reputations, and gain strategic advantages for future markets, not make money. Their estimated combined budgets for all work on all projects averaged US\$ 20 million in direct costs.

Moran found that small biotech firms working with public-private partnerships (PPPs) and sometimes with multinationals discovered new

drugs and developed them up to the point of clinical trials for only US\$ 2.2 - 11.5 million. Her detailed studies of every project led her to conclude that PPPs were working well on the whole, and contributing to research of neglected diseases. Overall, 40 R&D projects have cost altogether only US\$ 112 million. This sum includes 10 clinical trials, four of them in phase III trials.⁵² Those trials will add considerably more expense. When compared to public contributions to basic research of US\$ 41.5 billion, however, the Global Forum's greatest hopes seem possible. Governments have provided very little help so far in funding PPPs, and they need to expand their contributions to all three phases of research and development in ways that match the needs of biotechs and PPPs.

Moran's team also evaluated each new drug on eight criteria, including level of innovation, efficacy and affordability. The projects in large firms used much more costly approaches to discovering new drugs, and they scored lower on their value for low-income countries than did drugs discovered by small biotechs and PPPs. But large firms played an important role helping other teams with in-kind contributions.

In sum, a new landscape of small firms, venture capitalists, and public-private partnerships has already formed, and their costs of innovation as well as the cost of development are a fraction of the R&D costs of US\$ 800 million to US\$ 1 billion per new drug widely cited in official documents.

Redirecting public funds to maximize new drugs

Moran correctly points out that the large multinational corporations are focused on drugs that will generate at least US\$ 500 million in annual sales and on R&D to find more of them.

“As a result many multinationals have downsized, spun off or closed down their less lucrative infectious disease divisions, often leading to a significant loss of skills, compounds and knowledge relevant to neglected disease R&D.”⁵³ The new model for research on neglected disease is based on a no-profit no-loss basis, and companies involved reduce their research costs to a minimum. PPPs help with funding, coordinate researchers across projects and help with trials. The multinationals involved focus on relatively inexpensive, early-stage research. Thus government use of APCs, Moran observes, would shift this work (which is happening already without the billions in APCs) from its current low cost, non-profit basis to a high profit basis where profits from patent protection drive the research agenda. Soon government would not be able to sustain the contribution of billions every year. Based on the team's interviews with the multinationals, the report states, “most companies were not seeking additional direct funding for early R&D, describing their in-house spend on this [research for neglected diseases] as ‘a sunk cost’ and ‘not an issue’... There is a clear disjunct between these views and current government thinking which, as noted previously, is focused on ‘commercializing’ R&D ... by using very large ‘pull’ incentives ...”⁵⁴

Critical help, however, can be extended to small biotechs and their venture capital or other funding sources by providing several kinds of expertise and resources. First might be an office with professional employees who are expert in and experienced with neglected disease markets and with how small firms can negotiate with key operators in them to do trials, to manufacture and to sell. This is a key to small business development for high-income countries. Second, small firms, where more discovery is taking place, need good returns but are open to flexible arrangements. One option

is for governments and foundations to use their generous donations to pay off successful projects so they can make a profit quickly and then focus on developing long-term sustainable procurement contracts. These could be designed to fund several needs for new drugs or vaccines: building up manufacturing capacity and the ability of LMICs to deliver them, providing long-term sustainable procurement, and funding offices dedicated to helping get new products

through the maze of governmental and regulatory regulations. Moran’s report and these recommendations hold promise to turn around the Global Forum’s observation on its website that “research capacity in many low- and middle-income countries remains low...” While generally true, R&D initiatives in countries like Brazil, Cuba, China, India, and South Korea are promising and can be strengthened in the targeted ways suggested.⁵⁵

Table 2
Contrasting Models of Advanced Purchase Commitments

Feature	Advanced Commitment for Malaria or AIDS: No Effective Vaccine (CGD Model)	Advanced Commitment for Rotavirus or a Disease with an Effective Vaccine (Proposed Model)
Primary goal IP	To create incentives for basic research to discover effective vaccines and test them for approval Sponsor keeps all IP rights	To create a stable, long-term market for an effective vaccine at low, cost-plus prices, by paying for licensing rights and manufacturing know-how, as well as a 10-year supply; to relieve suffering and death now Sponsor sells all rights needed to sell vaccine at low price to poorer populations
Cost	\$3–\$5 billion in 2005, compounded at 11% thereafter	\$1–\$3 billion in 2005
Time frame	10–15 years to hopeful success	Start now, for 10 years
Payout	Nothing until primary goal achieved	Start now; multiple payouts to achieve whole-system goals of good delivery systems and regional manufacturing capacity
Capacity to deliver	Not addressed	Central to the design

Source: Donald W. Light. Making practical markets for vaccines. *PLoS Medicine*, October 2005, Volume 2, Issue 10, page 0936.

Complementing research with guaranteed purchasing

These recommendations suggest that advanced purchases should be used quite differently from the prevalent model for using APCs for purchases 10-15 years into the future, after a successful product has been discovered, developed, tested and approved. From both a moral and practical point of view, designing a purchase commitment for existing but underused vaccines could address the 4.4 million deaths a year and far more people afflicted now, for the same amount as the cost of an APC for malaria that might save five million deaths per year a decade or more in the future. Morally, giving priority for yet unborn infants and children over real people afflicted and dying now is indefensible. Table 2 summarizes the principal dimensions of how the G8 could spend their money.

There are many impracticalities in trying to write a contract for something that does not exist and may or may not exist 10-15 years from now.⁵⁶ These involve legal and liability issues not addressed even in the legal appendices of *Making Markets for Vaccines*. What global and policy leaders need is a report that provides a toolkit for doing modified advance commitments that would

be the “pull” complement to the “push” effort by funders and researchers to discover and test new drugs for neglected diseases. That toolkit would offer different options for addressing the need to help developers get through phase III trials and approval, the need to be paid through a long-term contract that helps verify there is a market for other funders and small firms to enter, and the need to help specific countries in the ways they need most to store and deliver the new products. That is, a good advanced purchase commitment would reach back with a helping hand to promising, late-stage developers and forward to willing LMICs who need assistance in actually delivering the new product to people who can benefit from it. A good toolkit would look at options in the context of what is happening on the push side. It would come up with a number of push-pull options for decision-makers to consider.

To summarize, the predominance of public funding for basic research, the relatively low costs to date achieved by PPPs for R&D for neglected diseases and diseases of poverty, and the new landscape of innovation in pharmaceuticals that they have created, offer great promise for publicly-funded agents to significantly close the ‘10/90 gap’ through making *practical* markets in countries with great needs but small budgets.

¹. Global Forum for Health Research. *The 10/90 Report on Health Research 2003-2004*. Geneva: Global Forum for Health Research, 2004.

². Global Forum for Health Research. *Monitoring Financial Flows for Health Research 2004*. Geneva: Global Forum for Health Research, 2004.

³. On page 31, *Monitoring Financial Flows for Health Research 2004* gives much higher percentages of pharmaceutical R&D for basic research and exhibits them in Chart 2.12. The source given is the Canadian report, *A Comparison of Pharmaceutical Research and Development Spending*. But its source is the industry’s trade association, which uses self-reported, unverified information from its members and which has a great vested interest in maximizing this percentage. Their unsubstantiated claim is that “basic research has grown as a share of pharmaceutical R&D”, but this is not verified by independent sources. Rather, many recent reports on the industry indicate that the major companies are doing less basic research

and letting others take the long-shot, high risks. This makes good business sense. This example of one official report drawing on another government report, which repeats trade association data, illustrates how such data cross over into official legitimacy and how all organizations have little choice but to rely on and repeat the industry's unverified numbers. The NSF survey is used here as a more reliable source. On page 84, the information from page 31 is repeated, only in a way that can be misread as pertaining to national government contributions to R&D, when even the trade association applies it to industry contributions.

4. Commission on Health Research for Development. *Health Research: Essential Link to Equity in Development*. Oxford University Press, New York, 1990.
5. *Monitoring Financial Flows for Health Research 2004*, page x.
6. Kremer M, Glennester R. *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton: Princeton University Press, 2004.
7. Center for Global Development. *Making Markets for Vaccines: Ideas into Action*. Washington D.C.: Center for Global Development, 2005: 1-115.
8. U.S. Senate Select Committee on Small Business. *Competitive problems in the drug industry*. Washington D.C.: U.S. Government Publications Office, 1979.
9. Bard PE. *Fifteen Years of Results in Pharmaceutical Research Throughout the World, 1975-1989*. Paris: Rhone-Poulenc Sante, 1990.
10. Prescrire International. A review of new drugs and indications in 2002: Financial speculation or better patient care? *Prescrire International*, 2003, 12(64):74-77.
11. U.S. Food and Drug Administration. CDER NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type. U.S. Food and Drug Administration, 2005 (Oct).
12. Goozner M. *The US\$ 800 Million Pill: The Truth Behind the Cost of New Drugs*. Berkeley: University of California Press, 2004.
13. Malone MS. The smother of invention. *Forbes*, 2002 (24 June): 32-40.
14. Reback GL. Patently absurd. *Forbes*, 2002: 45-48.
15. See Center for Global Development (note 7 above) and *Monitoring Financial Flows 2004*, page iii.
16. National Science Foundation. *Research and development in industry: 1999*. Arlington, VA: National Science Foundation, 2002.
17. Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2002*. Washington D.C.: Pharmaceutical Research and Manufacturers of America, 2002.
18. See Goozner (note 12 above).
19. Boston Consulting Group. *A Revolution in R&D*. Boston: Boston Consulting Group, 2001.
20. See Goozner (note 12 above).
21. Government Accounting Office. NIH-Private Sector Partnership in the Development of Taxol. Washington D.C.: U.S. Government Accounting Office, 2003.
22. Angell M. *The Truth About the Drug Companies: how they deceive us and what to do about it*. New York: Random House, 2004.
23. The PhRMA report indicates that the percentage devoted to synthesis and extraction declined by nearly one fourth over the previous two years. The only categories whose proportions rose were phase IV trials (8.8% in 2000), which many regard as market research, and "other" which rose to nearly a quarter of the entire industry's R&D budget.
24. U.S. Office of Technology Assessment. *Pharmaceutical R&D: Costs, Risks and Rewards*. Washington D.C.: OTA, 1993, p. 15.
25. Patented Medicine Prices Review Board. *A Comparison of Pharmaceutical Research and Development Spending*. Ottawa (CA): PMPRB 2002.
26. See U.S. Office of Technology Assessment (note 24 above).
27. Relman A, Angell M. America's other drug problem: how the drug industry distorts medicine and politics. *The New Republic*, 2002, (4,587):27-36.

- ²⁸ Pogge TW. Human rights and global health. *Metaphilosophy*, 2005, 36:182-209.
- ²⁹ See U.S. Office of Technology Assessment (note 24 above).
- ³⁰ Tax Policy Center. Marginal rates of the Federal Corporation Income Tax, 1942-2002. Washington, D.C.: Tax Policy Center, 2002.
- ³¹ Grabowski HG, Vernon J, DiMasi JA. Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics*, 2002, 20(suppl. 3):11-29.
- ³² Bindra G, Sturgess J. *Assessment of Current Competitiveness of Canadian R&D in the Pharmaceutical Industry*. Ottawa: Industry Canada, 1996.
- ³³ Andrews EL. Hitting the tax-break jackpot. *The New York Times* 2005 (1 Feb);C1-2.
- ³⁴ The New York Times recently reported that 25 of Merck's 31 manufacturing facilities were outside the United States. Berenson A. Revamping at Merck to cut costs. *The New York Times* 2005 (29 Nov);C1,C7.
- ³⁵ Johnston DC. Study finds U.S. companies shifting profits overseas. *The New York Times* 2004 (13 Sept);C2.
- ³⁶ See above Bard (note 9).
- ³⁷ See above Kremer (note 6) and Center for Global Development (note 7).
- ³⁸ Kremer M, Towse A, Williams H. Briefing Note on Advance Purchase Commitments. London: Department for International Development, Health Systems Resource Centre, 2005.
- ³⁹ Light DW. Making practical markets for vaccines. *PLoS Med*, 2005 (Oct), 2(10):0934-0938.
- ⁴⁰ Farlow A. *The global HIV enterprise, malaria vaccines and purchase commitments: where is the fit? A response to 'Making Markets' and 'Strong Medicine'*. Oxford: Oxford University, 2005.
- ⁴¹ Farlow A. Over the rainbow: the pot of gold for neglected diseases. *Lancet*, 2004, 364(9450):2011-12.
- ⁴² Farlow A, Light DW, Mahoney RT, Widdus R. Concerns regarding the Center for Global Development Report, "Making Markets for Vaccines". Geneva: Commission on Intellectual Property Rights, Innovation and Public Health, 2005.
- ⁴³ Pharmaceutical R&D Policy Project. *The New Landscape of Neglected Disease Drug Development*. London: Wellcome Trust and London School of Economics and Political Science, 2005.
- ⁴⁴ For the record, US pharmaceutical corporations appear in Table 2.3 of *Monitoring Financial Flows for Health Research 2004* to be below their proportionate share of revenues among high-income countries.
- ⁴⁵ There appear to be inconsistencies between Chart 2.8 and Table 2.2.
- ⁴⁶ *Monitoring Financial Flows for Health Research 2004*, page ix.
- ⁴⁷ DiMasi JA, Hansen RW, Grabowski H. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 2003, 22:151-185.
- ⁴⁸ Government Accounting Office. *NIH Clinical Trials: Various Factors Affect Patient Participation*. Washington D.C.: Government Accounting Office, 1999.
- ⁴⁹ See above Pharmaceutical R&D Policy Project (note 43).
- ⁵⁰ See above Pharmaceutical R&D Policy Project (note 43).
- ⁵¹ See above Pharmaceutical R&D Policy Project (note 43).
- ⁵² See above Pharmaceutical R&D Policy Project (note 43).
- ⁵³ See above Pharmaceutical R&D Policy Project (note 43).
- ⁵⁴ See above Pharmaceutical R&D Policy Project (note 43).
- ⁵⁵ See two recent articles on innovative developing countries:
Morel C et al. Health innovation networks to help developing countries address neglected diseases. *Science*, Vol 309, 15 July 2005.
Morel C et al. Health innovation in developing countries to address diseases of the poor. *Innovation Strategy Today*, 2005, Volume 1, Number 1.
- ⁵⁶ See above Farlow (note 31).

Commentary by Adrian Towse

Adrian Towse has been Director of the Office of Health Economics at Oxford University since 1992. His interests include the use of “risk-sharing” arrangements between health care payers and pharmaceutical companies to manage the introduction of new health technologies and economic issues around the use of public-private partnerships for the development of treatments for less developed country diseases.

The ‘10/90 gap’ reflects in part the shortage of R&D into diseases predominantly found in low- and middle-income countries (LMICs), as highlighted by Jeffrey Sachs in the Report of the Commission on Macroeconomics and Health (Macroeconomics and Health: Investing in Health for Economic Development, World Health Organization 2001). Increasing basic research is an essential part of the challenge. This research will increase understanding of disease and enable potential medicines and related interventions to be identified and developed.

If we therefore want more products for neglected diseases and diseases of poverty we not only need incentives for development, we also need more basic research. Light’s conclusion is that it must come from the public sector is not surprising but it is important. His analysis shows that whilst the private sector accounts for 50% of all R&D, it only accounts for 17.5% of basic research. This is to be expected. Most basic research is done in the public sector and most applied research is done in the private sector. As research (on the author’s calculations) accounts for around 50% of all R&D, this means that the private sector accounts for around 82.5% of all applied R&D. This suggests an appropriate division of labour. Basic research has many “public good” characteristics. It is hard to expropriate the benefits and so justify commercial investment. You can’t patent most basic research findings. The converse is true of applied research (translational research and product development.) There has been a blurring of boundaries over the last couple of decades as

companies invest in basic research to get “first mover” knowledge of disease and universities invest in some translational work in order to exploit their basic research and turn it into something they can get a commercial return on by licensing to the private sector. Again this seems to make sense, i.e. to be efficient, but the fundamentals are that the public sector does most basic research and the private sector does most applied research.

Unfortunately the paper does not go on to tackle how we get more basic research, but to make a series of criticisms of the biopharmaceutical industry and of some of the public policy initiatives under discussion to increase applied R&D. I comment briefly on some of these.

It is simply not the case that we only need first-in-class drugs for neglected diseases, as the author argues – look at the portfolios of the Institute for One World Health (iOWH), DNDi, TDR, MMV and TB Alliance and at my report for the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) (available at <http://www.who.int>). In some cases we need breakthrough first-in-class products, in other cases follow-on products or new indications or formulations for existing products.

The author argues that this means that “taxpayers are in effect partners in developing every drug... companies in other industrial sectors and citizens help subsidize pharmaceutical research. One might think of them as partners in funding corporate research

for new drugs”. This is a confusion with the role of governments (and other third-party payers and individual patients) and that of buyers of drugs and vaccines signalling through their buying decisions what they want.

There is a fundamental problem with Light’s argument. Total or gross R&D costs are a business expense and are tax deductible. So are many other business costs. It is like saying the taxpayer is funding GM’s labour costs because wages are tax deductible in the motor industry so “companies in other industrial sectors and citizens help subsidize [motor vehicle manufacture]. One might think of them as partners in funding [wages to produce new cars].” Does this mean the taxpayer should tell GM what type of cars to produce? Given GM’s apparent current difficulties in designing cars that people want to buy, one might say it couldn’t get much worse, but that is not the point.

The author’s claim that new drug development costs are 10% of the DiMasi et al. numbers is not in my view substantiated. He argues that the costs for all new drugs are lower, which is true, as the DiMasi et al. figures are for the more “important drugs” – new molecular entities (NMEs). We want NME costs, not an average of all new drug approvals. He further down rates the estimate for the tax rate effect because he excludes the opportunity cost of capital – a risk adjusted return for investors – in favour of a risk free government bond rate. Unfortunately for companies, the taxpayer does not pick up the cost of failed projects. A return for taking risk is required. The high

cost of clinical trials per patient is another area of concern. The public sector can get better deals. However, the underlying resource cost is the same. What happens is that companies end up paying higher prices to hospitals and investigators. It is not clear that this would happen in the case of neglected diseases.

The author’s attack on advance purchase commitments (APCs) is a digression. There is no prevailing model for APCs. The Center for Global Development Report looks at early and late stage APCs, but gives a number of US\$ 3.2bn net present value for an early stage. This is to reward industry R&D including discovery costs, but it does not assume that all the basic research is done by the companies. The Moran et al. work the author cites shows that PPPs have made good progress. But her results show that a majority of projects involve big pharmaceutical companies. They also make significant “in kind” contributions. No PPP product has yet got to market and we are just entering the expensive part of the process. However, we now have product development portfolios in a number of key disease areas. Both the PPP and APC models offer important mechanisms to address the development gap.

What we need is to ensure that there is a similar new emphasis in the public sector in respect of basic research. Without strong publicly funded programmes of basic research into neglected diseases the new models for applied research will not be able to build on improved understanding of these diseases.

Chapter 4

Health technology and innovation: a Brazilian experience

by Reinaldo Guimarães, José da Rocha Carneiro and Wim Degraeve

Reinaldo Guimarães is Vice-President for Research and Technological Development at the Oswaldo Cruz Foundation (Fiocruz) in Brazil. He is a medical doctor with an MSc in Social Medicine. Since 1992 he has been coordinator of the Brazilian Directory of Research Groups, a project sponsored by the National Research Council (CNPq).

Chapter 4

In general terms, the global distribution of health research activities does not differ substantially from that related to other research fields. According to a 2005 study by G. Paraje et al.,¹ 90.4% of the health-related world bibliographic output is concentrated in 42 high-income countries, and the five leaders of this group (USA, UK, Japan, Germany and France) are responsible for 72.5% of the total output. The remaining 9.6% are distributed among all the other countries of the world. It is worth mentioning that, within middle-income countries, those classified as high middle-income have a smaller output when compared to the low middle-income countries. It is also worth noting that the five leading countries of this last group (China, Russian Federation, Brazil, Turkey and South Africa) are responsible for 4.4% of the 5.4% attributed to the whole group. If we add to those 4.4% the output from India (which is classified as a low-income country), we have a set of six developing countries which are responsible for a little more than 5% of the global output. For this group and a few other countries, a label of 'Innovative Developing Countries' (ICDs) was recently assigned.² This new terminology was derived from a conceptual framework proposed by R. A. Mashelkar,³ where the country's economic strength is juxtaposed with its autonomous R&D capacity. In that framework, one can identify a set of countries – IDCs – where the R&D capacity is fairly well developed but which are not in the same category in economic terms.

Brazil's health sector accounts for 7.5% to 8% of the country's gross domestic product (GDP). Around 40% belongs to the public sector. It encompasses a huge network of services and an important industrial complex responsible for the production of medicines, diagnostics, health equipment and vaccines. This complex

is quite technology-intensive although currently R&D activities are performed mainly abroad. A recent survey on financial flows for health research in Brazil, sponsored by the Ministry of Health,⁴ revealed that between 2000 and 2002, mean annual expenditures on health R&D reached US\$ 573 million. Some aggregated data from that survey are presented in Table 1.

This survey included all universities and research institutes with health research activities, as well as the ministries of Health, Science & Technology and Education and the three main state research support agencies. Data from the private sector were obtained from the National Survey on Innovation, performed by the Brazilian Agency of Geography and Statistics (IBGE). In the Ministry of Health survey, the private health sector was represented by the pharmaceutical (245 companies) and health equipment industries (368 companies). The data in Table 1 show a typical situation for an IDC, with three characteristics that reveal an existing, albeit immature national innovation system:

1. a reasonable amount of financial resources is devoted to health R&D (corresponding to 1.5% of national expenditure on health and to 3.3% of public national expenditure on health);
2. a small private sector share (23.7%);
3. an important local R&D capacity indicated by the use of only 3.5% of international financial resources.

To these should be added the modest financial participation of the Ministry of Health in the country's health R&D effort (5.7%).

Since the end of the last decade, the Brazilian government has been promoting a continuous

Table 1**Mean annual expenditures for health R&D activities, Brazil, 2000-2002 (US\$)**

Sources	2000-2002	Annual Mean	%
Federal Government	680,449,513	226,816,504	39.6
Ministry of Health	97,907,787	32,635,929	5.7
Ministry of Science & Technology	153,165,909	51,055,303	8.9
Ministry of Education	429,375,817	143,125,272	25.0
State Governements	571,479,120	190,493,040	33.2
State Education and S&T secretaries	412,450,191	137,483,397	24.0
State research support agencies	159,028,929	53,009,643	9.2
Public Sector	1,251,928,633	417,309,544	72.8
Private Sector	406,928,244	135,642,748	23.7
International Organizations	60,468,724	20,156,241	3.5
TOTAL	1,719,325,601	573,108,534	100.0

Source: Ministry of Health/SCTIE/DECIT

shift in the country's scientific and technological policy whose main objective is to contribute to the development of the Brazilian innovation system. It intends, amongst other aspects, to strengthen the involvement of the industrial private sector with in-country R&D and innovation and to support closer links between research institutes/universities with industry. Among the main initiatives already undertaken is the creation of 'sectoral funds', which are financial resources from the public and private industrial sectors for the support of R&D activities with a strong emphasis on partnerships between universities or research institutes and industries. Two funds were created specifically to finance health and biotechnological research. Also important was the promulgation of the Innovation Law that regulates such partnerships between institutes or universities and industrial companies. Finally, the establishment of a national policy for industry,

technology and foreign trade also represents an important step. This policy addresses industrial sectors as priorities, two of these being the pharmaceutical and biotechnological industries.

The Oswaldo Cruz Foundation (Fiocruz)

The Oswaldo Cruz Foundation (Fiocruz) is the largest health research institute in the country and the most important intramural research institute of the Ministry of Health. Founded in 1900, its main activities are research and capacity building, as well as laboratory reference and quality control services for the Ministry of Health. In addition, Fiocruz produces medicines, vaccines and diagnostics for the national and international market. It hosts 15 units, located in five Brazilian states.

In 2002, Fiocruz had 202 active research groups with 973 researchers (624 with a PhD degree) without counting students involved in research work. Fiocruz also hosts 15 active MSc and PhD programmes. In 2002, its R&D budget (excluding salaries) reached US\$ 22 million.

Since 2001, Fiocruz has been following new governmental policies with respect to science, technology and innovation. Some of the in-house initiatives that were created in support of these new policies are presented below. These include a technological forecasting project about companies working in the manufacture of health-related products in Brazil, one intramural capacity-building research programme, two intramural research-support programmes focused on the development of new products and processes involving neglected diseases, and a new unit dedicated to technological development and business management in public health.

The project 'Innovation in Health', launched by Fiocruz in 2003, is an initiative on technological forecasting in health that uses a qualitative methodology generally employed to formulate public policy proposals. It takes into account both macro and micro aspects, and operates based on the diversity of the points of view of stakeholders. The central idea is a dialectic construction that includes the products industry and the services sector. The 'Productive Complex in Health'⁵ and its development is based on the presentation of position papers prepared by nationally and internationally renowned experts. Papers are discussed in workshops, whose diversified composition includes the main stakeholders of the complex, as defined in the triple helix concept:⁶ industry, government and research institutions.

The Innovation Project developed this matrix with two horizontal components: (1) the burden of disease in a projection for the year 2015;

(2) intellectual property, patent protection and the trade-related aspects of intellectual property rights (TRIPs) agreement. These horizontal components guided the efforts in three vertical components: (1) vaccines and sera; (2) medicines and drugs; (3) reagents and diagnostic kits.

The preliminary results of the project indicate that it is necessary to contextualize the choice of priority targets before implementing proposals. Proposals for a new policy must be presented while considering a concrete analysis of each of the components of production. For instance, the policies for the industrial development of vaccines are not the same as for medicines and drugs. Vaccine coverage, at least within the government's National Immunization Programme (PNI), is acknowledged as one of the highest in the world. The same cannot be said about access to drugs. A substantial part of these vaccines is manufactured in government laboratories; this is very different from the vast majority of drugs that are bought from private laboratories or distributors, and that are manufactured both in Brazil and abroad. Due to its high purchasing power, the State has better prospects of defining a production and distribution policy in the vaccine segment.

Vaccines and sera

A basic change in the Brazilian scenario is proposed for the vaccine and serum segment, moving from the idea of self-sufficiency introduced in the 1980s to that of competitiveness. Generated in the vortex of a serum supply crisis at the beginning of that decade, the self-sufficiency proposal became one of the most successful Brazilian public health programmes, surviving through all changes of government since then without any major threat. Substantial public investments of close to two hundred million dollars provided major manufacturers with good manufacturing

status (GMP). Similarly, the creation of a strict control system, completely separate from the manufacturers, ensured that products attained international quality standards. The PNI, responsible for the supply and cold chain, was an essential element in reaching the internationally recommended coverage.

Documents discussed in the workshops focused on the international R&D scenario with regard to vaccines and the domestic capacity to manufacture the necessary immune biologicals, defined by the PNI. A national vaccine competitiveness programme (Inovacina) was proposed.⁷ The programme established priorities for short- and medium-term development and production, especially for public manufacturers, already responsible for the production of almost 80% of the vaccines distributed by the PNI. Although the proportion of imported vaccines is relatively small, whether as a finished or bulk product, it accounts for a substantial part of the costs because these are high added-value products. The proposed policy establishes a strategy that aims to introduce domestic manufacturers into the global market. This is not far from the concerns of the Global Alliance for Vaccines and Immunization (GAVI) and the Developing Country Vaccine Manufacturers' Network (DCVMN), as they recognize that supplying vaccines to the poorest countries in the world will only be assured by the success of these emerging manufacturers in their attempt to enter the global market. The mechanisms to ensure this can be found both in national partnerships with R&D sectors, universities and research institutes and in agreements for the transfer of advanced technologies developed abroad.

Medicines and drugs

In the medicines and drugs segment there is a different scenario. The private sector, at national and international levels, is responsible

for nearly the totality of production. Nevertheless, the Brazilian government, through the Unified Health System (SUS), is certainly the leading buyer of these products in order to supply the public network. For this reason, one of the main problems is the issue of access.⁸ The discussion addressed themes such as the role played by the introduction of generic drugs into the market, their different consumption patterns by socioeconomic classes and production by public and private laboratories. Another aspect reviewed import costs and government expenditures, the existing capacity for R&D in several technological pathways and the issue of patents. It became evident that a clear definition of strategic medicines and drugs, and available niches of development and production,⁹ is essential. Finally, the R&D potential of public manufacturers, as well as a proposal to establish a network of those manufacturers aimed at centralizing R&D efforts and decentralizing production,¹⁰ was discussed. All debates stressed the greater complexity of the medicines market as compared with that of vaccines in the Brazilian context. In the development of this segment, the Innovation Project provided strategic alternatives to guide government policy. But it was not considered appropriate to formulate a more daring proposal for that set of stakeholders, as was done in the case of vaccines. Those strategic alternatives imply local development, but also negotiations to transfer more complex technologies. Drugs and medicine production involving an organic synthesis pathway are shown as the most difficult to develop, especially taking into account the great complexity of *in silico* (computer-based) development. Greater possibilities could come from the pathway of pharmaceuticals from bio and, especially, *phyto* origins, given the existing R&D capacity in universities and also given recent efforts to incubate small private companies in friendly environments, scattered across Brazil.

Reagents and diagnostic kits

With respect to the segment of reagents and diagnostics kits, along with the marked concentration of producers and/or distributors of imported products, in-house production survives within health care and diagnostic services. However, even in these services, most of the certified products are imported. A remarkable effort is being made by small, private producers, usually from academic departments and generally incubated under production agreements instituted by official programmes related to universities, and supported by public funding agencies. Diagnostic automation has led the development of new procedures to combine reagents and equipment in kits. The machines, usually leased for use, require the matched purchase of reagents from a certain manufacturer. In an attempt to simplify the level of analysis, the Innovation Project decided to focus, in the first stage, only on diagnostics associated with public programmes, defined as a priority by SUS managers. In this extremely segmented market, new procedures emerge continuously. They are introduced into the private sector of diagnostics services, which widely dominates health care services, even selling services to SUS. There are often serious crises in this sector, due to the demands of society and of the Public Prosecutor's Office, which require the distribution of tests that are not included in the list of actions approved for reimbursement by SUS. Examples include HIV/AIDS diagnostic procedures, viral hepatitis, and the assays required for quality control of blood products.

In order to establish correct estimates of the needs of the Brazilian market for diagnostics, the Innovation Project decided to follow, in the first instance, two complementary paths: to estimate the value of diagnostic products by consulting import documents and monitoring public expenditures with diagnostic procedures.

Both paths showed major methodological limitations with regard to accuracy. In any case, it is quite clear that this segment requires a close partnership between the public and private sectors. The international sector has been asked to agree with a proposal for the transfer of advanced technologies and local production of technical assistance and equipment.

Public-private partnerships

When we think of partners and of public-private partnerships (PPPs), we must take into account the dual levels that exist in both partnership and technological development. The asymmetry between partners, present in different segments (vaccines, medicines, reagents), is not the same in all circumstances. There is a macroeconomic trend to incorporate advanced technology usually developed by 'big pharma', notably in the segment of drugs generated by chemical synthesis. This is also the case for technical assistance for diagnosis and for advanced vaccines, where R&D and production are increasingly similar to chemical synthesis pharmaceuticals. However, there is a microeconomic perspective in the relationship with academia and/or start-up incubator sectors, more often in the field of reagents and diagnostic devices but also in phyto-drugs, bio-drugs and vaccines. Finding a balance among the many trends demands additional financial support by R&D funding agencies and possibly the creation of experiments with venture capital. Nevertheless, it is impossible to ignore the predatory experience in this field: the complete and simple incorporation of promising private Brazilian companies by multinational corporations.

As mentioned before, in Brazil most of the capacity in health research resides in public universities and research centres, and interaction with private companies is still

infrequent. This is mainly due to lack of investment from private companies, as high interest rates and unfavourable circumstances for risk investment and small company start-up are major inhibitory factors. On the other hand, there is limited experience in technological development, transfer of technology, protection of intellectual property and interaction between the public and private sectors. In order to stimulate innovative research and technological development, the Oswaldo Cruz Foundation has created two intramural programmes.

The Programme for Technological Development of Health Products (PDTIS) focuses on technological development of potential products, such as new drugs, vaccines or diagnostics. As a starting point, a prospective analysis of the institutional capacity was carried out to spot applied research projects which envisage a product or service with potential impact for the public health system. In response to a call for applications, and after internal and external evaluation and project selection, four networks were created, respectively for the development of recombinant and DNA vaccines, for drugs and bio-insecticides, for diagnostics, and a more technical network for applied genomics and proteomics, aimed at the development of core services in genomics, proteomics and related fields, using techniques for the development of new tools and approaches for discovery. Each network harbours between 15 and 20 projects, at different levels of progress. Technological development often has a different meaning for (applied) research laboratories as compared with production-oriented sectors, and the definition of the full scope of product development in the different fields – from discovery, proof of principle, development, scale-up, pre-clinical and clinical evaluation, analysis of product and production parameters, to quality control, registration and transfer of technology – has improved understanding and

planning. From a total of approximately 70 projects, about 35 are currently interacting with Fiocruz's production units or with private companies. Transfer of the potential product or process to a production partner is the final goal of all projects and, thus, intellectual property, technical and economical feasibility, final cost for the public health system and technological capacity strengthening are important factors. Besides these aspects, project and portfolio management contribute to a gradual change in scientific and technological planning, execution and control within the institution.

The Programme for Technological Development in Public Health (PDTSP) was conceived in a similar way as the PDTIS programme. Here however the focus of development is centred on new methodologies and tools for the planning and evaluation of public health actions. As such, 65 projects are being funded in the fields of clinical studies, epidemiology, development of procedures and health education.

Technological development in an institution like Fiocruz falls between two worlds. On the one hand, (applied) research laboratories need to improve project planning, assuring the necessary quality and tracking standards, and keeping in mind economic parameters, potential for intellectual property and technology transfer. Frequently, the laboratory does not master all technical aspects for full development, presentation and use of the potential final product. On the other hand, production facilities for government programmes often lack scientific staff and innovative capacity for the conception and development of new products. Cooperation and networking involving multidisciplinary teams is mandatory, and the PDTIS and PDTSP programmes were conceived in this way, promoting inter-laboratory collaborations and often also involving external partners. The

institutional Management of Intellectual Property and Transfer of Technology (GESTEC) is responsible for contractual issues and legal protection of rights. In order to improve technological capacity and innovation, several technological platforms were established. These include large-scale DNA sequencing, proteomics (2D nuclear magnetic resonance (NMR) and mass spectrometry), bioinformatics, microassays, and support equipment such as fluorescence atom-coincidence spectroscopy (FACS), real time polymerase chain reaction (PCR), confocal microscopy, ELISA and smaller specialized equipment. Training of staff, the organization of services and appropriate data handling and quality control are challenges. However, in order to substantially expand the capacity of Fiocruz for the development of health care products, a new facility is planned: the Centre for Technological Development for Health (CDTS), dedicated to technological development and industrial interaction.

In addition to these two intramural product-focused programmes, there is another, focused on capacity building. The Strategic Programme for Support in Health Research (PAPES) selects 60 to 80 innovative research projects every two years, each with funding of around US\$ 20,000 per year, and 60 projects for junior scientists, with funding of US\$ 5,000 per year. The programme has gone through an overall evaluation process for the PAPES III phase (biennium 2003-2004) where external ad hoc reviewers evaluated the criteria of scientific productivity, the completion of set goals and a qualitative analysis. The programme has recently launched a call for new applications and, again, external reviewers, based on quantitative and qualitative criteria for the biennium 2006-2007, will select 80 larger and 60 smaller projects. Scientific merit, relevance, originality, but also the productivity of the proposing team are the key criteria in this competitive call for projects.

The Centre for Technological Development for Health (CDTS) was conceived to increase the capacity for development of biotechnological products as a contribution to national health programmes. Innovation in immune biologicals, drugs and diagnostics will be central goals, and will address both neglected diseases and other important targets of national priority in health improvement. The construction of the centre, whose general planning took about two years, is expected to start at the end of 2005, and completion is foreseen for the end of 2007. It is structured around flexible laboratories for product development with business partners, supported by a variety of technical labs (platforms for genomics, proteomics, protein and antibody production, bioinformatics, microarray and nanotechnology, chemical and biochemical analysis, etc.). Modern facilities, state-of-the-art equipment, proper infrastructure and appropriate managerial capacity with sound and ethical business practices will be functional settings for national and international scientific and technical cooperation. A facility with appropriate biosafety infrastructure for animal handling is included.

Conclusions

In light of the growing need for adequate and adapted products for the national health system, Fiocruz is developing a concerted effort to seriously improve its capacity to respond to these needs. It is clear that this effort involves the introduction of more effective cooperation with public and private development and production partners, within an adequate legal and cooperative framework. On the other hand, the public system and health policy planning also requires improved tools for public health

planning and monitoring. Institutional programmes were initiated accordingly, and the more advanced projects also receive the logistical support of product development teams, in which a small group of some five to eight specialists assist the laboratory team and help in reaching out to production partners. The current product development programmes are forerunners of the effort that will be concentrated in the CDTS.

-
1. Paraje G et al. Increasing International Gaps in Health-Related Publications. *Science*, 2005 (13 May), vol. 308, Issue 5724, 959-960.
 2. Morel C et al. Health Innovation Networks to Help Developing Countries Address Neglected Diseases. *Science*, 2005 (15 July), vol. 309, Issue 5733, 401-404.
 3. Mashelkar RA. Nation Building through Science and Technology: A Developing Country Perspective. *Innovation Strategy Today*, 2005, Vol. 1, Issue 1, 16-32.
 4. Ministério da saúde/DECIT/SCTIE. Fluxos Financeiros para a Pesquisa em Saúde no Brasil, mimeo, 2005. (in press)
 5. Gadelha CAG. O complexo industrial da saúde e a necessidade de um enfoque dinâmico na economia da saúde. *Ciência e Saúde Coletiva*, 2003, vol.8, no.2, p.521-535.
 6. Leydesdorff L. The triple helix: an evolutionary model of innovation. *Research Policy*, 2000, 29:243-255.
 7. Buss PM, Temporão JG, Carvalheiro JRC (organizadores). *Vacinas, Soros e Imunizações no Brasil*. Rio de Janeiro: Editora Fiocruz, 2005.
 8. Frenkel J. Prospecção econômica do segmento farmacêutico brasileiro: uma proposta de política integrada. Position paper presented to the Innovation Project Workshop, 2004.
 9. Antunes A et al. Prospecção tecnológica da indústria farmacêutica nacional. Position paper presented to the Innovation Project Workshop, 2004.
 10. Hasenclever L. Análise da capacitação tecnológica e a gestão das atividades de pesquisa, desenvolvimento e inovação dos laboratórios farmacêuticos públicos brasileiros. Position paper presented to the Innovation Project Workshop, 2004.

Chapter 5

Malaria research and development: an assessment of global investment

by the Malaria R&D Alliance

This report was prepared by the Malaria Research and Development Alliance with significant funding from the PATH Malaria Vaccine Initiative (MVI) and contributions from Medicines for Malaria Venture (MMV) and the Gates Malaria Partnership of the London School of Hygiene and Tropical Medicine (LSHTM).

The Malaria R&D Alliance is an alliance of malaria research and development organizations jointly advocating for global commitment for increased and sustained resources for malaria R&D. Goals of the alliance are to raise awareness about malaria and the critical need for R&D to combat the disease. The Multilateral Initiative on Malaria (MIM) is the current convenor of the Alliance.

Chapter 5

Introduction

The importance of research and development to combat malaria

Malaria causes more than one million deaths each year and exerts an enormous health and economic toll on developing nations. Despite the historic and continuously high disease burden that malaria imposes, little has been known about the amount of funding dedicated globally to the research and development of new tools and strategies for malaria prevention, control and treatment. In 2005, the Malaria R&D Alliance, a global coalition of research and development organizations working to find new and improved solutions to combat malaria, conducted a survey on global funding of R&D to combat malaria, the results of which are presented in this study.¹

A public health crisis

As of late 2004, the World Health Organization (WHO) reported that 3.2 billion people living in 107 countries were at risk of contracting malaria. WHO estimates that 300 million to 500 million new infections occur each year, resulting in more than 1.2 million deaths annually.² Malaria accounts for approximately 11% of the disease burden in Africa, where almost 90% of global malaria deaths occur.³ The overwhelming majority of malaria fatalities occur in children. Malaria is the number one cause of death in children under age five in Africa, accounting for 20% of mortality for this age group.

In a 2004 study, the Global Forum for Health Research calculated the trend in cause of death for children under five in low- and middle-

income countries. Their findings demonstrated that the child death rate from malaria approximately doubled between 1990 and 2002.⁴ Without the widespread implementation of effective control measures, it is estimated that the number of malaria cases will double over the next 20 years.⁵

Malaria is a classic neglected disease, characterized by a high disease burden in the developing world, a low disease burden in high-income nations, and a low level of funding in relation to the disease burden.

Objectives and key methodological elements of the study

The Malaria R&D Alliance's motivation for conducting this study was to establish an understanding of current global investment in research and development to combat malaria. In the last few years, there have been widely divergent estimates of annual malaria R&D funding, varying by many hundreds of millions of dollars.⁶ In order to determine an appropriate level of sustained malaria R&D resources, credible, comprehensive and updated data are essential.

The survey focused on 2004 – the most recent year for which complete data are available. Numerous analyses have been performed on the data submitted for 2004 as well as for previous years, in order to develop a more complete picture of the global investment of R&D to combat malaria.

Global investment refers to original source funds disbursed by the donor and funding community, including self-funding of intramural research (e.g. by the National Institutes of Health (NIH) and the private

sector). In order to avoid double-counting, funds received by a wide variety of funding managers were not counted in the annual global investment figure, but were tracked for cross-referencing and data integrity purposes, and to assist in determining investment categorization.

Data was collected through an online survey instrument, the design of which was based on the input of many experts in the fields of malaria R&D and resource tracking, and information gathered through an extensive literature review. Annual funding in the form of disbursements⁷ was measured, as it was deemed that disbursements give the most accurate picture of actual funds made available to conduct malaria R&D in any given year.

Funding was allocated to six R&D categories:

- basic research
- antimalarial drug discovery and development
- vaccine development and vaccine trials
- vector control research
- development of malaria diagnostics
- implementation research.

To encourage pharmaceutical and biotechnology companies to participate in the study and submit data, a policy was adopted to aggregate their responses for reporting purposes and not to share any individual company's financial data. Accordingly, survey contributions from pharmaceutical and biotechnology companies will be considered as one source of malaria R&D investment.

In addition to determining total investment in malaria R&D in 2004, detailed data were collected and catalogued in a relational database that can be examined in numerous ways, including by the type of organization supplying the funding (e.g. government versus private philanthropy) and by the areas in which the money is invested.

Survey administration and response

The online survey instrument was e-mailed to a distribution list of more than 150 organizations in May 2005. The list encompassed major and minor donors, a variety of funding managers and private companies, and a sample of large and small research entities. Financial data from 2002 through 2006 were requested. Financial submissions from 2004 represent the most current complete year available, hence 2004 is the focus of data analyses.

The presumed largest global funders of malaria R&D, 14 in all, completed the survey; the aggregate response rate from those contributors believed to be the 50 largest investors in malaria R&D was 92%. In addition, 33 other organizations responded to the survey. The majority of these were recipients of funding, and their responses enabled the survey team to cross-reference data and develop a better understanding of the overall flow of funds. Responses were received from organizations based in 20 countries on six continents, as well as from numerous multilateral entities.

Survey findings: malaria R&D investment

Donor and funder investment in malaria R&D in 2004

Reported global investment for research and development to combat malaria totalled US\$ 323 million in 2004. This investment is the sum of original source funding disbursed to support malaria R&D. The majority of this funding was contributed by donors to other organizations in the form of extramural grants and the balance was intramural (internal) funding.

Investment was heavily concentrated. Two organizations, the US National Institute of Allergy and Infectious Diseases and the Bill &

Melinda Gates Foundation, provided 49% of total malaria R&D investment in 2004 (US\$ 80.2 and US\$ 77.6 million respectively). Pharmaceutical and biotechnology company respondents in aggregate contributed more than US\$ 38 million in R&D funding, and the US Department of Defense invested US\$ 25.6 million.

The top 12 survey entities contributed more than US\$ 283 million in malaria R&D funding, which represents 88% of 2004 total investment. Table 1 displays total original source investment from those entities, ranging between US\$ 3.4 and US\$ 80.2 million in 2004.

Table 1
2004 malaria R&D investment by largest funders (> US\$ 3 million)

Survey entity	Total funding (US\$)
US National Institute of Allergy and Infectious Diseases	80,238,125
Bill & Melinda Gates Foundation	77,550,637
Pharmaceutical and Biotechnology Company Respondents ^a	38,108,877
US Department of Defense ^b (DoD)	25,633,821
Wellcome Trust	13,514,165
Swiss Agency for Development & Cooperation (SDC)	9,971,854
US Agency for International Development (USAID)	9,657,000
Netherlands Ministry for Development Cooperation (DGIS)	6,951,131
Medical Research Council ^c (MRC)	6,407,909
European Commission ^d (EC)	6,030,228
US Centers for Disease Control and Prevention (CDC)	5,861,000
UK Department for International Development (DFID)	3,363,237
Subtotal	283,287,984
Other sources	40,152,273
Total	US\$ 323,440,257

Notes:

- ^a Financial information aggregated for all pharmaceutical and biotechnology company respondents.
- ^b Survey submitted by Military Infectious Disease Research Program (MIDRP), which encompasses the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), the Army and Navy overseas labs in Indonesia, Kenya, Peru and Thailand and the US Army Medical Material and Development Agency (USAMMDA). This figure does not include the salaries of uniformed active duty personnel who work exclusively on malaria.
- ^c Includes UK National Institute of Medical Research funding
- ^d The European Commission figure encompasses EC disbursements reported by the EuropeAID Cooperation Office, as well as 2004 receipts credited to the EC by other survey respondents. The survey received from the European Commission's General Directorate Research office noted 2004 commitments of 37.25 million (approx US\$ 50.74 million). Most of this funding has not been included in the 2004 investment figure, as all survey calculations are based on disbursements.

Other large donors

Thirteen additional organizations, each of which invested more than US\$ 1 million in malaria R&D in 2004, are listed in Table 2. This table includes surveyed organizations that contributed between US\$ 1 million and US\$ 3 million of original source funding, as

well as organizations that did not complete the survey, but were identified in recipient surveys as having funded more than US\$ 1 million of malaria R&D.

The 25 donors and funders listed in Tables 1 and 2 account for 96% of total investment for malaria R&D in 2004.

Table 2

2004 malaria R&D investment by other significant donors

Survey entity	Total funding (US\$)
Anonymous donor ^a	5,000,000
Global Fund to Fight AIDS, Tuberculosis and Malaria ^b	4,170,523
Fogarty International Center	2,801,497
World Bank	2,289,880
National Center for Research Resources (NCRR-NIH-US)	2,162,934
Ellison Medical Foundation	1,811,986
Swiss Government – Ministry of Interior ^c	1,809,409
National Institute of Child Health & Human Development	1,261,697
Médecins Sans Frontières ^d	1,208,967
National Heart, Lung, and Blood Institute	1,206,000
Government of Australia ^e	1,191,352
Business Trust of South Africa ^f	1,137,882
Rockefeller Foundation	1,000,000
Total	US\$ 27,052,127

Notes:

^a Johns Hopkins Malaria Research Institute reported receipt of this anonymous donation to support malaria research.

^b South African Medical Research Council reported receipt of this funding for implementation research.

^c Swiss Tropical Institute reported receipt of this funding.

^d Drugs for Neglected Diseases Initiative reported receipt of this funding.

^e Australian Army Malaria Institute reported receipt of this funding.

^f South African Medical Research Council reported receipt of this funding.

Who received funding?

Flow of funds from donor organizations in 2004

Approximately one-half (US\$ 156 million) of the total investment flowed from funders directly to R&D entities conducting research.

Another one-quarter (US\$ 79 million) of total investment was granted to funding managers – organizations that foster collaboration with R&D entities, disburse research funding and manage research activities among numerous organizations working in a particular area of focus.

Figure 1: Funds flow of donor 2004 malaria R&D investment (US\$ millions)

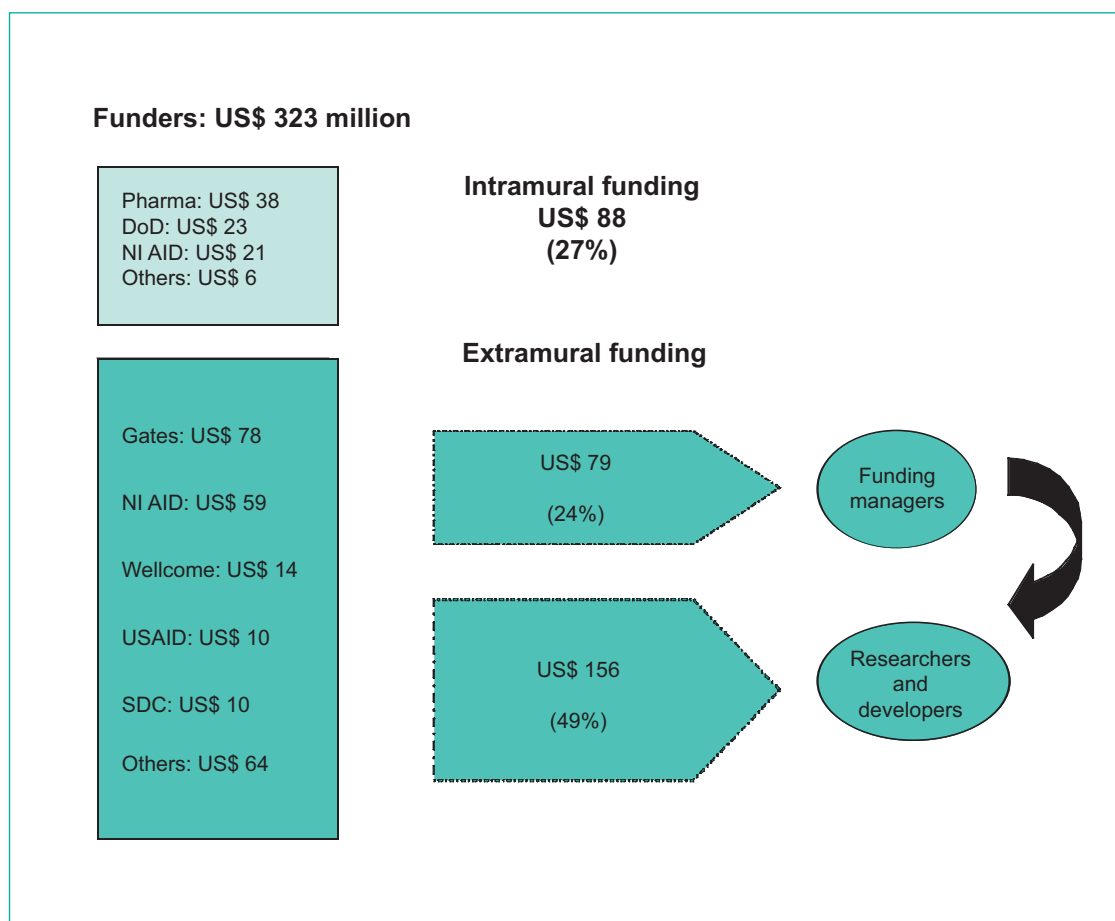


Figure 1 depicts the flow of malaria R&D funds from donor and funding organizations in 2004. Intramural funding represented 27% (US\$ 88 million) of total investment; extramural grants accounted for the remaining 73% (US\$ 235 million); details are discussed in the following sections.

Funding managers

Funding managers play a central role in the targeted distribution, management and monitoring of funds from donors to R&D entities. These organizations exist in a variety of forms: nongovernmental organizations

(NGOs), public-private partnerships (PPPs) and programmes such as the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Bringing together expertise and resources from multiple stakeholders, a number of funding managers are building and managing a large pipeline of new pharmaceutical products. By leveraging investments and managing projects with a focus on the public good, funding managers aim to accelerate the overall product development process by funding, partnering with and fostering relationships among pharmaceutical and biotechnology companies, government

agencies and academic or other research institutions. Several funding managers like the Multilateral Initiative on Malaria (MIM) and the African Malaria Network Trust (AMANET) focus more on scientific capacity building than on product development.

Funding managers are generally not the originators of funds, and hence have not appeared in the tables of top malaria R&D investors. That stated, significant levels of funding are received and disbursed by these organizations. Table 3 highlights funding manager survey participants and their 2004 receipts.

Table 3
Funding managers and 2004 funding received (US\$)

Survey entity	Funding received
Medicines for Malaria Venture	27,844,413
PATH Malaria Vaccine Initiative	24,831,823
TDR	13,372,128
Multilateral Initiative on Malaria	3,990,000
Africa Malaria Network Trust	2,710,947
Drugs for Neglected Diseases Initiative	2,115,741
European Malaria Vaccine Development Consortium	1,614,105
Institute for OneWorld Health	1,429,611
WHO Initiative for Vaccine Research	502,500
European & Developing Countries Clinical Trials Partnership	496,648
Total	US\$ 78,907,916

With aggregate receipts of almost US\$ 79 million, this group managed 24% of total 2004 malaria R&D investment, and received 34% of the total extramural funding. Private philanthropic organizations provided the majority of funds (US\$ 47.4 million or 60%) to funding managers in 2004. The Gates Foundation contributed 95% of private philanthropic funding to this group (US\$ 45.1 million), followed by the Rockefeller Foundation and the Wellcome Trust.

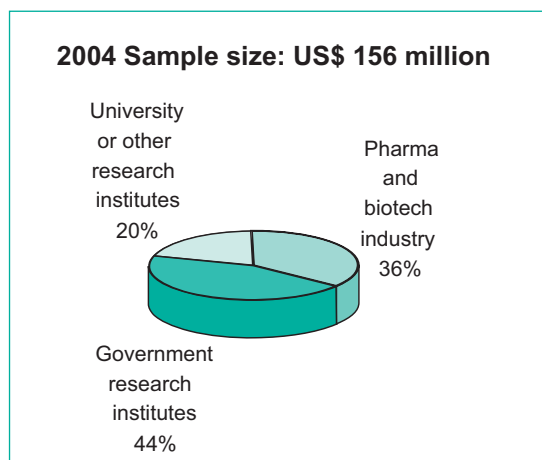
The largest funding managers came into existence within the past six years, and their involvement in research funding continues to grow. The five funding managers with the highest receipts in 2004 (representing 92% of total funding manager receipts) also submitted survey data for the years 2002 and 2003. The compound annual growth rate of funding received by this group during this period is greater than 31%. Seventy-five per cent of this growth was fuelled by increased support from

the Gates Foundation. A significant amount of the increase in malaria R&D funding in the last decade can be attributed to funds generated by this group.

Researchers and developers

Given its primary focus on sources of investment of R&D to combat malaria, this study did not attempt to survey every recipient of funding dedicated to malaria research. However, the study team did engage a broad sampling of research and development entities to participate in the survey, including many major government research institutions, pharmaceutical and biotechnology companies, universities and other externally funded research entities. In total, this group reported receiving US\$ 156 million of funding in 2004 to support malaria research and development (Figure 2).

Figure 2: 2004 funding by type of research entity



Forty-four per cent of this US\$ 156 million supported research activities in government research institutes. Four US government entities accounted for 77% of the total for this group: the US Department of Defense (DoD), the National Institution of Allergy and Infectious Diseases (NIAID), Centers for Disease Control and Prevention, and the National Institute of

Child Health and Human Development (NICHD). The majority of investment supporting government research institutes was intramural funding.

Pharmaceutical and biotechnology industry respondents reported more than US\$ 55 million of investments in research. The majority of the investment (69%) came in the form of intramural or in-house research and development by pharmaceutical and biotechnology companies, with the balance represented by research grants received from donors and funding managers. So while industry is receiving considerable funding to conduct malaria research and development (e.g. from public-private partnerships), it is also making significant internal investments.

Other research institutions, primarily universities, reported receiving 20% of all funding to research entities. There is considerable variation in the size of the research programmes. The London School of Hygiene & Tropical Medicine was funded for US\$ 6.9 million of malaria research, while several other entities were funded at less than US\$ 100,000. On average, surveyed university and other externally funded research institutes received about US\$ 1.8 million of funding.

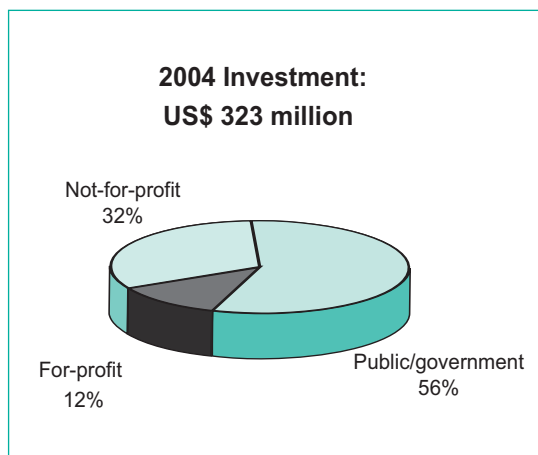
There was also variation in the categories of research funded at the different types of research institutions in this sample. Government research institutes were most heavily funded for *vaccine development*, with *drug development* being the next highest funded area. The pharmaceutical and biotechnology respondents were heavily focused on *drug development*. University and other externally funded research institutes were most heavily focused on *basic research*, to which almost 50% of their funding was allocated.

How was the funding allocated?

Categorization of investment in R&D to combat malaria in 2004

Malaria R&D investment in 2004 can be examined from many perspectives. Of particular interest are investment by sector (Figure 3), by geography for government giving (Figure 4), by type of research activity (e.g. *basic research* versus *drug development*) and by type of funding (extramural versus intramural).

Figure 3: Investment by sector



The public sector, comprised predominantly of government and multilateral funding agencies, is the largest investor in malaria R&D activities, providing US\$ 181.4 million (56%) of the US\$ 323 million total in 2004.

The not-for-profit sector contributed US\$ 102.5 million (32%) of total investment in 2004. Private philanthropic organizations reported donations of US\$ 95.4 million in 2004 and university research labs and other not-for-profit organizations accounted for an additional US\$ 7.1 million.

Investment by the for-profit sector was US\$ 39.5 million (12% of the total). The vast

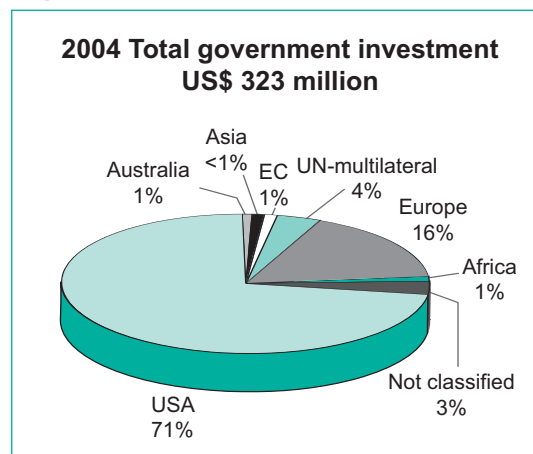
majority of this funding (96%) was in the form of intramural research and development by pharmaceutical and biotechnology companies, with the balance being comprised of corporate donations. ExxonMobil Foundation and BHP Billiton were the only two for-profit companies or company foundations contributing to malaria R&D outside of the pharmaceutical sector.

Geographical breakdown of public sector investment

The United States government invested US\$ 128.8 million in malaria R&D in 2004 (more than 70% of total public sector support and 39.8% of total investment). European governments and the European Commission (EC) provided US\$ 36.1 million of funding (20% of total public sector support and 11% of total investment), led by Switzerland, the United Kingdom, and the Netherlands at US\$ 12.2, US\$ 9.8, and US\$ 7 million respectively.

Funding by the United Nations and multilateral organizations (US\$ 7.2 million) includes US\$ 4.2 million from the Global Fund to Fight AIDS, Tuberculosis and Malaria to support *implementation research*, and World Bank funding of US\$ 2.3 million.

Figure 4: Government investment by region



Several governments in malaria-endemic countries, including India, Mozambique and South Africa, invested in malaria R&D.

Contributions from many governments have been captured through the survey submission of TDR. A significant portion of TDR's funding has been geographically linked back to the contributing governments, but some remains in the "not classified" category.

Investment by R&D category

Survey participants were requested to allocate funding to the six categories of malaria R&D described earlier in this report (Figure 5). All but 2% of the funding reported for 2004 was allocated to R&D categories.

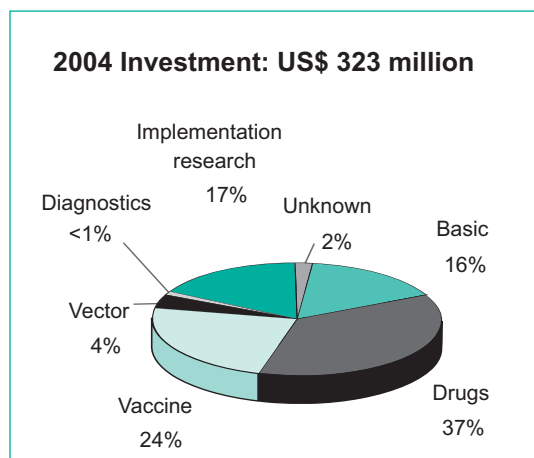
Antimalarial drug discovery and development received the largest amount of investment in 2004: US\$ 120.2 million (37% of the total). The largest sources of this investment were the pharmaceutical and biotechnology company respondents at US\$ 38.1 million, followed by the Gates Foundation at US\$ 28.2 million, NIAID at US\$ 21.2 million, and DoD at US\$ 11.7 million.

Vaccine development and vaccine trials was the next highest funded category, at US\$ 78.7 million (24% of the total). NIAID was the top investor in this category, with 2004 funding of US\$ 29.2 million, followed by the Gates Foundation at US\$ 24.8 million and DoD at US\$ 9.6 million.

Implementation research investment totalled US\$ 54.6 million in 2004. The Gates Foundation was the largest investor at US\$ 24.4 million, followed by the Swiss Agency for Development and Cooperation (SDC) at US\$ 8.0 million and the Global Fund at US\$ 4.2 million.

Basic research investment totalled US\$ 50.8 million in 2004. Three organizations

Figure 5: Allocation of 2004 funding by R&D category



contributed 67% of total basic research funding. NIAID was the largest investor at US\$ 18.8 million, followed by the Wellcome Trust at US\$ 8.7 million and the Medical Research Council (UK) at US\$ 6.4 million.

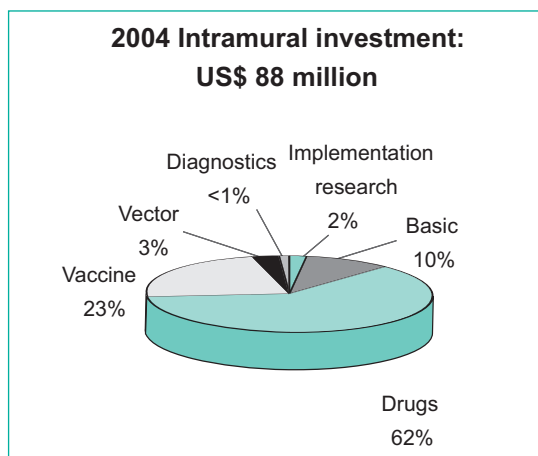
Vector control research totalled US\$ 11.9 million. The majority of this funding (64% or US\$ 7.6 million) was contributed by NIAID, followed by DoD at US\$ 1.9 million and the Wellcome Trust at US\$ 1 million. *Development of malaria diagnostics* received the lowest level of investment, at US\$ 718,000. Funds contributed (US\$ 200,000) by an anonymous donor to the Johns Hopkins Malaria Research Institute made up the largest component of funding, followed by contributions from the Swiss Government's Interior Ministry (US\$ 161,000).

Intramural versus extramural funding

Seventy-three per cent of the investment in malaria R&D in 2004 (US\$ 235 million) was in the form of extramural funding – or grants made by one organization to another. The balance (27% or US\$ 88 million) was reported as intramural funding, and was heavily concentrated in three survey entities:

pharmaceutical and biotechnology company respondents, NIAID and the US DoD. Pharmaceutical and biotechnology company respondents reported conducting more than US\$ 38 million in intramural research and development in 2004. Funding by the companies that responded amounted to 12% of the total investment in malaria R&D in 2004. The US DoD and NIAID reported US\$ 22.9 and US\$ 20.7 million of intramural research respectively in 2004. These three entities funded 93% of all intramural investment.

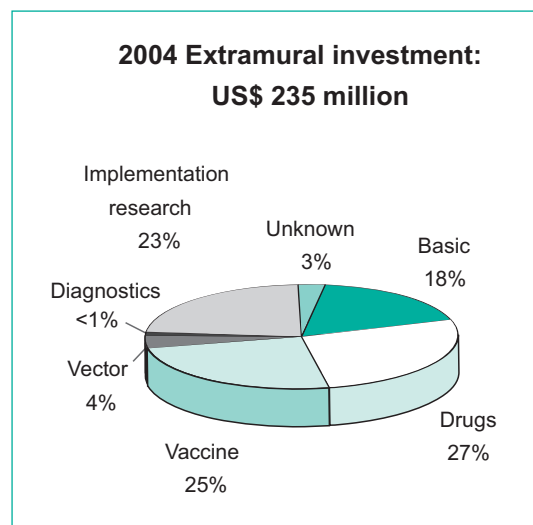
Figure 6: Categorization of 2004 intramural investment



Allocation of the US\$ 88 million of intramural funding by R&D category produces a different result from the categorization of the total US\$ 323 million investment.

Because of a high level of investment in drugs by the pharmaceutical and biotechnology respondents, the percentage of investment categorized as *drug discovery and development* is significantly larger in the intramural categorization than in the total funding categorization (62% versus 37% in total investment; see Figures 6 and 7). Offsetting decreases are recorded in *implementation research* (2% versus 17%) and *basic research* (10% versus 16%).

Figure 7: Categorization of 2004 extramural investment



The distribution of extramural funding is more even across R&D categories. *Drug discovery and development* remains the largest categorization but decreases to 27% (from 37% of the total investment allocation). *Vaccine development and vaccine trials* is the next largest category, at 25% (versus 24% in the total investment allocation). The percentage of extramural investment categorized as *implementation research* is 23% (versus 17% of total investment). Little change was observed in the other categories.

Funding for capacity building

Building local capacity to conduct research in malaria-endemic countries has become a new focus of funding over the past decade. Improving human resources and institutional capacity to conduct research in the countries most affected by malaria is believed to help advance R&D.

Because capacity building cuts across the various areas of research, it was not included as a separate category in the survey. However, respondents were asked to indicate how much of their reported malaria R&D funding was

specifically dedicated to capacity building. Survey respondents reported malaria R&D capacity-building funding of US\$ 12.4 million⁸ in 2004. This represents 3.8% of total 2004 investment. SDC reported the highest capacity-building investment at US\$ 3.2 million, followed by the Fogarty International Center (US\$ 1.9 million), the Netherlands Ministry for Development Cooperation (US\$ 1.9 million) and TDR (US\$ 1.6 million).

Perceptions of funding levels

Survey respondents overwhelmingly reported that they believed malaria R&D is underfunded. Only four of 74 respondents thought that malaria R&D was appropriately funded. Three-quarters of respondents believed that *antimalarial drug discovery and development*, *vector control research*, and *implementation research* were significantly or somewhat underfunded.

Malaria R&D investment in context

Current funding compared to past funding

This study calculates the investment in malaria R&D in 2004 to be US\$ 323 million.

In its 1996 study, *Malaria Research: An Audit of International Activity*, the Wellcome Trust reported that “total identifiable global expenditure on malaria research in 1993 was approximately US\$ 84 million.”⁹ Adjusting this figure for biomedical R&D inflation yields US\$ 119.1 million in 2004 dollars.¹⁰

The Wellcome Trust study primarily identified extramural support, and the authors noted that data from the pharmaceutical industry could not be obtained. Subtracting pharmaceutical and biotechnology industry respondent investment from the present study’s findings yields US\$ 285.3 million – which can be

compared to the inflation-adjusted Wellcome Trust figure of US\$ 119.1 million. Using these data, it can be inferred that real funding for malaria R&D has increased by an estimated US\$ 166 million between 1993 and 2004, with real growth at 8.3% per year, after accounting for biomedical R&D inflation.

What has driven this growth?

New donors – and new means for donors to use their resources efficiently – have both contributed to increases in funding. A significant component of the increased funding can be attributed to specific new donors, such as the Gates Foundation. NIAID funding also increased well above the inflation rate, from US\$ 13.1 million reported for 1993 to US\$ 80.2 million in 2004. Funding provided by these two organizations accounts for over 80% of the identified non-inflationary growth in investment between 1993 and 2004.

New public-private partnerships have provided foundations, governments and industry a well-managed and transparent conduit for increased investment and are another likely reason for increased resources devoted to malaria R&D.

Is malaria R&D funded at an appropriate level?

One way to address this question is to assess the burden that malaria and other diseases impose on global health, and compare malaria R&D funding with that of other diseases.

Malaria’s share of R&D funding

For 2001, the most recent year for which data are available, total global spending on all health-related R&D was estimated at US\$ 105.9 billion by the Global Forum for Health Research. The vast majority of these funds originated in high-income countries, and was spent in high-income countries on illnesses

affecting their citizens.¹¹ The private, for-profit sector was the largest source of health R&D funds, accounting for 48% of funding. The public sector was the next largest source, contributing 44% of funding. The remaining 8% of funding came from the private, not-for-profit sector. This is in sharp contrast to funding for malaria R&D in 2004, of which the private for-profit sector contributed 12% of funds, the public sector 56%, and the private not-for-profit sector 32%.

Malaria R&D investment in 2001 was estimated at approximately US\$ 288 million in a paper presented at Forum 8, the Global Forum's 2004 annual meeting in Mexico City.¹² The authors employed a bibliometric approach¹³ to determine R&D investment for eight disease areas. Investment in malaria R&D represented less than 0.3% of global R&D investment in 2001. Yet malaria's impact on humanity is

roughly ten times that amount, accounting for 3.1% of the global disease burden and overwhelmingly occurring in poor countries.

Comparing disease burden and funding levels

Cardiovascular diseases are the leading cause of death in the world and afflict rich and poor alike, accounting for 38.1% of deaths in high-income countries and 27.9% in low- and middle-income countries.¹⁴ Tuberculosis and dengue fever primarily afflict developing nations, so these also make interesting comparators, as does HIV/AIDS. The death toll from diabetes and malaria are somewhat similar, so diabetes has also been included in the comparison. Examining these conditions, as well as all medical conditions, helps put malaria R&D funding in perspective.

Table 4

Comparison of total health R&D and malaria R&D funding by sector

Sector	All health-related R&D ^a	Malaria R&D ^b
For-profit	48%	12%
Public	44%	56%
Not-for-profit	8%	32%

^a From the Global Forum's *Monitoring Financial Flows for Health Research 2004*, p. 15¹⁰ (2001 data)

^b Calculated from survey data (2004)

Disease burden – the impact of a disease on people – is tracked by WHO in terms of disability-adjusted life-years (DALYs), which have become a common unit of measurement in the public health community. R&D funding per DALY is US\$ 6.20 for malaria, whereas R&D funding average for all conditions is US\$ 71.07 per DALY.¹⁵ Cardiovascular diseases and diabetes are funded at US\$ 63.45 and US\$ 102.07 per DALY, respectively. Were malaria funded at the average rate for all conditions, it would receive over

US\$ 3.3 billion in annual R&D funding; it currently receives about 9% of this amount.

Low funding results in few scientific breakthroughs

Low R&D investment is reflected in limited drug development, as evidenced by Trouiller and colleagues in a 2002 study which found that between 1975 and 1999, only four drugs were developed to combat malaria and three for tuberculosis, while 89 were developed for

Table 5**Disease burden and funding comparison, 2001-2002 data**

Condition	Global disease burden ^a (million DALYs)	% Total global disease burden	Deaths ^a (million)	% Total global disease deaths	R&D funding ^b (US\$ million)	R&D funding per DALY
Cardiovascular	148.190	9.9%	16.733	29.3%	9,402	63.45
HIV/AIDS	84.458	5.7%	2.777	4.9%	2,049	24.26
Malaria	46.486	3.1%	1.272	2.2%	288	6.20
Tuberculosis	34.736	2.3%	1.566	2.7%	378	10.88
Diabetes	16.194	1.1%	.988	1.7%	1,653	102.07
Dengue	0.616	0.0%	.019	0.0%	58	94.16

^a DALY and death statistics are 2002 data, from WHO, *World Health Report 2004*

^b Estimate for 2001-2002 funding from Lewison, G., et al., 2004, "Outputs and expenditures on health research in eight disease areas, 1996-2001," presented at Forum 8, the Global Forum's 2004 annual meeting in Mexico City. The authors use a bibliometric approach to estimate R&D funding.

respiratory illnesses and 179 for cardiovascular diseases. Drug development follows perceptions of lucrative market segments. Cardiovascular drugs represented almost 20% of the US\$ 204 billion drug market in 1999, and respiratory drugs 9.3%, while malaria drug sales were at 0.1% of the worldwide total. On a sales per DALY basis, cardiovascular and respiratory drugs brought in US\$ 283 and US\$ 307 per DALY respectively, while malaria drug sales were US\$ 5 per DALY.¹⁶

The private sector is motivated primarily to pursue profitable market opportunities. Development of new drugs and vaccines is very expensive, costing hundreds of millions of dollars. Given the perception of low return on investment, private sector R&D expenditures on malaria are very low. To address this "market failure", continued and increased support from the public and not-for-profit sectors will be required to finance malaria R&D. Although malaria R&D is expensive, the return on investment is far more dramatic than perceived, not only in lives saved but also in economic returns in the disease-endemic countries.

What malaria R&D funding can buy

As noted, malaria R&D receives about 0.3% of global medical R&D spending, or roughly one-tenth of the amount suggested by its 3.1% share of the global disease burden. The US\$ 323 million investment identified through this survey is funding an array of highly complex research activities across six categories of R&D. As a general rule, progress in research is linked to funding. While determining appropriate funding for malaria R&D requires further study, survey respondents and published literature have provided some perspective on R&D costs and what malaria funding can buy.

In a 2003 survey of pharmaceutical firms conducted by the Tufts Center for the Study of Drug Development, the cost of developing a new drug was estimated to be over US\$ 800 million, including the cost of drug candidates abandoned during testing and the opportunity cost of capital.¹⁷ Medicines for Malaria Venture estimates that it will need between US\$ 150 to 200 million, including cost of failures, to develop one new combination antimalarial

Table 6**New chemical entities (NCEs) approved between 1975 and 1999 by therapeutic area, disease burden, and sales**

Therapeutic area	Approved NCEs 1975 – 1999 Number	% of total	NCEs per million DALYs ^a	Drug sales per DALY ^a (US\$)
Total for all therapeutic areas	1,393	100%	1.01	148
Tuberculosis	3	0.2%	0.11	11
Malaria	4	0.3%	0.10	5
HIV/AIDS	26	1.9%	0.37	44
Respiratory (non-infectious)	89	6.4%	1.44	307
Cardiovascular	179	12.8%	1.25	283

Source: Trouiller et al.¹⁶

^a Trouiller cites DALY data from WHO *World Health Report 1999*, and 1999 drug sales data

drug. This dramatic reduction in cost is due to the various advantages of operating as a public-private partnership, such as significant in-kind contributions from research partners including infrastructure costs, reduced project risk and cost through a portfolio approach and “piggy-backing” on existing research and knowledge in the public and commercial sector.¹⁸

Vaccine development is also complex and costly, especially when dealing with parasitic diseases as opposed to viruses such as flu or measles. In its 2003 report *State of the World’s Vaccines and Immunization*, WHO referenced “approximately US\$ 600 million a year invested in HIV vaccine research,”¹⁹ a figure corroborated by a recent report by the HIV Vaccines and Microbicides Resource Tracking Working Group.²⁰ In the case of malaria, the formidable opponent is a complex parasite that is innovative in the face of assault. A phase III trial for malaria vaccines may cost between US\$ 50 and US\$ 100 million or more. The failure rate for anti-parasitic vaccines is unknown, as none are yet commercially

available. This is because parasites are highly complex organisms, often having hundreds of times the antigenic targets²¹ of viral and bacterial organisms against which vaccines have been successfully developed.

These examples illustrate not only malaria-specific research costs, but also that progress is being made. Malaria research is a complex field, and the speed and success rate of scientific advances is largely dependent on available funding.

Conclusions: Global commitment to combating malaria

A child dies from malaria every thirty seconds, and malaria fatalities increased in the last two decades of the twentieth century. A variety of factors have driven the growing burden of malaria, including increased resistance to once-effective drugs and insecticides, and poor and/or deteriorating public health systems in many nations.

The international community has repeatedly emphasized that addressing malaria is essential to Africa and global development, notably through the UN Millennium Development Goal 6 (Target 8) to halt and begin to reverse the incidence of malaria and other major diseases by 2015. The Roll Back Malaria Partnership, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Multilateral Initiative on Malaria have all been formed in recent years and are working to translate that goal into action.

This report estimates that annual investment across all areas of malaria R&D totalled US\$ 323 million in 2004. It goes on to suggest that this amount is perhaps one-tenth what it should be relative to disease burden. The international community will need to increase funding significantly if it is to live up to its commitments and meet the challenge of malaria today and in the future.

Fortunately, public and private collaboration is on the increase, and, along with creative financing mechanisms, should assist the

international community to meet its commitment to combat malaria. And there is evidence that the R&D pipeline will produce the tools it promises, including long-term solutions for addressing malaria. For instance, the WHO Initiative for Vaccine Research listed 23 types of malaria vaccines in various stages of development in its April 2005 vaccine R&D status report.²² MMV reported that it had over 20 drug discovery and development projects in its portfolio as of 2005 and DNDi has two fixed-dose Artemisinin-based combination therapies in phase III clinical studies.²³

These and other advances in malaria R&D represent real progress, but their momentum and prospects for ultimate success will be undercut without adequate financial resources to support them. Despite its impact on life, health and economic development, malaria has long been a neglected disease. While further study is needed to reasonably estimate how much malaria R&D funding is needed, it is clear that current funding is not in line with the size of the problem and that significantly more support will be required.

-
1. Malaria R&D Alliance. *Malaria Research & Development: An Assessment of Global Investment*. Malaria R&D Alliance, November 2005. Available from: www.malariaalliance.org
 2. World Health Organization. *World Malaria Report 2005*. Geneva: WHO, 2005, p. 11.
 3. World Health Organization. *World Health Report 2004*, 2002 disease burden statistics based on DALY analysis. Geneva: WHO, 2005.
 4. Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2004*. Geneva: Global Forum for Health Research, 2004, p. 59; analysis based on WHO source data.
 5. Breman J. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *American Journal of Tropical Medicine and Hygiene*, 2001, 64(1,2) S, pp. 6-7.
 6. For example, see: WHO Commission on Macroeconomics and Health, December 2001, *Macroeconomics and Health: Investing in Health for Economic Development*, p. 79, (“Malaria research outlays are perhaps US\$ 100 million”). For a high estimate, see: WHO, 2003, *Communicable Diseases 2002: Global defence against the infectious disease threat*, p. 174 (“Worldwide spending on malaria research, estimated at US\$ 84 million in 1998, has soared to over US\$ 1 billion...”)
 7. Because of information or accounting system limitations, a few organizations could not provide actual disbursement data. These organizations generally provided budget data instead of disbursements. In most such cases, verification was received that budget data were a good proxy for actual disbursements.

8. This total does not include major infrastructure projects, as they were specifically excluded from the survey.
9. Anderson J, MacLean M, and Davies C. *Malaria Research: An Audit of International Activity*. London: The Wellcome Trust, 1996, p. 7. This figure was expressed in 1992 dollars.
10. The Bureau of Economic Analysis of the US Department of Commerce publishes a biomedical research and development price index based on National Institutes of Health data. See http://ospp.od.nih.gov/ecostudies/BRD_Distrib_2005, accessed on 7 September 2005.
11. Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2004*, pp. 13-14.
12. Lewison G, Rippon I, de Francisco A, Lipworth S. *Research Evaluation*, 2004. Vol. 13, 3 December 2004:181-88.
13. The authors describe the approach on p. 1 of their paper: “The method involved identification and analysis of research outputs – papers in the serial literature and indexed in the Science Citation Index – and their multiplication by the estimated cost per paper, determined from questionnaires sent to leading researchers.”
14. Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2004*, p. 58. Disease and death figures are 2002 data from the WHO *World Health Report 2004*.
15. The average for all conditions calculation is based on the Global Forum’s US\$ 105.9 billion estimate of 2001 health-related R&D spending divided by WHO’s 1.49 billion estimate of 2002 total disease burden in DALYs.
16. Trouiller P et al. Drug development for neglected diseases: a deficient market and a public-health policy failure. *The Lancet*, 2002, Vol. 359, pp. 2188-2194.
17. DiMasi J, Hansen R, Grabowski H. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 2003, 22(2), pp. 151-185.
18. Moran M et al. *The New Landscape of Neglected Disease Drug Development*. London: The Wellcome Trust, 2005, p. 54.
19. World Health Organization. *State of the World’s Vaccines and Immunizations – Rev. ed.* Geneva: WHO, 2003, pp. 9-10.
20. Preventive HIV vaccine investment was estimated at approximately US\$ 682 million for the year 2004; see: Lamourelle G, et al. *Tracking Funding For Preventive HIV Vaccine Research & Development: Estimates of Annual Investments and Expenditures 2000 to 2005*. HIV Vaccines and Microbicides Resource Tracking Working Group, 2005.
21. Hooks C. *Clinical Trials: Crucial Steps on the Road to a Malaria Vaccine*. Rockville, MD: Malaria Vaccine Initiative, 2004.
22. WHO Initiative for Vaccine Research website, http://www.who.int/vaccine_research/, accessed 18 August 2005.
23. Medicines for Malaria Venture website, <http://www.mmv.org>, accessed 18 August 2005.

Chapter 6

New prevention technologies: trends in resource flows for HIV vaccines and microbicides

*by Gabrielle Lamourelle, Polly Harrison, Jane Rowley and
Mitchell Warren for the HIV Vaccines and Microbicides Resource
Tracking Working Group*

Gabrielle Lamourelle is a Policy Research Associate at the International AIDS Vaccine Initiative. As part of the HIV Vaccines and Microbicides Resource Tracking Working Group, she co-authored several papers on funding flows for new HIV prevention technology research and development. She holds a BA in Sociology from the University of California at Berkeley.

Chapter 6

Introduction

In the 20 years since the identification of HIV as the cause of AIDS, the HIV pandemic has grown to be the greatest public health crisis facing the world since the 13th century. Over 65 million people have contracted HIV to date, and each day another 14,000 people are infected with the virus.¹ More needs to be done to expand access to existing prevention and treatment options – but there is also an urgent need simultaneously to develop additional prevention methods. Microbicides and HIV vaccines are two technologies currently under development that would provide people with new options for protecting themselves from HIV.

In 2001, the United Nations Special Assembly (UNGASS) on HIV/AIDS highlighted the importance of mobilizing massive new resources to mount an effective and comprehensive response to the epidemic. In particular, it called for increased investment in research related to HIV and AIDS and, more specifically, for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides.

There is increasing scientific confidence that it will be possible to develop a safe and effective preventive HIV vaccine and a safe and effective microbicide. There are also, however, many scientific challenges ahead and ensuring that both of these technologies are developed in a timely fashion will require greater global collaboration and coordination. The investment of significantly more resources will also be required, and should be built into a balanced portfolio approach to AIDS that incorporates both increased access to currently available interventions and services and greater investment in new interventions.

Methods: estimating resource flows for HIV vaccines and microbicides

In 2004, a collaborative project to track funding for preventive HIV vaccine and microbicide research and development (R&D) was initiated by the AIDS Vaccine Advocacy Coalition (AVAC), the Alliance for Microbicide Development (AMD), the International AIDS Vaccine Initiative (IAVI) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). The HIV Vaccines and Microbicides Resource Tracking Working Group was established to generate and disseminate detailed, comparable data on annual funding levels for preventive HIV vaccine and microbicide research, development and advocacy activities and on how these funds are being spent.

The HIV Vaccines and Microbicides Resource Tracking Working Group developed a systematic approach to data collection and collation in order to generate investment estimates that can be compared from year to year, from one technology to another, and across funders. Research results were published in mid-2005² and are being used in part to monitor implementation of the Global Commitment and Action Indicators adopted by the United Nations in 2001.

Estimating investments for HIV vaccines and microbicides

Investment figures were based on estimates of the level of funds disbursed each year and generated from the perspective of the funder. In other words, funds were allocated to the year in which they were disbursed irrespective of whether the funds were spent by the recipient in that year or in future years. Investment figures for individual years were developed

using these methods, however, they do not necessarily reflect the long-term commitments made by donors to the development of safe and effective microbicides and HIV vaccines. Variations exist across donors' funding cycles and fiscal years, and some funders choose to 'forward fund' projects, e.g., disburse resources in an individual year that are intended to fund research conducted over a number of years. In addition, public-private partnerships (PPPs), which require sufficient funds either banked or committed to enter into credible multi-year contracts, have become increasingly important players in HIV vaccine and microbicide research and development.

In developing these estimates, we distinguished between primary funders and intermediary organizations. 'Intermediary' organizations receive resources from multiple funders and use these resources to fund their own work as well as the work of others. For example, the Contraceptive Research and Development Program (CONRAD), the International Partnership for Microbicides (IPM), IAVI and the South African AIDS Vaccine Initiative (SAAVI) were classified as intermediary organizations. In order to avoid double counting, intermediary organizations were classified as recipients rather than funders. All

identified primary funders of HIV vaccine or microbicide R&D were allocated to one of three categories: public, philanthropic, or commercial sector funders (see Table 1).

A broad definition of R&D was used and data were collated not only on product development efforts, but also on support for clinical trial preparations, community education and advocacy and policy efforts directed at accelerating HIV vaccine or microbicide development and use. However, we excluded research that may have benefits or links to, but that was not directed primarily at, the development of microbicides and HIV vaccines (e.g., platform technologies).

A four-step process was followed to estimate annual investment levels for both microbicide and preventive HIV vaccine R&D (see Box 1). All primary funders were asked to provide data on annual disbursements,³ as this gives a more accurate picture of annual investments than commitments or pledges made.⁴ However, not all organizations were able to provide disbursement data, and for these organizations commitment data were used instead.⁵

In the case of commercial organizations, we contacted the main companies engaged in HIV

Table 1

Public, philanthropic and commercial sector primary funders

Public sector	<ul style="list-style-type: none"> ● national governments (including government research bodies, international development assistance agencies and other government funding agencies) ● European Commission ● multilateral agencies
Philanthropic sector	<ul style="list-style-type: none"> ● private, not-for-profit organizations (e.g., foundations, trusts and non-governmental organizations) ● charities ● corporate donations ● individual gifts and bequests
Commercial sector	<ul style="list-style-type: none"> ● biotechnology companies ● biopharmaceutical companies

Box 1

Process followed to estimate annual HIV vaccines and microbicides investments

Step 1: Identifying key funding agencies

A list of all organizations involved in funding preventive HIV vaccine and microbicide R&D was drawn up based on funders identified in previous resource tracking efforts, supplemented by discussions with key individuals working in the HIV vaccine and microbicide fields. As new funders were identified, they were added to the list.

Step 2: Collecting publicly available information

For each of the funders identified, the publicly available information was reviewed for data on annual investment levels. Information sources consulted included: government reports, annual reports, US Securities and Exchange Commission (SEC) filings, published studies and articles, 'grey' literature, scientific presentations and website postings.

Step 3: Contacting the funding agencies identified

Public sector

Letters were written to all of the public-sector funders identified asking them for information on funds disbursed since 2000 and future commitments in their local currency. Information requested included:

- description of the projects or programmes funded
- duration of grants/contracts/awards
- total funding committed
- funding disbursement by year since 2000
- projected disbursement or future funding commitments by year.

Agencies contacted included national research funding agencies (e.g., Agence Nationale de Recherches sur le Sida (ANRS) in France and the Canadian Institutes of Health Research (CIHR)), overseas development agencies (e.g., the Department for International Development (DFID) in the UK and the Agency for International Development (USAID) in the US) and multilateral organizations (e.g., UNAIDS, the World Bank and the World Health Organization (WHO)). Each national agency was also asked to suggest other national agencies that should be contacted.

Philanthropic sector

Letters were written to all of the identified philanthropic funders known to have awarded more than US\$ 100,000 to either technology between 2000 and 2004. The letters were similar to those sent to public-sector funders and asked for the same information. For smaller funders, disbursement estimates were based on information collated from intermediaries and Internet searches and, where no information was readily available, the organizations were contacted directly.

In the case of corporate donations, data were only collected on cash donations. No attempt was made to include in-kind support such as goods, services and donated staff time owing to the difficulties in valuing these contributions.

Commercial sector

Each of the main companies identified was contacted in writing, in person or by phone and asked to provide information on its own internal funding (i.e., companies were asked not to include funds received from external sources such as research agencies or intermediary organizations).

Step 4: Reviewing, checking and analysing the information collated

The financial information received from each funder was reviewed against the project inclusion criteria and cross-checked against the data collected from other informants. Any issues or questions were followed up with the funder. In the case of US agencies that track microbicide funding explicitly, we have made use of their self-reported figures rather than examining each grant individually.

For those organizations that did not respond after repeated follow-ups, annual disbursements were estimated based on publicly available information, supplemented by discussions with experts working in the field.

The estimates for each sector were then reviewed for consistency to ensure that similar definitions were used and to eliminate double counting.

vaccine and microbicide R&D as of mid-2005 and asked them to provide us with information on their levels of investment from 2000 to 2004 as well as their expected investment in 2005, excluding direct or indirect funding from the public sector and intermediary agencies. The project scope, however, had to be scaled back given the time available for this study. Many of the companies contacted did not specifically track R&D funding for these technologies or were otherwise reluctant to share sensitive information on funding, citing concerns about proprietary business issues. As a result, industry estimates are for one year (2004) and presented as a range based on data collected and discussions with experts in the field.

All figures included are reported in current US dollars and have not been adjusted for inflation. Funding information provided in other currencies was converted into US dollars using the appropriate International Monetary Fund (IMF) annual average exchange rate,⁶ except for those funds where the actual rate received was known.

Estimating annual expenditures

The total level of funding made available in a particular year and the level of funds actually spent in that year do not always match. For example, a funder may provide a large sum of money in one year for use in future years or a research programme may be delayed, postponing expenditures.

The Resource Tracking Working Group had hoped to collate detailed data on annual microbicides and HIV vaccines expenditures, including their breakdown by expenditure category. However, this information on microbicides was not available within the project time frame for expenditures made by US government funding agencies, which accounted for 65% of the funds invested in 2004. As a result, data are presented only on HIV vaccine expenditures.

In estimating annual HIV vaccine expenditures we distinguished between funding provided by primary funders to universities, not-for-profit organizations or companies and funding they provided to intermediary organizations like IAVI and SAAVI. For each of the intermediary organizations we collated data on their annual expenditures. It should be noted that our annual expenditure estimates are first-order estimates, and that actual annual expenditures could be higher or lower because non-intermediary expenditure estimates are based on disbursement figures rather than on actual expenditure data.

Expenditures were allocated across five categories of product development activity or stage using project descriptions provided by informants. The categories used were (1) basic research, (2) pre-clinical research, (3) clinical research, (4) cohort and site development, and (5) advocacy and policy development.⁷

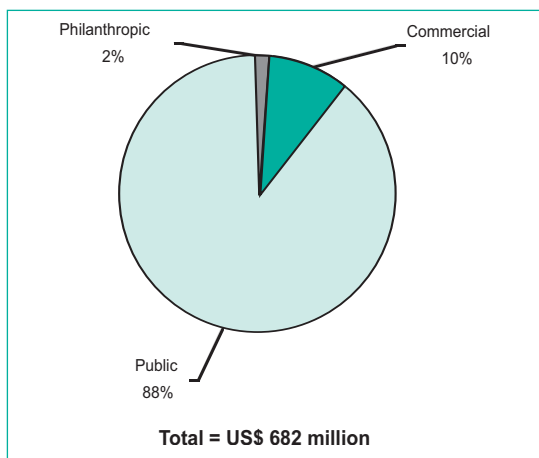
Results

Investments in preventive HIV vaccine R&D

In 2004, the public, philanthropic and commercial sectors together invested approximately US\$ 682 million in preventive HIV vaccine R&D. Of the three sectors, public agencies and institutions dominated funding for HIV vaccine R&D, accounting for 88% of total investment in 2004. In contrast, the commercial sector accounted for 10% and the philanthropic sector for 2% of funding in that year (see Figure 1).

Over the last five years there has been a marked increase in the level of investment in the development of preventive HIV vaccines. Between 2000 and 2004 investments from non-commercial (public and philanthropic) sectors almost doubled from US\$ 327 million to US\$ 614 million, and by April 2005

Figure 1: Sources of funding for preventive HIV vaccine R&D, 2004



disbursements and firm commitments from the same sources had already reached US\$ 627 million (see Table 2).

The **public sector** is the main source of funding for preventive HIV vaccines. In 2004 public-sector sources invested US\$ 602 million, or 88% of the combined global funding in that year. If one looks at **non-commercial** sources alone, the public sector provided 98% of funding available for HIV vaccine R&D in 2004. Overall public commitment to and investment in HIV vaccine research, development and advocacy has grown considerably over recent years. From 2000 to 2004, funding from these sources nearly doubled from an estimated US\$ 307 million to about US\$ 602 million.

The United States provides the largest portion of public funds and in 2004 accounted for 86% of the total funds invested by that sector. For the same year, European national governments and the European Commission together accounted for just over 9%, while national governments from the rest of the world accounted for just under 5%. Multilateral organizations such as WHO, UNAIDS and the World Bank combined accounted for under 0.5% (see Table 2 and Figure 3).

The Resource Tracking Working Group identified three countries that invested more than US\$ 10 million (Canada, the United Kingdom and the United States) in public-sector funds in 2004 and thirteen countries that invested more than US\$ 1 million (see Table 3.) In addition, the European Commission (EC) invested approximately US\$ 12 million in that year. If one looks at the cumulative funds disbursed for HIV vaccine R&D between 2000 and 2004, the top five countries (excluding the EC) in descending order were: the United States, Canada, the United Kingdom, the Netherlands and France.

The sources of funding for HIV vaccine R&D vary widely within the public sector. For example, 95% of United States funding identified in 2004 came from health and research agencies such as the NIH. The NIH alone accounted for 88% (about US\$ 452 million) of US public-sector funding – and about 75% of global public-sector investment. In many other countries reviewed for these estimates, development funding agencies were equally important sources of funds for HIV vaccine R&D. The three multilateral agencies (UNAIDS, WHO and the World Bank) included provided primarily development funding.

The **philanthropic sector** accounted for US\$ 12 million or about 2% of the total funds disbursed for HIV vaccine R&D in 2004. As seen in Table 3, levels of total philanthropic funding have varied considerably over the last five years, with a low of US\$ 7 million in 2001 to a high of US\$ 112 million in 2002. The funding increase observed in 2002 reflects the inclusion of a US\$ 100 million multi-year challenge grant awarded by the Bill & Melinda Gates Foundation to IAVI and disbursed in full to IAVI that year.

Total **commercial sector** HIV vaccine investment in 2004, excluding funding from

Table 2

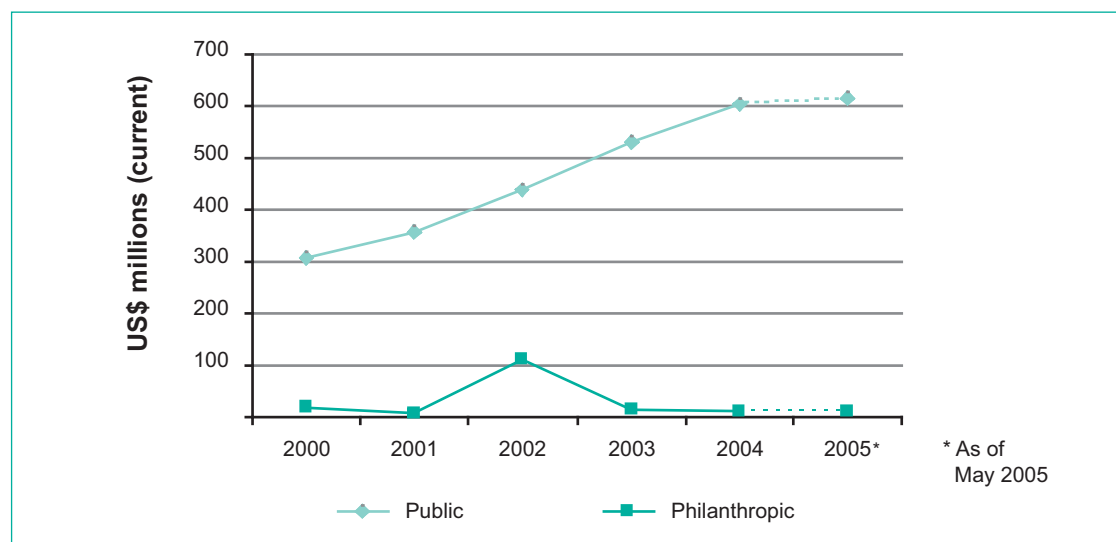
Annual investment in preventive HIV vaccine R&D by the public and philanthropic sectors between 2000 and 2005 (current US\$ millions) (2005 estimates represent actual disbursements and firm commitments made as of April 2005.)

	2000	2001	2002	2003	2004	2005
Public sector						
- US	272	314	376	463	516	568
- Europe ^a	23	32	39	44	57	39
- Other ^b	10	12	21	24	28	8
- Multilaterals	2	2	2	2	2	2
Total public	307	359	436	532	602	617
Philanthropic sector						
Total philanthropic	20	7	112	15	12	10
Non-commercial (public & philanthropic)						
Total non-commercial	327	366	548	547	614	627

^a This figure includes funding from the European Commission

^b Other includes all national public sector funding apart from funding from the US and Europe

Figure 2: Annual investment in preventive HIV vaccine R&D between 2000 and 2005 by the public and philanthropic sectors (2005 estimates are based on actual disbursements and firm commitments made as of April 2005.)



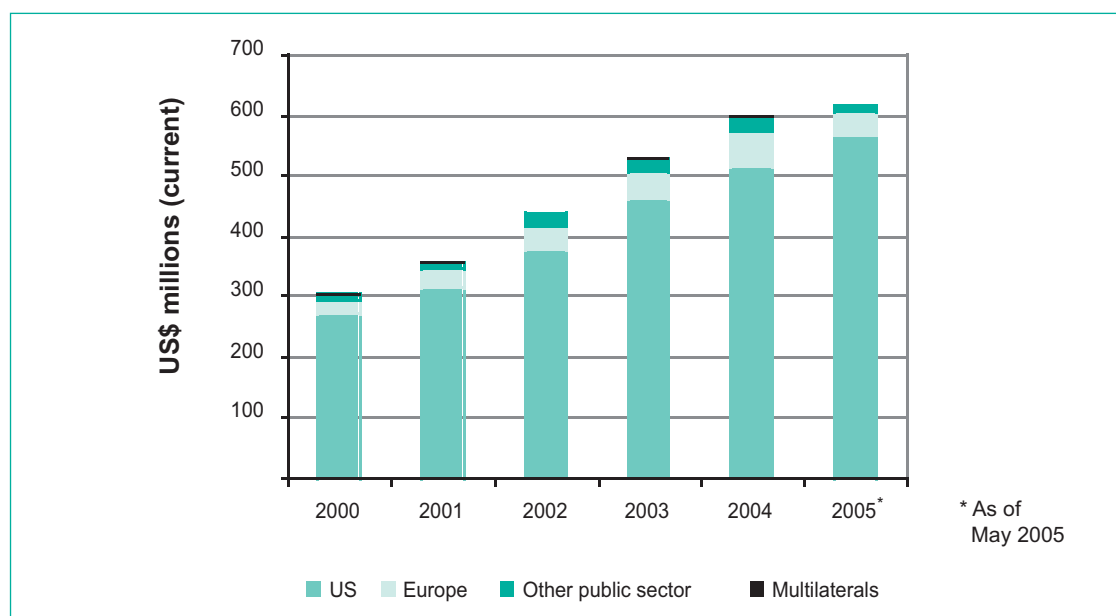
external sources, was estimated to be US\$ 68 million (range US\$ 54 million to US\$ 82 million). The majority of this funding – about 87% – comes from large pharmaceutical companies (see Table 4).

Many of the pharmaceutical and biotechnology companies active in HIV vaccine R&D receive extensive programme funding from external sources such as public-sector agencies (e.g., National Institutes of Health (US) and Agence Nationale de Recherches sur le Sida (France)) or public-private partnerships (e.g., IAVI and

SAAVI). Therefore, total expenditures by the commercial sector are considerably greater than the estimated US\$ 68 million in funds invested from their internal sources.

The Resource Tracking Working Group identified three companies (Chiron Corporation, Sanofi Pasteur and Wyeth-Ayerst Lederle) that invested between US\$ 5 million and US\$ 10 million from their own funds in HIV vaccines in 2004, and one company – Merck & Co. – invested more than US\$ 10 million in internal resources.

Figure 3: Annual public sector investment in preventive HIV vaccine R&D, 2000 to 2005



Expenditures on preventive HIV vaccine R&D

In 2004, **total expenditures** by the public, philanthropic and commercial sectors on HIV vaccine R&D were estimated to be US\$ 686 million, and were concentrated on basic and pre-clinical research activities. Of the five categories across which expenditures were

allocated, basic research and pre-clinical research together accounted for approximately 67% of the funds spent. In comparison, support for clinical trials accounted for 22%, cohort and site development for 10%, and advocacy and policy development for 1% (see Figure 4). Trends in expenditures from non-commercial sources (i.e. public and philanthropic funding exclusively) indicate a near doubling in

Table 3**National public sector investment in preventive HIV vaccine R&D by country in 2004**
(Countries are listed alphabetically within each category.)

US\$ 50k to 500k	US\$ 500k to 1 mn	US\$ 1 mn to 5 mn	US\$ 5 mn to 10 mn	US\$ 10 mn to 25 mn	Over US\$ 25 mn
Australia China Cuba India Thailand	Brazil Finland Russia	Denmark France Germany Japan Netherlands Norway Sweden	Ireland Italy South Africa	Canada United Kingdom	United States

spending between 2000 and 2004, from US\$ 318 million to US\$ 618 million. While total expenditures have grown considerably over this period, the allocation of non-commercial funds across the above five categories has held fairly steady.

Over the last five years intermediary organizations, and in particular IAVI and SAAVI, have become increasingly important players in the development of new prevention technologies such as HIV vaccines. While the public sector continues to dominate global expenditures, the share of non-commercial expenditures by intermediary organizations has grown from 5% in 2000 to 13% in 2004. IAVI is currently the largest of the PPPs engaged in HIV vaccines and accounted for about 10% of global expenditures in 2004.

Resource flows for microbicide R&D

Public and philanthropic investment in microbicide R&D reached US\$ 142 million in 2004. This represents a marked increase in the level of investment by the public and philanthropic sectors over the last five years. Between 2000 and 2004, investments from these sectors more than doubled, from an estimated US\$ 65 million to approximately US\$ 142 million, and by May 2005 disbursements and firm commitments of funding for 2005 from the same sources had already reached US\$ 163 million (see Table 5 and Figure 5).

The **public sector** is the primary source of funding for microbicide R&D. In 2004, the public sector invested an estimated US\$ 124 million in microbicide research, development

Table 4**Annual investment in preventive HIV vaccines by the commercial sector in 2004**

Pharmaceutical companies	US\$ 59 million (87%) (range 47 to 71)
Biotechnology companies	US\$ 9 million (13%) (range 7 to 11)
Total	US\$ 68 million (range 54 to 82)

and advocacy – about 87% of the combined global funding in that year from non-commercial sources. Public-sector funding for microbicide research, development and advocacy has increased considerably over the last five years, growing more than three-fold from US\$ 36 million in 2000 to US\$ 124 million in 2004.

The United States dominates public-sector funding for microbicides and, in 2004, provided 74% of the total funds made available by the public sector. For that same year, European national governments and the European Commission together accounted for just over 24%. National governments from the rest of the world and the multilateral organizations reviewed (WHO, UNAIDS and the World Bank) together accounted for about 2% (see Table 5 and Figure 6).

The Resource Tracking Working Group identified three countries (the Netherlands, the United Kingdom and the United States) that invested more than US\$ 5 million of public-sector funds in 2004 and seven countries that invested more than US\$ 1 million that year (see

Figure 4: Breakdown of HIV vaccine expenditures, 2004

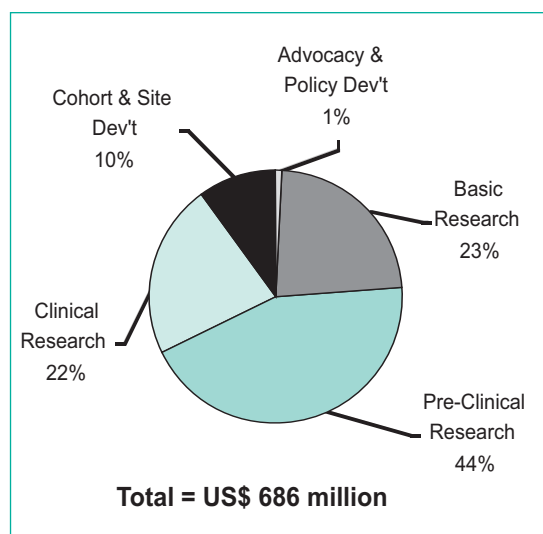


Table 6). In addition, the EC invested approximately US\$ 6 million for microbicide development during 2004.

While the United States, and in particular the US National Institutes of Health, continues to dominate public-sector funding for microbicides, the proportion of resources from European funders has grown over the last five years. Between 2000 and 2004, the share of funding from European public-sector sources (including the EC) grew from 2% to 24%. Over the same period, the proportion of public funding originating from US sources declined from 97% to 74%.

In terms of cumulative funds disbursed for microbicide R&D between 2000 and 2004, the top five countries (excluding the EC) in descending order were: the United States, the United Kingdom, the Netherlands, Ireland and Norway.

The sources of public-sector funding for microbicide R&D vary widely from country to country. In some countries the majority of funding comes from health and research agencies, while in others international development agencies provide most or all of the public funding available for microbicide development. The United States is unusual in having significant funding identified from both types of agencies. In 2004, the NIH, primarily a health and research funding agency, accounted for 72% of US public-sector funding. In that same year, USAID provided about 24% of US public resources for microbicide R&D.

In 2004, funding from the **philanthropic** sector totalled US\$ 18.1 million, or 13% of the total funds disbursed for microbicide development from non-commercial sources. As seen in Table 5, philanthropic funding levels have varied considerably over the five-year period studied – from a low of US\$ 3 million in 2001

to a high of US\$ 29 million in 2000. The funding increases observed in 2000 and 2002 reflect multi-year awards by the Bill & Melinda Gates Foundation to CONRAD (US\$ 26 million) and the Population Council (US\$ 20 million) that were disbursed in full in the years in which they were awarded. The expenditure of these funds by the recipients, however, was spread over several subsequent years.

While a detailed analysis of industry investment in microbicides was not completed during the timescale of this research, preliminary data suggest that between US\$ 3 million and US\$ 6 million was invested by the commercial sector in microbicide R&D in 2004, excluding external resources. The Resource Tracking Working Group identified fifteen biotechnology or biopharmaceutical companies that were actively engaged in microbicide R&D in 2004 and/or 2005. Virtually all of the companies engaged in microbicide R&D were funded from

external sources, predominantly public-sector agencies such as DFID and the NIH, or from intermediary organizations such as CONRAD and the International Partnership for Microbicides. Although investments from companies' own financial resources are generally small and supplementary to any external funding they receive, small – sometimes 'virtual' – private companies have played crucial roles in the development of a number of current microbicide candidates. Of the five candidates currently in late-stage clinical trials, four were developed by such companies.

Discussion

Research approach

The HIV Vaccines and Microbicides Resource Tracking Working Group has generated a great deal of information on R&D funding flows from 2000 to 2004. These figures represent the

Figure 5: Annual investment in microbicide R&D by the public and philanthropic sectors between 2000 and 2005 (2005 estimates are based on actual disbursements and firm commitments made as of May 2005.)

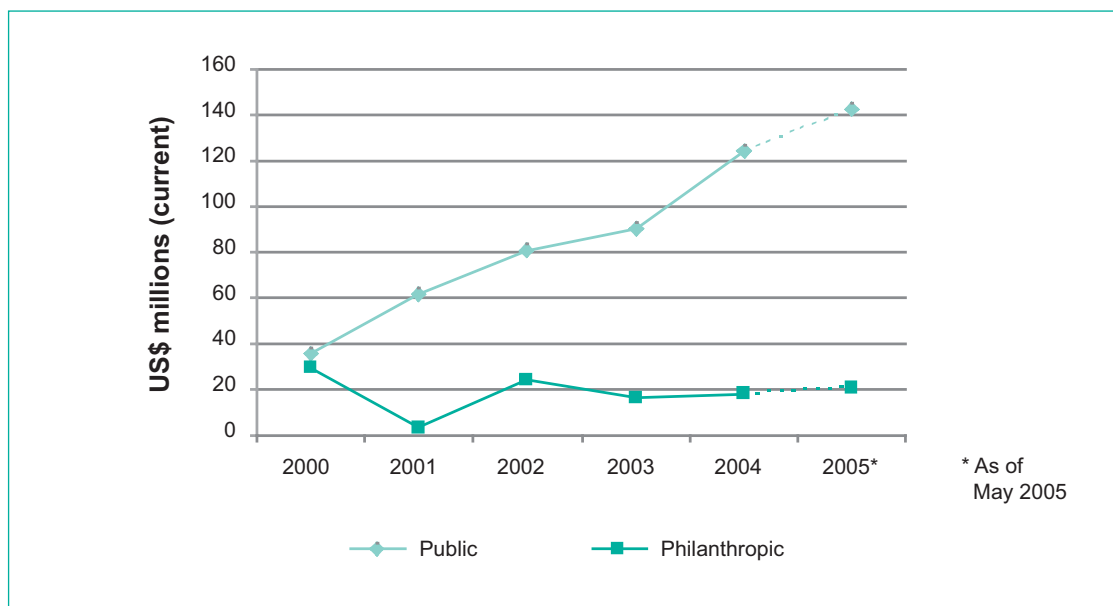


Table 5

Annual investment in microbicide R&D by the public and philanthropic sectors between 2000 and 2005 (2005 estimates are based on actual disbursements and firm commitments made as of May 2005.)

	2000	2001	2002	2003	2004	2005
Public sector						
- US	34.6	61.3	75.3	78.8	92.0	99.3
- Europe ^a	0.7	0.4	5.1	10.6	29.9	37.8
- Other ^b	0.3	<0.1	0.2	0.9	2.0	5.0
- Multilaterals	<0.1	0.3	0.4	<0.1	0.2	0.2
Total public	35.7	62.0	81.0	90.2	124.2	142.3
Philanthropic sector						
Total philanthropic	29.4	3.4	24.8	16.9	18.1	21.1
Non-commercial (public & philanthropic)						
Total non-commercial	65.1	65.4	105.8	107.1	142.3	163.4

^a This figure includes funding from the European Commission

^b Other includes all national public sector funding apart from funding from the US and Europe

most complete picture currently available of resources invested in the research and development of preventive HIV vaccines and microbicides.

The approach employed to generate the estimates included both direct and indirect methods. While labour-intensive, this approach provided the level of detail necessary to ensure data comparability across funders and over time. Collecting comparable and reliable international funding data, however, is a challenge and there are gaps that reflect missing or incomplete information.

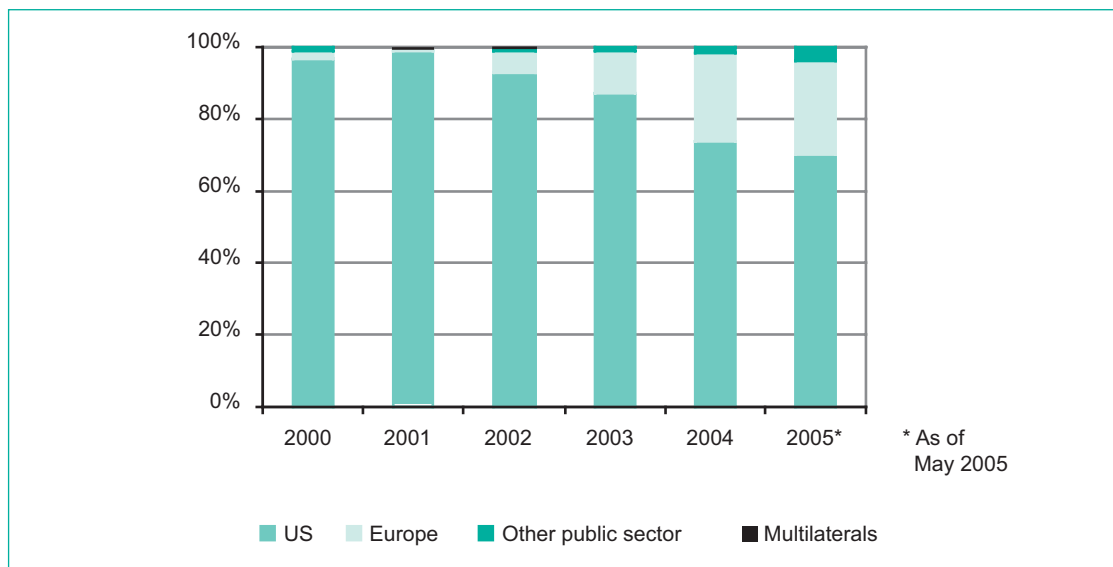
The development of a regular, systematic approach to collecting these types of data, at both the national and international levels, will enhance the timeliness and value of resource

tracking efforts. Such improvements are important if researchers, policy-makers and advocates intend to use these types of figures to monitor and evaluate current levels of effort or to identify trends in investment, spending and research focus.

Enhancing resource tracking

Data gathered for the public and philanthropic sectors are more comprehensive than those obtained for the commercial sector. This reflects both how companies track their own funding and corporate concerns about divulging proprietary business information. Future estimates would benefit from stronger collaboration with industry in tracking their R&D resource flows. Creative approaches must be developed to track both commercial-sector

Figure 6: Annual public sector investment in microbicide R&D, 2000 to 2005*



investments from their own resources and to estimate the level of external funding they receive directly from public sources, philanthropic funders and intermediary organizations. This sort of detailed information is essential if investment estimates are used to assess the impact public policies have on both commercial sector investment levels and their research portfolio priorities.

Information on investment levels, however, reveals only part of the resource flow picture; it is also important to understand what portion of resources committed are spent each year and how. Additional effort should be spent gathering detailed information on the breakdown of expenditures by stage of product development, including subdividing some of these categories. For example, the category

Table 6

National public sector investment in microbicide R&D by country in 2004

(Note: only countries investing more than US\$ 50,000 are included. Countries are listed alphabetically within each category.)

US\$ 50k to 500k	US\$ 500k to 1 mn	US\$ 1 mn to 5 mn	US\$ 5 mn to 10 mn	US\$ 10 mn to 25 mn	Over US\$ 25 mn
Australia	Denmark	Canada	Netherlands	United Kingdom	United States
Belgium	France	Ireland			
China		Norway			
Germany		Sweden			
Italy					
South Africa					

'pre-clinical research' subsumes a wide range of activities, from early discovery through translational work. Gathering these detailed data is no small undertaking and, in the case of some funders, may require the individual audit of numerous grants. Still, collection of this type of information, combined with estimates of funding needs and absorptive capacity, will be important in identifying areas where additional resources and effort could be focused to shorten the development timeline or increase the likelihood of success.

Trends in R&D investments

Over the last five years, public-sector funding for preventive HIV vaccine and microbicide R&D has increased substantially, and current commitment and disbursement figures suggest that funding levels in 2005 will be higher than in 2004. This increase in funding reflects both greater contributions from existing donors and growth in the number and geographical distribution of funders as new donors have become engaged in this important work. The number of countries investing more than US\$ 1 million in microbicide R&D grew from one in 2000 to seven in 2004. Likewise, the number of countries investing more than US\$ 1 million in preventive HIV vaccine R&D increased from seven to thirteen over the same period.

With respect to commercial sector investment in HIV vaccines, it was not possible to make a precise comparison with estimates of 2002 investment levels generated using a similar, but not identical approach to this project.⁸ However, the available evidence suggests that overall funds invested by the commercial sector from internal sources have declined in recent years. In large part, this is due to the completion of VaxGen's phase III clinical trials. Following the completion of those trials, the company's priorities shifted away from HIV vaccines to developing vaccines effective against bioterror

agents. In 2002, VaxGen invested between US\$ 30 million and US\$ 32 million in HIV vaccines from its own sources; in 2004 the company made no investment in this area.

In contrast, overall funding from the philanthropic sector is projected to increase substantially in the next few years. In particular, in February 2005 the Bill & Melinda Gates Foundation announced several Requests for Proposals (RFPs) for HIV vaccine research, pledging up to US\$ 360 million over the next five years. These awards – expected to begin disbursement in 2006 – will be used to support HIV vaccine R&D as part of the Global HIV/AIDS Vaccine Enterprise endorsed by the Group of Eight at their 2004 summit at Sea Island, Georgia, USA.

Financial resources for microbicide and HIV vaccine R&D are only one component of the significant contributions made by the public, philanthropic and commercial sectors. For example, the public sector provides considerable non-financial support, particularly in countries in the developing world where trials are planned or are underway. Government-salaried collaborators and government-sponsored hospitals and clinics play crucial roles in the safe and ethical conduct of clinical trials, as do national regulatory authorities and ethics committees. These and other non-cash contributions are not trivial and have grown over the last five years as increasing numbers of research sites are readied for or initiate clinical trials.

Conclusion

The current pace of the HIV/AIDS epidemic necessitates an expanded, comprehensive response, including the development of new prevention methods such as HIV vaccines and microbicides. Global funding levels, however, are significantly less than what will be required

to mount an accelerated search for either technology. The Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise estimates that expenditures of the order of US\$ 1.2 billion each year will be needed to accelerate the search for an HIV vaccine,⁹ and a recent analysis by the International Partnership for Microbicides (in draft) suggests that annual funding for microbicide R&D needs to increase to US\$ 280 million a year over the next five years. Even at the notably greater investment levels committed over the last five years, a significant gap remains between current funding levels and the level of funding required to develop these important prevention tools.

In addition to increasing funding levels, the time to success could be appreciably reduced with increased and sustained political commitment, coordination and action. This includes support for conducting goal-oriented basic and applied research; designing and implementing clinical trials; developing and sustaining clinical trial infrastructure; strengthening capacity of national regulatory agencies; assuring capacity for

manufacturing pilot lots of product for trials; conducting process development to ensure that any licensed product can be manufactured at scale at a reasonable price; establishing large-scale manufacturing capacity; and undertaking policy and advocacy activities directed at accelerating microbicide and HIV vaccine development and use.

While the HIV Vaccines and Microbicides Resource Tracking Working Group has not collected data on overall financial commitments to HIV/AIDS, anecdotal evidence suggests that the significant funding growth for microbicides and preventive HIV vaccines observed over the last five years has been in addition to, not at the expense of, funders' commitments to expanding access to prevention and treatment tools already available. The dramatic increase in global resources committed to the HIV/AIDS field is encouraging and must be met with action to ensure a truly comprehensive response to the epidemic; one which accounts for treatment, care and prevention needs today while working to develop the prevention tools of the future.

-
- ¹ UNAIDS/WHO. *AIDS Epidemic Update 2004*. Geneva: UNAIDS/WHO, 2004.
 - ² A preliminary report was published in March 2005: *Public and Philanthropic Investments in Preventive HIV Vaccines and Microbicides: 2000 to 2004* and the final report on vaccines, *Tracking Funding for Preventive HIV Vaccine Research and Development: Estimates of annual investments and expenditures 2000-2005*, was published in June 2005. The report *Tracking Funding for Microbicide Research and Development: Estimates of Annual Investments 2000-2005* was published in August 2005.
 - ³ Organizations were asked to provide data based on the calendar year if possible and, if not, based on their fiscal year. For organizations for which the fiscal year and the calendar year did not match we treated the fiscal year as equivalent to the calendar year in which it predominantly occurs. For example, the fiscal year 1 April 2004 to 31 March 2005 was treated as 2004 and the fiscal year 1 July 2004 to 30 June 2005 was treated as 2005.
 - ⁴ The Organization for Economic Cooperation and Development (OECD) makes a clear distinction between disbursements and commitments. Disbursements reflect the amount actually spent by a donor and record the actual release or transfer to a recipient of financial resources, goods or services valued at the cost to the donor. A commitment, on the other hand, is a firm obligation expressed in writing and backed by the necessary funds to provide a particular level of support.
 - ⁵ For example, the US National Institutes of Health (NIH) and Agency for International Development (USAID) figures are based on commitments and are charged against the year in which the commitments were made.
 - ⁶ For investments made in 2005, the 2004 IMF annual average exchange rates were used (www.imfstatistics.org).
 - ⁷ For more information, see: HIV Vaccines and Microbicides Resource Tracking Working Group. *Tracking Funding for Preventive HIV Vaccine Research and Development: Estimates of Annual Investments and Expenditures 2000-2005*. HIV Vaccines and Microbicides Resource Tracking Working Group, 2005.
 - ⁸ See IAVI. *Global Investment and Expenditures on Preventive HIV Vaccines: Methods and Results for 2002*. New York: IAVI, 2004.
 - ⁹ Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise. The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan. *PLoS Med*, 2005, 2:e25.