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Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options

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Preface

Many factors shape the health of individuals and the great variability of health within and across populations. Genetic endowments, of course, play a role. Economic status strongly affects outcomes by working through a range of more proximal determinants—including consumption of food that is adequate in quantity and quality, access to clean water and satisfactory sanitation, adequate shelter and access to health services. Poverty, thus, is a major cause of poor health—and it also perpetuates it: investments in health have become essential to economic growth policies that seek to improve the lot of the poor. Education, like economic status, works through multiple channels to influence health. Educated individuals quickly learn and adopt sanitary behaviours, more efficiently use food, more effectively utilize health services for themselves and their families and are more likely to avoid health risks such as tobacco use. Measured effects of education on health prove consistently large.

Half of all the gains in human life expectancy of the past several thousand years have occurred in this century. Some of these gains have resulted directly from the improvements in economic and educational standards that have recently transformed the material lives of most—but far from all—of the world's population. Improvements in income and education account, however, for only part of this century's remarkable improvements in health. At the turn of the century the people of a country with an income level of US$ 5 000 per capita (in purchasing power adjusted for inflation) would typically have had a life expectancy under 50 years; today the number is close to 75. Why this enormous difference *after* controlling for income? Important as income and education undoubtedly are, another factor—advance in scientific knowledge and its application both in creating powerful interventions and in guiding behaviour—has, perhaps, become even more important.

What are the implications for policy? One is that if knowledge gains prove even partially as important for future health improvements as they have in the past century—and this Report points to a number of reasons for expecting this to be so—then investments in health R&D will continue to have high payoffs in health status and economic productivity. Assuring an adequate level of R&D investment then holds strong claim on health budgets—a claim for more than the approximately 3% now committed. Equally important—or more important—is that the investments be *efficient* in generating useful new knowledge and products.

This Report deals with policy for health R&D investments of particular relevance to the poor in low-income and middle-income countries. We estimate these investments to have been about US$ 2 billion annually in the early 1990s (out of a total of something over US$ 50 billion spent globally on health R&D). The Report addresses the central question of how best to focus R&D investments when resources are tightly constrained. It also addresses the institutional question of how to create an incentive and information environment that leads to efficient utilization of R&D investments, including the related issues of competitive resource allocation and of appropriate incentives for engaging the private sector more fully. Since most of the products of health R&D can be shared by many or all countries—in that sense they are international "public goods"—the Report deals with an additional set of issues involving the generation and coordination of international collective action. Collective action has been neglected, and the Report suggests directions that might be taken to correct this.

This Report results from the deliberations of the Ad Hoc Committee on Health Research Relating to Future Intervention Options and of staff work undertaken to inform those deliberations. Two lines of thought led to the formation, under the auspices of the World Health Organization, of the Ad Hoc Committee. The first, summarized in the preceding paragraphs, pointed to the central role that advances in knowledge have played (at least in the past century) in driving the enormous improvement in human health. In particular, the World Bank's *World development report 1993: investing in health* (World Bank 1993) had reached this conclusion and pointed to the importance of improving the use of international assistance for health by paying more careful attention to the role of knowledge generation and dissemination. At about the same time several private foundations that had actively supported tropical disease research noted not only that their own efforts were likely to decline but, also, that replacement funding sources remained to be identified. These foundations and a range of other investors in health R&D then joined with WHO in establishing the Ad Hoc Committee to address priorities for health R&D, prospects for funding, and institutional changes (at both the national and international level) that might enhance the productivity of ongoing R&D expenditures.

The Ad Hoc Committee's mandate was broad: in addition to research, it was to address *development* of the products and procedures that translate research findings into practical tools (and, therefore, it was to pay careful attention to the role of the private sector); it was to include considerations of nutrition and family planning; it was to address issues of behavioural science and health systems research as well as biomedical and clinical R&D; and it was to operate under the assumption that, at best, only very limited additional resources from outside the health sector would be available for financing health R&D in the future.

The composition of the Ad Hoc Committee reflected this broad mandate. Its core membership included the chairs or representatives of the scientific advisory panels for WHO programmes with major research components; but membership was extended to be broadly representative of the disciplines contributing to health R&D. (The Committee Chair, for example, is an econo-

mist; the Co-Chair an immunologist.) Senior representatives of research-oriented pharmaceuticals houses served on the Committee, as did a number of individuals with experience in the highest levels of public service. The Report results from their deliberations (mostly in small groups) over a period of several years. While all members of the Committee agree with the broad thrust of the Report, it is fair to say that each member of the Committee—including the Chair—will differ with a number of specific points in the Report. The Committee sought to inform debate with its Report; no effort was made to reach consensus on every point.

Too often priorities for public sector health R&D investments are determined with little concern for the magnitude of the problem to be addressed, for the extent to which scientific judgement supports the possibility that new products and initiatives will be more cost-effective than available alternatives, or for ongoing efforts elsewhere. These considerations figure prominently in private sector product development decisions. The Committee endeavoured to generate information relevant to an analytical approach that combines use of available quantified data with informed judgement. This approach facilitated identification of specific high priority product development opportunities and led the Committee to the conclusion that available R&D resources would be more productive if concentrated on these "best buys" rather than remaining dispersed.

Because of limited time and resources, this approach could not be applied across the whole field of health R&D. The Committee nonetheless generated a wealth of information that was useful in its work and that, we hope, will prove valuable to others in assessing policy for health R&D and resource allocation. In particular, the Committee's commitment to careful consideration of the problem of the *magnitude* of disease burden has led to a major reassessment of global patterns of cause of death and disease burden, to assessment of burden resulting from major risk factors (to guide resource allocation concerning prevention), and to projecting burden forward to the year 2020. This work on disease burden substantially revised and extended work undertaken earlier for the World Bank and the World Health Organization. Annexes 1 and 2 summarize findings from this effort; detailed results appear in a series of companion volumes to this Report, the Global Burden of Disease and Injury Series, edited by C. J. L. Murray and A. D. Lopez and published by Harvard University Press for the World Health Organization and the World Bank.

What, then, are the conclusions reached and directions suggested? The Committee concluded that four challenges to health systems will remain important for a decade or more to come and that specific R&D initiatives would contribute significantly to meeting these challenges.

- Despite progress there remains a huge and unnecessary burden of infectious disease among the poor that can be addressed with available cost-effective interventions. Addressing this *unfinished agenda* is mostly a matter of political will and (modest) commitment of resources. But R&D can help through operational and behavioural research to facilitate implementation (often by developing and evaluating linked packages of care, such as the proposed Mother-Baby package) and by selective development of new tools, including improvements in vaccines.
- A more global class of challenges results from the *continually changing nature of microbial threats.* New pathogens—such as HIV—and evolution of drug-resistant variants of familiar ones (e.g. ones causing tuberculosis and malaria) create needs for biomedical understanding, for understanding of systemic determinants of the spread of drug resistance, and for new drugs and vaccines.
- Low-income and middle-income countries increasingly face major (and hitherto neglected) epidemics of noncommunicable diseases and injury. Selected psychiatric conditions, heart disease, stroke and road-traffic accidents dominate the disease profile we project for these countries for the year 2020. R&D is required to ascertain ways of preventing and managing these conditions under budgetary constraints far more stringent than in the high-income countries, which have dealt with the problems far longer.
- Finally, *health systems themselves vary greatly in how efficiently and equitably they provide services.* Research can assist decision-makers to solve specific problems, to learn from the experience of others, and to place the performance and characteristics of their systems into international and historical context. Such research should pay careful attention to measurement of performance and should include investigation into health systems and their finance, the determinants of the behaviour of health care providers and the behaviour of individuals and households.

In some cases additional resources (probably from lower priority areas within national health budgets or health aid budgets) will be required to meet these R&D needs adequately. In many cases institutional change will be necessary to create the information and incentives required for efficient resource allocation. At the international level resource allocation has often lacked focus (resulting in failure to bring results to the point of application) and has neglected important conditions and issues while providing (relatively) generously for less important ones. Reform is needed. Successful models of competitively driven international funding (and experience-sharing) networks should be applied to currently neglected clusters of conditions. For development of new drugs and other tools, the Report proposes establishing a Health Product Development Facility to address problems that the private sector now neglects; this would be accomplished in part by improving incentives for engaging private sector talent.

In addition, and importantly, a mechanism is needed for exchanging ideas about progress and priorities in R&D, for tracking flows of funding and identifying im-

portant gaps, and for creating an environment where investors and research institutions can agree on approaches to close those gaps. To meet this need, the Committee proposes creation of a Forum for Investors in International Health R&D. The Report elaborates these proposals.

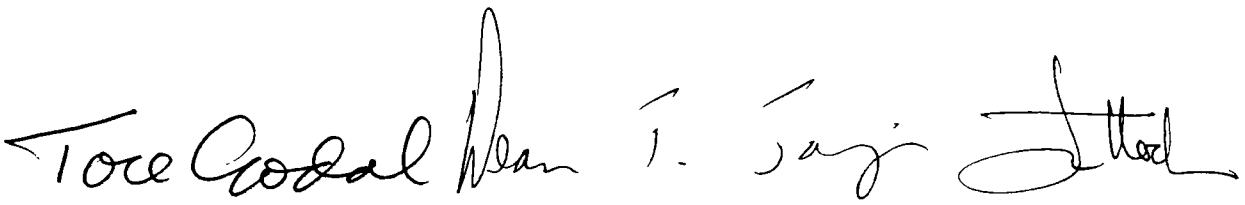
Global challenges demand, in some sense, a global response. All nations share the fruits of R&D. Even though each country may invest a relatively modest sum towards collective goals, the aggregate effort potentially benefits all substantially. Collective action is the economically rational approach to "public goods" such as R&D; here, responsibility for catalysing collective action lies principally in the hands of the global community. Far from overshadowing action at the national level, global efforts help both to make national R&D efforts more productive and to lead to a global result that exceeds the sum of national ones.

Thus, among the many competing demands on the funds allocated to international assistance for health, those contributing to generation of the new knowledge, products and interventions that can be shared by all have special merit.

Yet the commitment to R&D has been declining. If the international system collectively fails to invest in productive R&D—or to generate incentives for individual countries or the private sector to do so—then, in all likelihood, great opportunities to improve human welfare and productivity will be missed entirely. The challenge to donors in times of budgetary stringency is to recognize that their own comparative advantage lies in supporting the generation and dissemination of knowledge—knowledge that, with its multiplier potential for empowering individuals and health systems, can yield a health impact that far exceeds what donors can achieve with their limited capacity to finance or deliver services.

We complete this preface at the final meeting associated with the Ad Hoc Committee's work. That meeting—convened by the Swiss Agency for Development and Cooperation, and hosted by the World Health Organization in Geneva, 27–29 June 1996—brought together researchers, government officials, NGOs and investors in research to review the final draft of this Report. Participants in the meeting raised a range of critical points and suggested changes in emphasis or priority; but, on the whole, the meeting conveyed a broad sense of agreement on the direction the Report suggests. In particular, participants endorsed the Report's recommendation for a Forum on International Health R&D that brings together investors in R&D with other stakeholders for discussions on priorities—discussions to be informed by ongoing analytic efforts. We have every hope that the forum will prove to be a mechanism for mobilizing the efforts that will lead to a growing knowledge base for improving the health, well-being and productivity of the poor.

29 June 1996



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Addresses, phone numbers and brief biographical sketches of the study participants may be found in Appendix A.

Acknowledgements

Three individuals made critical contributions to the Committee's work. Dr Thomas Nchinda of WHO both managed and informed the Committee's work throughout the past two years; his good cheer and substantive contributions were of great value. Mr Leslie Evans of the Center for Pacific Rim Studies, University of California, Los Angeles, served as Production Editor for the Committee's Report; in this role he contributed to and managed the editing process, oversaw typesetting and layout and made all arrangements for publication. His skill, long hours and good humour contributed enormously. Ms Phyllida Brown, a free-lance science writer, wrote the Report. Working closely with the Committee and WHO staff, she translated ideas, background materials, fragmented draft materials and the Committee's conclusions and recommendations into clear English. She played an invaluable and central role in the Committee's work.

The Report's genesis lay both in recognition of the central role that generation of new knowledge has played—and, in all likelihood, will continue to play—in improving health and in the concern of several agencies that fragile funding prospects threatened future health R&D relevant to the needs of low-income and middle-income countries. In particular, the Edna McConnell Clark Foundation, the John D. and Catherine T. MacArthur Foundation and the Rockefeller Foundation convened a meeting in Bellagio, Italy, in 1993 to address the problem of providing a solid financial basis for health R&D. The proposal for this Committee's work emerged from that meeting. Other agencies then joined the original three in providing WHO with the financial resources to undertake this effort; these included the Wellcome Trust, the Canadian International Development Research Centre, the International Health Policy Programme, the World Bank and the bilateral development assistance agencies of the governments of Australia, Norway, Sweden, Switzerland and the United Kingdom. The financial contribution of these agencies, their ongoing support and their critical reactions to early drafts facilitated the work of the Committee throughout.

We close on a sad note. Professor B.O. Osuntokun, a member of the Ad Hoc Committee and a distinguished neurologist, died during the period of the Committee's work. All of us who worked with him on this effort remember him with respect and fondness.

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Accompanying volumes

An important input to and product of the Committee's work was a major revision of available data on mortality by cause and the burden of disease, extension of that work to assess burden from selected risk factors and projections of mortality and burden to the year 2020. Results appear in a 10-volume series—the Global Burden of Disease and Injury Series, edited by Christopher J. L. Murray and Alan D. Lopez. The series is being published by Harvard University Press on behalf of the World Health Organization and the World Bank.

Two volumes in the series appear simultaneously with this Report; the remaining volumes will appear over the coming year. Available now are:

1. *The global burden of disease: methods, results and projections*—edited by Christopher J. L. Murray and Alan D. Lopez. Cambridge, MA, Harvard University Press, 1996.
2. *Global health statistics: incidence, prevalence and mortality estimates for over 200 conditions*—by Christopher J. L. Murray and Alan D. Lopez. Cambridge, MA, Harvard University Press, 1996.

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Abbreviations and acronyms

ACHR—Advisory Committee on Health Research
ACTION TB—programme of Glaxo Wellcome
APOC—African Programme for Onchocerciasis Control
ARI—acute respiratory infections (also used to refer to the WHO ARI control programme)
BCG—*bacille Calmette-Guérin*
CDD—Diarrhoeal Disease Control programme (WHO)
CDR—Division of Diarrhoeal and Acute Respiratory Disease Control (WHO)
CG—Consultative Group
CGIAR—Consultative Group on International Agricultural Research
CHRD—Commission on Health Research for Development
CIMMYT—Centro Internacional de Mejoramiento de Maíz y Trigo
CIOMS—Council for International Health Organizations of Medical Sciences
CMR— Centre for Medicines Research
COHRED—Council on Health Research for Development
DALY—disability-adjusted life year
DEC—diethylcarbamazine
DOTS—directly observed treatment, short course, for tuberculosis
EHIP—Essential Health Interventions Project (Tanzania)
EMEs—established market economies*
ENHR—Essential National Health Research
EPI—Expanded Programme on Immunization
EPI-plus—Expanded Programme on Immunization plus micronutrient supplements and locally relevant antigens
FAO—Food and Agriculture Organization
FDA—Food and Drug Administration
FSE—formerly socialist economies of Europe*
GDP—Gross Domestic Product
GPA—Global Programme on AIDS (WHO)
GPV—Global Programme for Vaccines and Immunization
GUF—general university funds
HHMI—Howard Hughes Medical Institute (USA)
HRP—Special Programme of Research, Development and Research Training in Human Reproduction (WHO)
IARC—International Agency for Research on Cancer
ICDDR,B—International Centre for Diarrhoeal Disease Research, Bangladesh
IDRC—International Development Research Centre (Canada)
IFPRI—International Food Policy Research Institute
IHPP—International Health Policy Programme
IHRCs—international health research centres
IMSC—Integrated Management of the Sick Child (also referred to as IMCI, Integrated Management of Childhood Illness, now the official name)
INCAP—Instituto de Nutrición de Centroamérica y Panamá
INCLEN—International Clinical Epidemiology Network
IRRI—International Rice Research Institute
ISNAR—International Service for National Agricultural Research
LAC—Latin America and the Caribbean*
MDR—multidrug-resistant
MDT—multidrug therapy
MEC—Middle Eastern crescent*
MRC—Medical Research Council (UK)
NCD—noncommunicable disease
NGO—nongovermental organization
NIAID—National Institute of Allergy and Infectious Disease (USA)
NIH—National Institutes of Health (USA)
NSF—National Science Foundation (USA)
OAI—other Asia and islands*
OCP—Onchocerciasis Control Programme
ODA—official development assistance
OECD—Organization for Economic Cooperation and Development
ORS—Oral Rehydration Solution
ORSTOM—L'Institut Français de Recherche Scientifique pour le Développement et Coopération *(Note: acroynm continues to be used, although it represents the old, no-longer-used name Organisation de Recherche Scientifique des Territoires d'Outre Mer)*
ORT—oral rehydration therapy
OTA—Office of Technology Assessment (USA)
PCR—polymerase chain reaction
PEM—protein-energy malnutrition
PMA—Pharmaceutical Manufacturers Association
RCS—research capability strengthening
REMO—rapid epidemiological mapping of onchocerciasis
SAMRC—South Africa Medical Research Council (South Africa)
SAREC (Sweden)—Swedish Agency for Research Cooperation with Developing Countries
SIC—Standard Industrial Classification
STAC—Scientific and Technical Advisory Committee (of TDR)
STD—Science and Technology Development Programme (of the European Union)
STDs—sexually transmitted diseases

*These are regional groupings of countries as used in this Report. Appendix C lists all eight regions and the countries included in them.

TAC—Technical Advisory Committee
TDR—UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNDP—United Nations Development Programme
UNFPA—United Nations Population Fund
USAID—United States Agency for International Development

Summary

A new set of threats to health has joined the familiar problems of infection and malnutrition in developing countries. Over the next 25 years, as populations age and the tobacco epidemic takes hold, most developing regions are likely to see noncommunicable diseases become their leading causes of disability and premature death. Both the pace of these changes in developing countries and the sheer numbers of people affected will exceed anything experienced in the industrialized world. At the same time, malnutrition and the infectious childhood killers continue to take a heavy and unnecessary toll, despite successes in their control, and HIV and drug-resistant strains of major pathogens complicate these problems by their unpredictability and global reach.

While the industrialized countries are expected to grow richer still in coming decades, most developing regions are likely to see more modest income growth, and in India and sub-Saharan Africa that growth may be minimal. Yet the governments of middle-income and low-income countries must somehow respond to the multiple and complex health needs ahead of them. To do so effectively, they will need new information, tools and policy instruments that they can obtain only through research and development. But finances and capacity for R&D are limited, and in order to make the best use of both, priorities must be set and incentives for efficiency created.

This Report is the outcome of a review of health needs and related priorities for research and development in the low-income and middle-income countries. It is intended as a resource to assist decision-making by governments, industry and other investors on the allocation of funds to, and within, health R&D. It was prepared by a Committee (the Ad Hoc Committee on Health Research Relating to Future Intervention Options) convened under the auspices of the World Health Organization at the request of a number of these investors. Box S.1 provides the Ad Hoc Committee's terms of reference. Since most of the world's ill-health is borne by the people of low-income and middle-income countries, the Report focuses on their needs. But its messages are not restricted to the developing nations; in a world where people and economies are increasingly interdependent and the boundaries between regional health needs increasingly blurred, no region can consider itself immune to the problems of others. The Report is therefore intended also to contribute to an agenda for *international* action in which individual nations' agendas inform global priorities, and global needs and experience influence national agendas.

This Summary is in two parts. The first explains the Committee's methods and conclusions in assessing R&D needs and opportunities; the second sets out our recommendations.

Findings of this Report

The challenges ahead

Health needs in developing regions are changing radically (see Figure S.1). Table S.1 shows the scale of the change overall and Table S.2 highlights the particular impact of tobacco on global health. In the Committee's view, four key challenges face governments and health systems:

- *First, they still face the traditional threats to maternal and child health*

  The world's poorest regions still suffer a heavy—and largely avoidable—toll of premature death and disability from childhood infectious diseases, malnutrition, and maternal and perinatal conditions such as unsafe childbirth and low birthweight. While progress against these old, familiar conditions has been spectacular in recent decades, they still account for more than one-third of the entire burden of disease worldwide today and almost half the burden in the low-income and middle-income countries.

- *Second, the populations they serve face a continually changing threat from microbial evolution*

  All populations are threatened by microbes at a time of spreading antimicrobial resistance and greater human mobility. Particularly unpredictable threats include: the TB bacterium *Mycobacterium tuberculosis*; the pneumonia-causing bacterium *Streptococcus pneumoniae,* often called simply pneumococcus; the malaria parasite *Plasmodium falciparum*; and the human immunodeficiency virus (HIV).

- *Third, they must respond to the emerging epidemics of noncommunicable diseases and injuries by developing cost-effective interventions to prevent, diagnose and treat them*

  Heart disease, mental illnesses, cancers, strokes and chronic respiratory diseases are fast emerging in the middle-income and low-income countries as their populations age and become increasingly exposed to certain risk factors for noncommunicable diseases, such as tobacco. Yet only a limited number of the existing treatments for these diseases, treatments developed largely in the industrialized world, are cost-effective. Also, partly because of population aging and partly because of secular changes the numbers of some forms of injury such as those caused by road-traffic accidents and interpersonal violence appear to be rising, calling for new responses from the health sector.

- *Fourth, countries vary enormously in how efficiently and equitably they provide health services; the chal-*

Box S.1 Terms of reference of the Ad Hoc Committee

The Ad Hoc Committee on Health Research Relating to Future Intervention Options was formed in January 1994 under the auspices of the World Health Organization. Management within WHO was assigned to the Directors of the UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) and (then) Division of Diarrhoeal and Acute Respiratory Disease Control (CDR). Following extensive consultations within WHO and without, the two WHO Co-Directors issued letters of invitation to membership in the Committee. The objectives of the review were:

1. To identify high and low priority R&D areas in terms of:
   (i) disease burden potentially addressed;
   (ii) the cost-effectiveness of currently available alternative interventions;
   (iii) judged success probabilities of the effort;
   (iv) the potential for cost saving or health gain, where it can be estimated, of a successful effort; and
   (v) placement relative to efforts ongoing or likely to be funded in the OECD countries.
2. In light of the above to assess:
   (i) the strength of the case for increased donor finance of R&D; and
   (ii) which areas, given available budgets, should receive more funding and which should receive less.
3. To update the assessment provided by the Commission on Health Research for Development (1990) of finances for and institutional structure of existing capacity and to assess:
   (i) the potential role and cost of new institutions in light of findings concerning objectives 1 and 2; and
   (ii) the desirability of various degrees of additional structure to link existing entities in order to stabilize and increase funding; to fill R&D gaps quickly; and to improve accountability to the donor, scientific and developing country official communities.

[from the Committee's draft mandate, attachment I, 9 December 1993.]

The intended outcomes of the review were two-fold:

1. To serve as a resource of potential use to *national* decision-makers; and
2. To propose an agenda for *international* action:
   - to develop "products" and interventions of benefit to many countries;
   - to facilitate transfer of relevant "best practice" across national boundaries.

lenge is how to improve efficiency and equity in light of experience

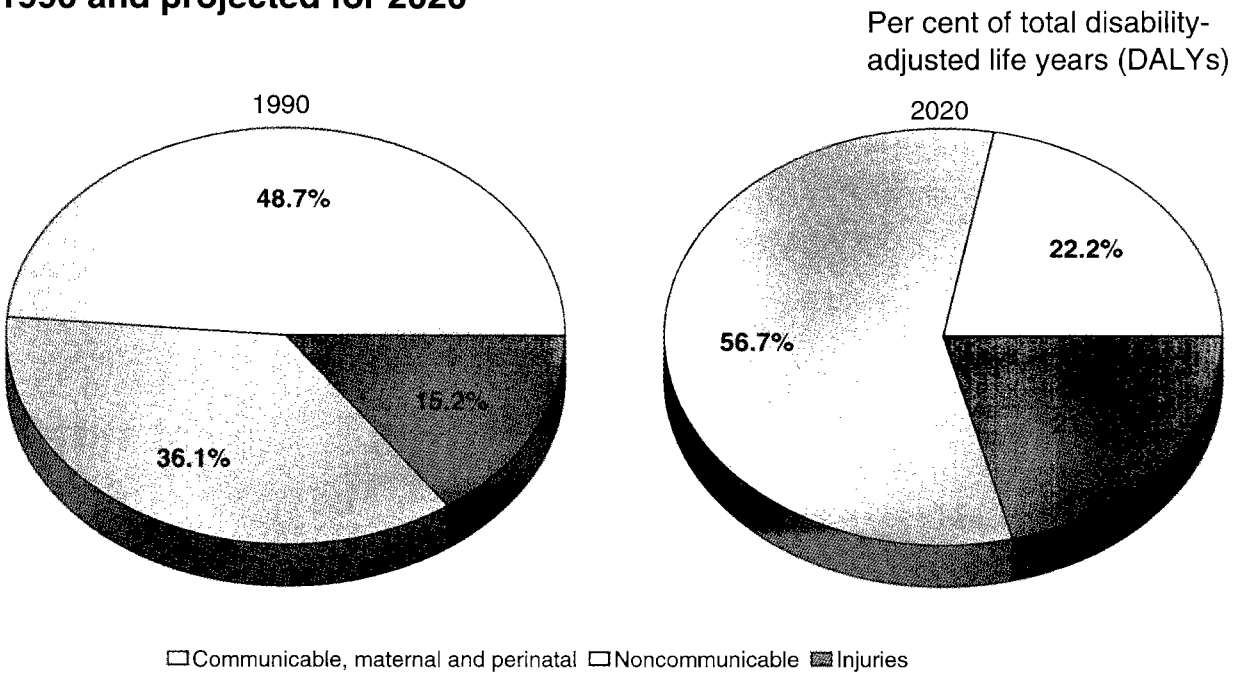
Millions of people are still denied adequate health care, and population health needs are growing more complex. Governments in both rich and poor countries are struggling to meet a rising demand for services in the face of spiralling costs, yet their task is being hampered by a lack of information about the most effective ways to achieve this. Many countries are pressing ahead with health system reform without knowing how best to provide equitable, efficient and high-quality services, and making development plans without knowing how to quantify the impact on health of other sectors of the economy such as education or employment. Learning from the experience of good practice can greatly increase the value of reform.

Responding with R&D

The responses to these challenges must be on many fronts, of which research is only one. But R&D, the Committee believes, will be as vital for the future as it has been in the past 100 years. There are many health problems that remain unsolved because too little is understood about them, or because there are too few or no tools yet available to prevent or treat them, or because the existing tools are not being put to the most efficient use for technical or policy reasons. In all these respects, R&D is needed, ranging from biomedical to the health policy sciences.

R&D has an outstanding track record of improving health; governments can ill afford to neglect it in face of the challenges ahead. Past R&D has delivered technologies for the prevention, treatment and control of disease that have improved health and paid invaluable dividends. For example, vaccines for a handful of childhood diseases such as diphtheria and whooping cough have cut the burden of disease in under-fives by almost a quarter and now avert the deaths of about three million children a year. In the United States alone, the major childhood vaccines save between US$ 3 and US$ 30 for every US$ 1 invested in them. Research has also delivered knowledge that individuals, households and policymakers can use to avoid disease and promote better

Figure S.1 The disease burden in demographically developing regions, 1990 and projected for 2020



Note: This Report uses as its principal measure of disease burden the disability-adjusted life year (or DALY); this combines years of healthy life lost from disability with those lost from premature death. The Report also conveys, however, data on burden as measured by numbers of deaths and years of life lost (YLL) from premature death.

Source: Annex 1

health. For example, the stream of evidence that tobacco use is harmful has persuaded a growing number of governments to introduce antismoking measures, and more and more individuals with access to health information are quitting the habit.

The future promises even greater dividends. Advances in molecular biology—particularly in human genetics, developmental biology, immunology and neuroscience—are bringing new insights into the pathogenesis and treatment of many diseases. At the same time, new tools such as recombinant DNA technology, combinatorial chemistry and powerful data analysis capacity have transformed the landscape in which scientists work, enabling much greater productivity. The combined effects of these conceptual and technical advances make R&D an increasingly powerful engine for improving health and, potentially, controlling costs.

Hard choices: how should resources be allocated?

If investors seize the opportunity to direct resources to the areas of greatest need and promise, R&D could deliver substantial gains for global health. But hard choices must be made if the best results are to be achieved. The Committee has therefore explored systematic approaches to resource allocation in order to make the best use of limited funds. Our focus has been on strategic research and on intervention development and evaluation. (The Ad Hoc Committee did not address priorities for fundamental research, which are driven by considerations other than health needs, and were therefore outside its scope. We stress, nevertheless, that all strategic and other research described here rides on the back of progress in fundamental research, which is a *sine qua non* for its success.)

Our methods are essentially simple and are intended to provide some systematic steps that investors might use to help guide their decisions about resource allocation. Our intention is not, of course, to attempt to prescribe actions for any individual country, but to indicate broad priorities. These steps are not intended to replace judgement, but rather to inform it. They are offered with the caveat that committees can deal only with what is known or readily envisaged, and the recognition that progress can come from unexpected directions.

Table S.1 The changing pattern of disease burden, demographically developing countries, estimates for 1990 and projections to 2020

1990			2020		
Rank	**Cause**	**% total**	**Rank**	**Cause**	**% total**
1	Lower respiratory infections	9.0	1	Unipolar major depression	5.6
2	Diarrhoeal diseases	8.1	2	Road-traffic accidents	5.2
3	Perinatal conditions	7.3	3	Ischaemic heart disease	5.2
4	Unipolar major depression	3.4	4	Chronic obstructive pulmonary disease	4.3
5	Tuberculosis	3.1	5	Cerebrovascular disease	4.2
6	Measles	3.0	6	Tuberculosis	3.5
7	Malaria	2.6	7	Lower respiratory infections	3.4
8	Ischaemic heart disease	2.5	8	War	3.3
9	Congenital anomalies	2.4	9	Diarrhoeal diseases	3.0
10	Cerebrovascular disease	2.4	10	HIV	2.8
11	Road-traffic accidents	2.2	11	Perinatal conditions	2.7
12	Chronic obstructive pulmonary disease	2.1	12	Violence	2.4
13	Falls	2.0	13	Congenital anomalies	2.4
14	Iron-deficiency anaemia	1.9	14	Self-inflicted injuries	1.8
15	Protein-energy malnutrition	1.7	15	Falls	1.6
16	War	1.6	16	Bipolar disorder	1.5
17	Tetanus	1.4	17	Osteoarthritis	1.5
18	Violence	1.3	18	Tracheal, bronchial and lung cancers	1.5
19	Self-inflicted injuries	1.3	19	Alcohol use	1.4
20	Drowning	1.2	20	Cataracts	1.3
21	Pertussis	1.1	21	Malaria	1.3
	All other causes	38.4	22	Measles	1.3
			23	Schizophrenia	1.2
			24	Liver cancer	1.2
			25	Cirrhosis of the liver	1.1
			26	Stomach cancer	1.1
			27	Obsessive-compulsive disorders	1.0
				All other causes	33.2
Total	**All causes**	**100**	**Total**	**All causes**	**100**

Note: Causes of disease burden, as % of total DALYs, by rank. All causes with burden of 1% or more shown.
Source: Annex 1

The main methods we have used are summarized here, and the case of malaria is shown for illustration in Box S.2, which concludes that R&D to develop malaria vaccines is an excellent health investment. By contrast, for certain health problems, we have concluded that specific new interventions are not worth developing: a vaccine for leprosy, for instance, would be unlikely to be more cost-effective than the existing multidrug therapy. In yet other cases, we have concluded that R&D resources might be better redistributed from one health problem to another to maximize overall health gains.

The five-step process discussed in Box S.2 is clearly not suitable for assessing all types of health need. Our fourth challenge—the inequities and inefficiencies of health services and the lack of information to guide policy formulation—must be assessed differently. Inefficient and inequitable services and "unhealthy" policies in other sectors make their impact by increasing the burden of *many* different diseases and conditions in a population and, by the same token, improvements to services or policies may reduce the burden from many different conditions. Changes to health policy may also produce benefits that cannot be measured in terms of disease burden at all, e.g. reductions in cost or extensions of access. The Committee has therefore used other quantitative information, for example, comparative data on different countries' health care expenditures, to supplement consultation with technical experts as a means to inform judgements about priorities.

The following section summarizes our findings for each of the four challenges. The assessments reported here are merely a first step, limited by the time and resources available to the Committee. We hope that future efforts will extend the approach and apply it in a more rigorous fashion. At the same time, we believe that even limited application has provided useful guidance in thinking about R&D needs.

Table S.2 Tobacco will be the biggest killer of all: per cent of all deaths and disease burden attributable to tobacco, by region, estimates for 1990 and projections for 2020

	Deaths (% of total)		DALYs (% of total)	
Region	1990	2020	1990	2020
1. Established market economies	14.9	14.9	11.7	17.0
2. Former socialist economies	13.6	22.7	12.5	19.9
3. India	1.4	13.3	0.6	10.2
4. China	9.2	16.0	3.9	16.1
5. Other Asia and islands	4.0	8.8	1.5	6.1
6. Sub-Saharan Africa	0.9	2.9	0.4	1.7
7. Latin America/Caribbean	3.3	9.4	1.4	6.8
8. Middle Eastern crescent	2.4	12.3	1.2	7.3
World (1 through 8)	6.0	12.3	2.6	8.9
Established market economies and former socialist economies (1 and 2)	14.5	17.7	12.1	18.2
Demographically developing countries (3 through 8)	3.7	10.9	1.4	7.7

Note: See Appendix C for a listing of the countries included in each regional grouping.

Source: Annex 2

Needs and opportunities: priorities for R&D on the major challenges

Challenge 1: An "unfinished agenda" of childhood infectious disease and poor maternal and perinatal health.

The burden

Every year, some eight million children in low-income and middle-income countries die from just five conditions: pneumonia, diarrhoeal disease, malaria, measles and malnutrition. Others suffer infections that are preventable by readily available vaccines, and debilitating infestation by parasitic worms that can be treated for a few cents. Every year, more than half a million women die as a result of complications of pregnancy and childbirth. About 25 million women risk an unsafe abortion rather than carry an unwanted pregnancy to term, and some 70 000 of them die of the consequences. An unknown number are harmed by the physical effects of badly managed labour. About 120 million women who would like to avoid becoming pregnant are not using contraception because they lack access to acceptable methods. The result is much unnecessary suffering for those women, families with more children than they can care for and births too close together. For many babies born into poverty and deprivation, there is a high price, too: death or disability may result from a range of perinatal conditions, including low birth weight. Women bear most of the burden of unsafe sexual activity, whose consequences include the complications of unwanted pregnancies and sexually transmitted infections. Some 26% of the global deaths of women between 30 and 44 years of age—compared to 2% of global deaths of men—are caused by unsafe sexual activity. The importance of unsafe sexual activity as a cause of ill-health is most clearly seen in sub-Saharan Africa where it accounts for 48% of the deaths in women aged 30–44.

While ill-health of all kinds is more prevalent among people on low incomes, conditions on this "unfinished agenda" are borne almost exclusively by the very poor. Moreover, these conditions are not only consequences of poverty, they are also among its causes.

Taken together, the major childhood and sexually transmitted infectious diseases, malnutrition and poor maternal and perinatal health today account for more than half of the total disease burden in sub-Saharan Africa, almost half in India, and—even though these conditions are virtually unknown in the wealthy countries—*more than one-third of the entire global disease burden.*

The Committee's projections to the year 2020 show a marked decline in the burden from this unfinished agenda, but that decline cannot be taken for granted and, without sustained effort, may not be achieved. On this a note of warning is in order. For example, while the Committee's baseline projection for China assumes a decline of under-five mortality rates to 1.4% by 2020 (Appendix Table AC.2), this rate appears to have been steady (or even rising) at about 4.4% for a decade. There is no ground for complacency concerning continued progress.

R&D investment in maternal and child health falls far short of the scale of need. At a period when overall health R&D investment worldwide reached about US$ 56 billion annually, R&D spending on diarrhoeal disease, for example, was just US$ 32 million a year and on pneumonia was between US$ 48 million and US$ 68 million a year. Moreover, much of this spending was directed towards the development of interventions that primarily benefit people in the industrialized countries, such as travellers. Between them, these two childhood killer diseases account for about 15% of the entire global burden of disease, but the combined R&D spending on them comes to no more than $100 million, or 0.2% of the total invested in health R&D. There is clearly a strong case for significantly increased investment in these conditions (see Figure S.2).

Box S.2 Steps to inform R&D resource allocation

Step 1. How big is the health problem?

Calculate the burden attributable to the disease, condition or risk factor (such as malaria, malnutrition or tobacco use)

The Committee has used the disability-adjusted life year, or DALY, as its principal unit for measuring disease burden in populations.

This unit is used in addition to traditional measures of mortality and morbidity. Like all epidemiological assessments, measures of disease burden are subject to uncertainties, but the Committee believes there are considerable advantages in the approach taken.

The DALY expresses both time lost through premature death and time lived with a disability, so it captures the impact on populations of important non-fatal, but disabling, conditions such as some mental illnesses. One DALY represents a year of healthy life lost; the larger the number of DALYs, the greater the disease burden.

A major contribution of this Report (summarized in annexes 1 and 2) is calculation of 1990 burden estimates for 96 conditions and selected risk factors. These estimates are then projected forward to 2020. (An important by-product of this effort is a set of estimates by cause that is consistent with demographers' estimates of total deaths; failure to ensure consistency leads to the serious overestimates and biases that continue to appear even in widely distributed publications.)

Step 2. Why does the disease burden persist?

Identify the reasons for the persistence of the burden of the disease or condition in a population

The Committee has analysed whether a given condition persists mainly because of (a) lack of knowledge about the disease and its determinants, (b) lack of tools, or (c) failure to use existing tools efficiently. The answers suggest the types of R&D that are needed most in response. For example, if inadequate knowledge is the primary reason, more strategic research is needed, whereas if the primary reason is failure to use the existing tools efficiently, then operational and health policy research is appropriate.

Step 3. Is enough known about the problem now to consider possible interventions?

Judge the adequacy of the current knowledge base

Does the research community have enough information now to move ahead with the development of new interventions such as drugs, vaccines, clinical algorithms and policies? If so, proceed; if not, more strategic research is needed. (Often there will be partial knowledge and the two routes will proceed in parallel.)

(Box S.2 continued)

Step 4. How cost-effective will these interventions be? Can they be developed soon and for a reasonable outlay?

Assess the promise of the R&D effort

Is the desired intervention expected to be cost-effective in terms of its cost per DALY averted? Will it be more cost-effective than any existing interventions? (Anything that costs less than US$ 30 for each DALY averted is an excellent buy in low-income countries, and anything that costs less than US$ 150 is still attractive.) Can the desired intervention be developed for a reasonable amount and within a reasonable time?

Step 5 How much is already being done about the problem?

Assess the current level of effort

How much are investors worldwide currently allocating to R&D on this problem? Should more be invested, or would resources be better used elsewhere in R&D?

Example of the five-step process: malaria

In the case of malaria, there is a high burden (almost 3% of global DALYs in 1990 and almost 10% of DALYs in sub-Saharan Africa). The burden is judged to persist partly because of failure to use existing tools efficiently, and partly because of inadequate tools—there is no vaccine and most drugs rapidly encounter resistance. Although some strategic research is still needed, researchers know enough now to assess certain development opportunities. We have estimated the relative cost-effectiveness in different circumstances of hypothetical vaccines and other interventions, such as insecticide-impregnated bednets. Malaria vaccines emerge as an excellent target for R&D investment. Provided they could be delivered with other child immunizations, malaria vaccines could cost as little as US$ 11 for each DALY they avert and sometimes less than US$ 1—extraordinary value for money even in the poorest country. Based on current knowledge, researchers estimate that a first generation or second generation malaria vaccine could be produced for an investment in the order of US$ 50 million within 10 years. Compared with malaria's share of the global disease burden, current spending on R&D on the disease is very small—little more than 0.1% of the total spent on health R&D in a year. We conclude that malaria vaccines are worthy of significant R&D investment.

The R&D response

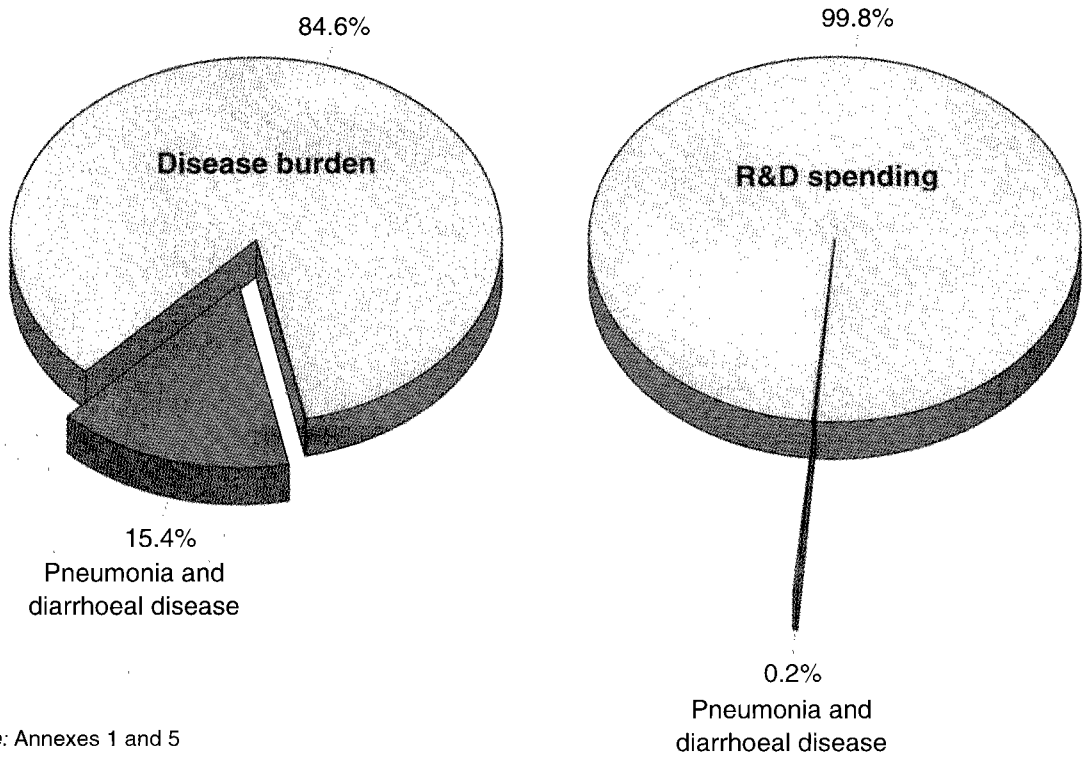
In principle, the world already knows what to do about most childhood infections and about making pregnancy and childbirth safe. Considerable suffering, waste and loss of life could be avoided now with existing interventions, often at low cost, and with striking potential gains for global health. But the massive persisting burden indicates that the existing interventions are not being used to the full—partly because no one knows *how* to make them more effective than they currently are, partly because resources are not being used efficiently to target the areas of greatest need.

In the Committee's view, R&D on this unfinished agenda should focus on operational research to make existing interventions more efficient and more responsive to the needs of households and populations, while health policy should be developed to ensure that resources are allocated to these basic and avoidable problems. Alongside these efforts, there should be concerted R&D in biomedical science to develop new tools, such as contraceptives and vaccines, in key areas of need.

Packages of essential interventions. In recent years, operational research has focused on the idea of grouping certain essential health interventions together into *packages*. Packages of interventions improve care and increase efficiency by making the best use of contact between health workers and concentrating on the needs of whole people rather than single conditions. They also offer health service providers a clearly identifiable vehicle for ensuring basic needs are met. In short, proper packaging provides an essential bridge between the availability of an intervention and its actual implementation in the day-to-day operations of a health system.

Researchers have estimated that a handful of essential packages, including those for care of the sick child, immunization, family planning and obstetric services, could in principle avert more than one-third of total disease burden in low-income countries for just US$ 12 per person per year. By any standard, these packages are expected to be highly cost-effective in low-income countries: none is likely to cost more than US$ 50 for each year of healthy life gained, and most would cost US$ 30 or less. The key task for R&D will be to find out how to

Figure S.2 Monumental mismatch: disease burden (DALYs) and R&D spending for the two largest killers, 1990



Source: Annexes 1 and 5

turn these principles and estimates into real, efficient, high-quality services in different environments.

This Committee believes that a key step towards better maternal and child health is likely to be the development, evaluation and refinement of selected packages of essential services in low-income countries, where the burden of these conditions is heaviest and the potential gains of averting them greatest. This will require behavioural research into the factors that influence households' use of services, and operational research into the delivery of those services. Priority packages include the package for the Integrated Management of the Sick Child; an augmented form of the Expanded Programme on Immunization incorporating additional immunogens and micronutrients; a package for the care of mother and infant in pregnancy, delivery and the first week of life (the so-called Mother-Baby package); and packages of family planning services. Additional packages worthy of further R&D include a possible set of services for schoolchildren incorporating micronutrient supplementation and anthelminthics, and a Healthy House package, consisting of improvement of the physical environment through safer water supply, latrine construction and some vector control activities. Intersectoral action at local level would be essential to make these approaches effective.

Better understanding of malnutrition. Finally, some strategic research is needed to improve the knowledge base on the massive health problem of malnutrition. Malnutrition results from the interaction of two factors: inadequate food intake (which is particularly severe in girls) and illness from infectious and parasitic disease. More work is required to understand the relative contributions of these two factors in different environments—information that could greatly increase efficiency in guiding the choice of interventions. Strategic research must also investigate further the impact of fetal and infant malnutrition on adult health, and particularly on predisposing individuals to cardiovascular disease and non-insulin-dependent diabetes.

Of the priorities identified by the Committee for R&D into maternal and child health, a short list of "best buys" has been selected for investors' particular attention.

These are chosen because they address a major problem which is currently under-resourced, hold the promise of high health return on investment, and may be developed quickly. Several would be of particular benefit to women and girls, whose health needs have been disproportionately neglected by traditional public health. The list is shown in Box S.3.

Challenge 2: Continually changing microbial threats.

The burden

At a time of spreading antimicrobial resistance and greater human mobility, four communicable diseases or disease clusters have been identified by the Committee as sources of major threats and uncertainty for global health now and in the coming decades. They are: tuberculosis, pneumococcus (the cause of almost half of the life-threatening pneumonias that afflict children in low-income and middle-income countries), malaria, and the cluster of sexually transmitted diseases including HIV/AIDS. We group these conditions together because the problems of controlling each of them is amplified by earlier or ongoing changes in genetic structure—changes that facilitate transmission or attenuate the power of existing drugs. Many other conditions share the challenge posed by genomic change; our discussion focuses on just a few because of their enormous contribution to disease burden and because developing the capacity to deal with these major pathogens will facilitate efforts against the others.

Mycobacterium tuberculosis kills more people than any other single microbe, and takes a disproportionately heavy toll on economically productive adults. In 1990, its share of the disease burden was almost 3% and this is rising, most steeply in Africa. The control of TB is threatened by inefficient treatment regimes, the spread of HIV, demographic trends and the emergence and spread of multidrug-resistant strains of the bacterium. *Streptococcus pneumoniae*, the cause of pneumococcal disease, carries almost as great a death toll as TB and a slightly higher disease burden. Moreover, drug-resistant strains are emerging worldwide. The control of malaria is also threatened by the emergence and spread of drug-resistant strains of the principal parasite, *Plasmodium falciparum*. In addition, its mosquito vectors are increasingly resistant to insecticide control. Sexually transmitted diseases including HIV/AIDS are currently thriving as a consequence of rapid urbanization, socioeconomic upheavals and wars, the market for migrant labour and changing patterns of sexual behaviour. The toll of HIV is expected to continue rising well into the next century; its share of global disease burden could treble by 2020.

There is clearly some overlap between Challenge 1 and Challenge 2. For example, women will be unable to

Box S.3 Best buys for R&D on the unfinished agenda of maternal and child health

Strategic research

- Understand the relative importance, in different environments, of increased nutrient intake and of control of infectious disease as means to reduce malnutrition

Package development and evaluation

- Evaluate and refine the package for the Integrated Management of the Sick Child
- Develop, evaluate and refine the Mother-Baby package for pregnancy, delivery and neonatal care
- Evaluate the implementation of a range of family planning packages offering a wide choice of methods

New tools to improve package content

- Evaluate the efficacy and optimal dosage of candidate rotavirus vaccine in low-income countries
- Evaluate the efficacy of candidate conjugate pneumococcal vaccine and effectiveness of existing vaccine against *Haemophilus influenzae* B in low-income countries
- Develop and evaluate ways to increase efficiency in the Expanded Programme on Immunization by simplifying delivery and maximizing use of opportunities for immunization
- Evaluate promotion of insecticide-impregnated bednets, possibly for inclusion in a future Healthy Household package
- Develop new contraceptive methods, particularly to widen the choice of long-term but reversible methods, post-coital methods for regular and emergency use, and methods for men

enjoy reproductive health and safe motherhood without protection from sexually transmitted diseases. Such protection, of course, requires the diagnosis and treatment of those diseases, which might be provided as an integral part of reproductive health care. Similarly, the assault on pneumococcal disease and malaria is indisputably part of the unfinished agenda of R&D against childhood infectious killers. That said, these conditions merit separate discussion because ongoing genetic changes in these pathogens requires additional R&D responses to develop the new drugs, vaccines and diagnostics essential for effective treatment.

These diseases already cause significant disease burden. Projections of their future impact are subject to serious uncertainties. Our projections, based for the most part on simple assumptions about the relation between patterns of disease and socioeconomic change, indicate that HIV and TB will grow, but that communicable diseases *overall* will decline if current economic and technological trends continue. However, the projections do not take account of the possibility of increasing drug resistance in major killers such as malaria or pneumococcus. The progress of recent decades could be halted or reversed if, for example, severely drug-resistant strains become more widespread and treatment begins to fail because of them.

Current R&D investment on TB, pneumococcus and malaria fails to reflect needs. Spending on HIV is considerably higher. Much of the spending on HIV to date has been devoted to clinical evaluations of chemotherapeutics in the established market economies. Resources might better be targeted to reducing the global burden of AIDS if more of the total currently spent on HIV research were directed towards developing cost-effective interventions, including a vaccine, for the low-income countries, and if more strategic research were to concentrate on the subtypes of HIV-1 that predominate in high-prevalence areas. Equally, there may be a relatively high payoff from redirecting a modest proportion of AIDS research funding to TB—the leading cause of death in HIV-positive people—and to STDs, which are a significant factor in the spread of HIV.

The R&D response

In the Committee's view, the burden from these continually changing microbes persists mainly because of a lack of effective tools for their control. There are, of course, effective interventions, but these are already inadequate for *current* needs. For example, only a minority of people with TB receive directly observed treatment; and women have little or no control over the use of condoms, still the only effective means to protect against HIV infection in sexual intercourse. If resistance to antimicrobial agents accelerates, or patterns of risk worsen, the available tools will become even less adequate.

New tools. The Committee believes, therefore, that the priority is for biomedical R&D to develop more tools to combat these microbes. In the case of TB, researchers must develop strategies for extending the coverage of directly observed treatment, short-course (DOTS) to a much higher percentage of the affected population. That might be done by making the treatment more acceptable, for instance by combining drugs into formulations that reduce the number of pills that people must take or the frequency with which they must see health workers, or by developing long-acting depot chemotherapeutics. A second priority is to develop better tools for preventing infection, either through an improved vaccine or by chemoprophylaxis.

For pneumococcus, an immediate priority is to evaluate candidate conjugate vaccines through clinical trials in low-income countries. Vaccines for malaria are likely to prove highly cost-effective investments for R&D. Simple, effective and low-cost diagnostics for STDs are needed, particularly for women, not only because they will enable the reduction of the currently high burden of undetected, untreated gonorrhoea, chlamydia and other common infections, but also because treatment of these STDs is likely to slow the spread of HIV. A cost-effective vaccine for HIV that protects against the globally prevalent subtypes is a high priority. Finally, women need vaginal microbicides to protect themselves against infection.

More knowledge about the microbes and means to slow the spread of resistant strains. Researchers have already built up much of the knowledge base that they need to develop these interventions. However, there are some areas where new knowledge, and therefore strategic research, is required. Investment in sequencing the genomes of *M. tuberculosis, S. pneumoniae* and *P. falciparum* will equip researchers with the means to accomplish much faster and more systematic searches for candidate vaccines and drug targets. Equally, researchers must look for public health and clinical strategies to track and to slow the emergence of resistant strains of these organisms. Box S.4 suggests some best R&D buys to counter these continually changing microbial threats.

Challenge 3: Low-income and middle-income countries face epidemics of noncommunicable diseases and injuries.

Rapid aging of populations in the developing regions creates a serious policy challenge. In many middle-income countries, the proportion of the population aged 65 and over is expected to increase by between 200% and 400% between 1990 and 2025. In most European countries, this aging has occurred over a period two to three times as long.

Mainly because of these changes in the age structure of populations, but partly also because of increased exposure to certain risk factors, the total burden from noncommunicable diseases and injuries is growing in low-

Box S.4 Best buys for R&D on continually changing microbial threats

For strategic research

- Sequence the genomes of the major pathogens
- Investigate influences on the spread of antimicrobial resistance and approaches to monitoring resistant strains, with the aim of identifying ways of slowing their emergence

For intervention development

- Develop effective strategies to extend the coverage of directly observed treatment, short-course (DOTS) for tuberculosis
- Develop an effective prophylactic for tuberculosis (e.g. single-administration depot chemoprophylaxis)
- Conduct trials of conjugate pneumococcal vaccines
- Develop a malaria vaccine
- Develop an HIV vaccine
- Develop improved methods for the diagnosis, prevention and treatment of STDs, including vaginal microbicides

income and middle-income countries and will continue to grow in the coming decades (even though age-specific rates are declining).

Noncommunicable diseases

The burden

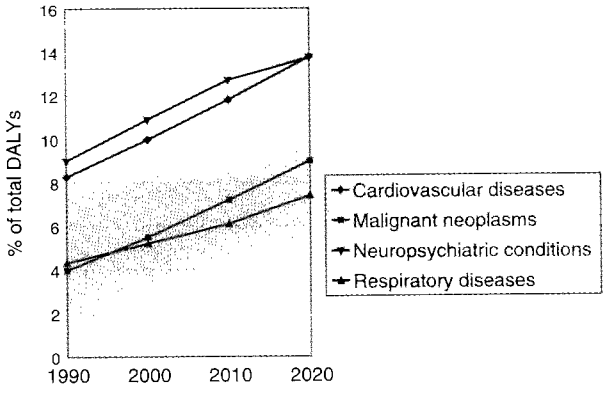
In 1990, noncommunicable diseases accounted for just over 40% of the total loss of healthy life worldwide. By 2020, their share is expected to reach about 60%, with the brunt of the increase being borne by the low-income and middle-income countries. In India, the burden of all noncommunicable diseases is expected to almost double in the next 25 years. In China, noncommunicable diseases are expected to account for more than three-quarters of the total burden by 2020 (although, as already noted, recent reversals in China in control of childhood mortality introduce a caveat); in Latin America and the Caribbean they will account for more than two-thirds of the total.

Among these noncommunicable diseases, psychiatric and neurological conditions—particularly unipolar major depression, alcohol dependence, bipolar affective disorder (manic depression) and schizophrenia—emerge as major, neglected problems for global health. Together, all psychiatric and neurological conditions already make up more than 10% of global disease burden and their share is projected to climb to almost 15% over the next 25 years. By 2020, unipolar major depression is expected to be the leading cause of disease burden in developing regions and the second biggest cause worldwide. Women will bear a particularly heavy share of this disorder. In sub-Saharan Africa, the burden from psychiatric and neurological diseases is expected to double. Figure S.3 illustrates these trends.

Cardiovascular disease will, by 2020, account for a further 15% of all global burden, with most of the increase coming from ischaemic heart disease and strokes. Diabetes mellitus, a condition closely associated with cardiovascular disease, will account for another 1% of burden. Cancers—led by lung cancer—and respiratory disease will double to almost 10% of total disease burden.

We have estimated the contribution of various known risk factors to the total disease burden. Better quantitative knowledge of the importance of specific risk factors, such as tobacco use, occupational hazards and air pollution, may help to guide disease prevention strategies and inform policies for public health. The giant shadow of tobacco hangs over the developing world, its projected impact on total disease burden dwarfing any other risk

Figure S.3 Trends in selected noncommunicable diseases, 1990–2020, demographically developing regions



Source: Annex 1

factor or any single condition. By 2020, tobacco is expected to kill *well over 8 million people a year*. In China by 2020, tobacco is expected to account for almost a fifth of the nation's entire disease burden, and some 50 million of the population who are now under the age of 20 will eventually be killed by it. Alcohol misuse also emerges as a significant risk factor for disease.

The R&D response

While research into most noncommunicable diseases except for the psychiatric disorders has been well supported in the established market economies, until recently the middle-income and low-income countries have paid them much less attention. Thus, basic data on mortality, morbidity, risk factors and current approaches to prevention and treatment are simply not available in many countries, so a reliable picture of current status and trends cannot be obtained.

Reliable basic data on prevalence of and trends in noncommunicable diseases and risk factors. The Committee considers it essential that countries devote resources to strategic epidemiological research in order to assemble reliable data on morbidity, mortality and disability. Cost-effective, simple and accurate methods for data collection must be developed and evaluated, such as the use of disease surveillance points. In addition, epidemiologists should measure the impact on disease burden of modifiable environmental and behavioural risk factors, such as tobacco use, diet—including malnutrition *in utero* and in infancy—and physical inactivity. While the burden of these risk factors has begun to be assessed in the industrialized countries, differences between populations may be significant. For example, the interactions between tobacco and high-fat diet, or birthweight and childhood infection on subsequent patterns of heart disease may vary from population to population.

Development and evaluation of cost-effective interventions. While this strategic epidemiological research continues, countries cannot afford to delay the development of cost-effective interventions to prevent, diagnose and treat noncommunicable diseases. Perhaps the single most important set of interventions will be policy instruments to prevent the uptake of tobacco in young people, to tax tobacco and to control its marketing. Pricing disincentives and other antismoking measures effectively reduce demand in the established market economies, but it is not clear that governments in countries where the health impact of tobacco has yet to be felt can simply import the same policies wholesale. Behavioural and epidemiological research and policy development are needed in the low-income countries to rapidly identify and implement locally relevant, effective disincentives to tobacco use and to limit the power of the tobacco companies.

Beyond tobacco control, another priority is to improve the efficiency of existing tools for the treatment of psychiatric diseases. Awareness of this group of conditions among primary health workers is generally poor, and since many affected individuals are thought to go undiagnosed, the *available* cost-effective treatments are not reaching many of those who need them. Development and evaluation of methods for training of health care workers (per service and in-service) will thus be important for the psychiatric and other noncommunicable conditions. Psychiatric diseases will create a huge burden, particularly among women. It will be important, therefore, to increase awareness and knowledge of these conditions among primary health workers, through practical measures such as training programmes, manuals and treatment guidelines. As cost-effective algorithms for diagnosis and care of some mental illnesses are developed, it may be possible to consider incorporating these into existing packages of essential services.

Similarly, cost-effective algorithms for the prevention, diagnosis and treatment of cardiovascular disease and cancers are needed. Many of the interventions developed to deal with these diseases in the rich countries—such as coronary artery bypass surgery or the aggressive treatment of certain cancers—are not cost-effective and offer no solution to countries with lower incomes. Yet a considerable number of cost-effective algorithms, for example for the secondary prevention of stroke and heart attack, and effective pain relief for inoperable cancers, may be developed relatively quickly.

In addition, countries need to perform audits on the range of treatments currently being used by health workers to treat noncommunicable diseases. Limited existing evidence, for example on the treatment of stroke, suggests that a wide range of therapies are in use, some of them adopted without considering their cost-effectiveness or proven efficacy.

Injuries

The burden

The epidemic of injuries may be among the most neglected health problems of the late 20th century. By injuries we mean both *unintentional* injuries (such as the consequences of road-traffic accidents, falls, fires and drownings) and *intentional* injuries (such as the consequences of interpersonal violence, suicide and war). The burden of all injuries is expected to equal that of all communicable diseases worldwide by 2020, and to exceed it in China and Latin America.

Among unintentional injuries, road-traffic accidents are expected to increase sharply from their 1990 position as the ninth biggest cause of lost years of healthy life worldwide, to become the third biggest cause in 2020, and the second biggest in developing regions. The increase is expected for demographic reasons, and because accident rates rise temporarily when road net-

works and vehicle numbers expand rapidly. By 2020, road-traffic accidents are expected to account for more than 5% of total global disease burden—one in every twenty lost years of healthy life worldwide. In India, road-traffic accidents could become as important a cause of burden as TB.

It should be stressed that, compared with age-related noncommunicable diseases, the available data on injuries and the understanding of their determinants are subject to large uncertainties, and that projections of their future impact are therefore more difficult to make. Much more intensive effort will be needed to develop a full understanding of injuries as a health problem.

Among intentional injuries, an ongoing secular increase in the rate of homicides and other violent interpersonal crimes is expected to continue. This increase appears to be associated with urbanization, rapid economic development and overcrowding and is almost certainly enhanced by behavioural and environmental risk factors such as alcohol misuse, the availability of firearms and exposure to violent behaviour in others. Women remain particularly vulnerable, and special attention to the problem of violence against women is an essential element of this agenda. Alongside the rise in interpersonal violence there is also likely to be an increase in the burden of war-related injuries, driven largely by demographic change, particularly in sub-Saharan Africa. The long-term psychological impacts of war and of violence are only now beginning to receive research attention.

The R&D response

Better data and understanding of the determinants of injuries. Epidemiologists must work to improve data on the incidence and prevalence of injuries and to improve quantitative information on the impact of preventable risk factors such as alcohol misuse. This will provide the basis for assessing preventive interventions and technologies. Collaborative research with sectors other than health will be essential: for example, collaboration with the transport sector to assess the contributions of poorly maintained vehicles to the total number of collisions, and to evaluate the impact of safety measures such as speed limit enforcement, compulsory seat-belts, drunk-driving campaigns, alcohol taxes and pedestrian protection measures. Collaboration with industry and the agricultural sector will be needed to evaluate occupational safety procedures.

Develop emergency services to respond to rising need. A second priority is R&D to improve the emergency treatment of injuries, particularly among poor urban populations and women, whose exposure to risk is greatest and whose access to services is often poor. In addition, the development of cost-effective rehabilitation measures is a priority. It is unlikely that strategies currently used in the established market economies can be imported without modification; instead, community-based assessments of need should stimulate locally relevant solutions.

Box S.5 Key investments for R&D into noncommunicable diseases and injuries

- Establish a Special Programme for Research and Training on Noncommunicable Diseases and Healthy Aging
- Establish a Special Programme or Initiative for Research, Training and Capacity-Building on Injuries

In order to focus efforts on noncommunicable diseases, healthy aging and injuries, we conclude that two specific new programmes or initiatives should be established: a Special Programme for Research and Training on Noncommunicable Diseases and Healthy Aging, and a Special Programme or Initiative for Research, Training and Capacity-Building on Injuries. The form that these initiatives or programmes should take is not for the Committee to specify: what matters is that there should be a rapid increase in high-quality and *productive* R&D relevant to the needs of developing regions. Existing centres of excellence, such as those researching injuries in Latin America and South Africa, should be central to the development of the initiatives. As well as commissioning key strategic research and intervention development, the programmes should actively foster increased capacity in neglected areas and raise awareness of their importance among investors. The programmes will clearly require increased support from those with an interest, such as the health ministries of middle-income countries.

Challenge 4: Health care systems vary greatly in their performance—in how efficiently they improve health conditions, extend access and contain expenditure growth; yet there remains a surprising lack of information on the performance of systems and on how policies have affected performance.

The problem

In the 1990s more than at any other time in recent history, health has risen high on the political agenda of many countries. Spiralling costs and rising demand are putting health systems under strain. Health care swallows up a very substantial 8% of the entire world's productive wealth yet millions of people—mostly poor people—still receive inadequate or unsatisfactory services. Meanwhile governments are realizing that the health sector, for all its expense, is only one of many players

that determine whether a population is sick or well. Some of the biggest threats to people's health, such as tobacco use, and some of the greatest potential benefits to it, such as a decent education, are outside the control of the traditional health sector altogether.

If governments are to develop "healthy" policies that will help to reduce disease burden in their countries' populations, they will need to quantify the interactions between the health of the population and the economy, and to gauge the potential benefits of interventions in other sectors, such as agriculture, education and transport. They must also know what people need—and want—from their health services, and understand from examples of good practice how to organize and deliver those services fairly and efficiently.

Yet the necessary information is often not available. Many countries are reforming their health systems today without knowing which policies and structures work, and which do not—in short without having the opportunity to learn from their own experience and that of others. Many have only the most rudimentary knowledge of outcomes or of resource flows within their health sector—a degree of ignorance which would be inconceivable in any other industry or employer of such size. Lack of knowledge about outcomes limits the capacity to assess trends in a country's performance over time or for national decision-makers to compare their country's performance with that of others.

The R&D response

Governments need to know the patterns of current and projected disease burden and the demand for health services, at population and household level. They must have effective indicators of health system performance, so that they can measure the impact of reforms such as the decentralization of services. They also need to quantify the interactions between health and other sectors if they are to formulate effective broader policies. Ideally, data would be internationally comparable so that countries could learn from each other and have benchmarks for judging their own performance.

As the first step towards facilitating these crucial national activities, the Committee proposes the establishment of a new internationally-supported Special Programme for Research and Training on Health Systems and Policy. Its agenda could be divided into three broad domains:

- **Domain 1:** *generic and comparative research issues in health systems and health policy*, such as the interactions between health and social and economic policy, consequences of different provider payment mechanisms, and the impact of different approaches to health sector reform. This domain also concerns the policy issue of selecting, implementing and evaluating packages of health interventions, informed by assessments of the quality of care and cost-effectiveness.

- **Domain 2:** *the development of indicators and tools.* Indicators of health need and intervention outcome are needed—both demographic and epidemiologic, and at the level of households. These will include measurement of disease burden. In addition, indicators of input and process descriptors will be required to measure resource flows, to build national health accounts and to analyse policy. Finally, a key element of R&D in health policy is the development of tools that assist the translation of policy into practice. Examples of these tools include model legislation, essential drugs lists and well-maintained databases that all can share.

- **Domain 3:** *efforts to facilitate national activity.* Health policy and health systems research at national level is essential, and good national information is a precondition for the international comparisons that themselves provide the context by which national policy-makers can judge the performance of their own systems. These efforts should incorporate capacity-building and advocacy, including the development of institutions and individuals through networks, training at doctoral level and other levels, and fellowship schemes.

Box S.6 Key investment for R&D to inform on health policy

- Establish a Special Programme for Research and Training on Health Systems and Policy

The work of this programme could center in three areas: (1) research and data collection in health systems policy, including evaluating health intervention packages; (2) development of international standards of measurement of health system performance and tools such as model legislation to implement goals; and (3) support to national activity through training programmes and advocacy.

Building stronger institutions for global health

The four major health challenges we have discussed will demand the best and most timely responses that the health research community has to offer. Yet that community—a loose "system" made up of investors, research networks and research institutions in every specialty—is currently falling short of its potential to rise to the challenge. The distribution of resources and effort across the spectrum of health problems appears to reflect uneven advocacy and special pleading rather than rational and coordinated responses to need. Some work is duplicated, significant gaps remain, and the dispersion of resources constrains capacity to focus resources on high-priority problems.

Weaknesses in the current system

We summarize three broad weaknesses in the system here, and discuss solutions to each of them.

Too few good scientists dealing with problems of the poor. There are sharp inequalities between regions in health research capacity. The regions where disease burden is greatest, and changing most rapidly, are severely disadvantaged by the small numbers of their scientists, the invisibility of the work of their scientists, and the lack of incentives for excellence and productivity. Movement of skilled scientists to institutions of established productivity outside their own countries and underinvestment in scientific infrastructure leave Latin America, Africa and the Middle East with just 13% of the world's scientists between them. Within the health sciences, the regional imbalance in research capacity is particularly acute for noncommunicable diseases and health policy. For those productive scientists who remain in low-income and middle-income countries, some create admirable centres of excellence, but for too many more, good work is often hampered by isolation, poor career structures, lack of leadership and inadequate resources. At the same time institutions' ability to respond to rapidly changing scientific agendas may be hampered by rigid management structures, lack of autonomy and noncompetitive resource allocation.

The Committee proposes a range of policies that governments and research institutions may use to help them attract and support productive research scholars. Among them are the internationalization of some of finance, staffing and substantive mandate; autonomous management; an element of stable core funding together with some competitive allocation of resources; and ongoing international collaboration. Efficiency could be markedly enhanced by reallocating resources to institutions that perform well at the expense of less productive ones; governments (or international agencies) that fail to reward performance through competitive allocation of project funding and career opportunities are likely to spend large amounts with no useful return in either R&D output or institutional development.

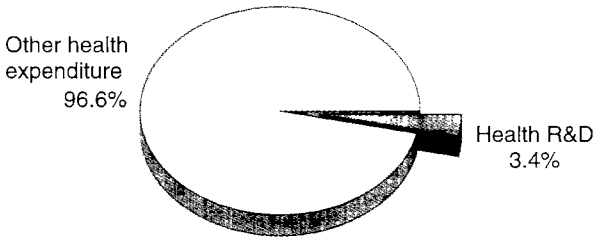
The untapped strength of the private sector. The international health system has failed to engage the capacity and skills of the private sector in working to improve the health of poorer populations. The private sector's traditional contribution to health lies in the development of new drugs, diagnostics, devices and medical equipment. There are also nontraditional areas, such as health education materials, where its skills may be highly valuable. Yet the existing patent system generates few incentives to invest in markets where the possibility of recovering one's investment is perceived to be poor because the patients have no money, and where risks are perceived to be higher than in the industrialized countries. Conversely, the public sector frequently lacks the experience, the resources and the capacity to move in where the private sector is absent, although there have been notable successes. Attempts to explore new incentives and ways to increase cooperation between the two sectors have, however, met with some success.

To harness the private sector's skills, capacity and output, the Committee proposes that governments consider a range of measures including initiating public sector support for product development and trials; providing industry with market information; providing guaranteed markets; streamlining regulatory controls to the minimum necessary for good standards; carefully designing tax relief schemes; and establishing financial incentives within the patents system. As a means to speed up and focus efforts on key products for priority health problems, we propose the creation of an internationally funded Health Product Development Facility or Alliance. This facility or alliance would enable, and if necessary, directly manage the speedy development of a highly focused list of drugs, vaccines, diagnostics and other interventions that are needed to combat major disease burden in low-income populations. The facility would draw much of its expertise and management from the pharmaceutical industry and have regular scientific review. It would concentrate on essential products that are currently neglected, for example the best buys discussed earlier. While public sector support and direction will be essential, the facility's roles should include catalysing new and nontraditional sources of funds. Although private sector involvement needs to be encouraged, the facility should turn pragmatically to any institution that shows the most promise for meeting objectives.

Deepening neglect of the health problems of the majority. The international health community has collectively failed to allocate R&D resources rationally to the most debilitating global health problems. This neglect of the problems of low-income and middle-income countries has deepened as political will to support health research has faltered.

As a share of the world's total expenditure on health, research claimed just 3.4% in 1992 (see Figure S.4). No government, whether in developed or developing regions, accords research more than about 5% of its total domestic health spending, and for most the share is be-

Figure S.4 Estimated per cent of global health spending on health R&D, 1992



Source: Annex 5

low 2%. For example, South Africa spends no more than 1.7% of its total health budget on R&D, while for Mexico the figure is no more than 0.5%.

This overall neglect of research leads, not surprisingly, to acute neglect of the needs of poorer populations. Of a total of almost US$ 56 billion invested in health research in 1992, we estimate that 95% was invested in health problems that primarily preoccupy the industrialized world, and just 5% was devoted to the health needs of developing regions. Our assessments of R&D spending on specific health problems showed, for example, that the combined amount spent per year on R&D into three leading conditions—pneumonia, diarrhoeal disease and TB—totalled just US$ 133 million, or 0.2% of the world's total health R&D expenditure. Yet between them, these diseases make up almost one-fifth of global disease burden.

This already stark imbalance is likely to be exacerbated by a recent steep decline in official development assistance (ODA) from the established market economies to the developing countries. Bilateral ODA has fallen by more than a fifth since the early 1990s, and within the overall allocation, assistance to the health sector has fallen more rapidly. The declining investment suggests a lack of advocacy for health at the highest levels, and a failure of the international community to match its rhetoric concerning poverty reduction with resource allocations that invest in the human capacities of the poor. The fragmented nature of the health and health R&D communities may have contributed to this failure.

Bringing the fragmented system together. The Committee believes that there should be a mechanism to enable the review of global health needs, the assessment of R&D opportunities and the monitoring of resource flows. Our emphasis is on improving the information and incentive environment in which decentralized decisions are taken for resource allocation; we see no role for centralized decision-making.

A new collaboration, which might be called the Forum for Investors in International Health R&D, could bring governments, other investors and scientists together to perform these functions. Such a mechanism could be created through consolidation of existing health research structures. The proposed forum would base its reviews on analytic data on the health needs of countries and regions and on resource flows in health research. Its aims would be to identify existing effort and fill important gaps in global health research, particularly those that affect poor populations, and to help reduce overlap and waste. To perform effectively, it would need access to high-quality analyses of disease burden, reasons for the persistence of that burden, estimates of the cost-effectiveness of interventions and assessments of national health system performance.

The proposed forum would take advice from existing scientific advisory groups already involved in enabling health research at national and international levels, such as the WHO's Advisory Committee on Health Research system, scientific and advisory groups of existing international research programmes, and bodies such as the Council on Health Research for Development, the International Clinical Epidemiology Network and the International Health Policy Programme. Its recommendations and conclusions would be presented to existing programmes for implementation.

Such a forum could give the fragmented health research community a stronger voice and a means, through its analytic and monitoring activities, to facilitate the rational allocation of resources to address global needs. If WHO were to take the lead in the establishment of such a forum with the help of other key players, the advantages would be many, including a speedy aggregation of dispersed international R&D resources.

Recommendations

The following paragraphs draw together the Committee's conclusions into 17 recommendations for action. Collectively they provide a broad agenda for better harnessing the proven potential for science to improve human health; at the same time each individual recommendation is designed so that it can be implemented singly. Collectively the recommendations address the major problem areas we have discussed and draw on the full range of disciplines contributing to health R&D, although, of course, the potential contributions of the disciplines varies across problem areas (see Table S.3).

Table S.3 R&D to address major health problems: suggested emphases of activity, by broad discipline

	Disciplines		
Health problem area	Biomedical science	Epidemiology, demography and behavioural sciences	Health policy sciences
Childhood infections, malnutrition and poor reproductive health	++	++	++++
Evolving microbial threats	++++	++	++
Noncommunicable diseases	+	++++	+++
Injuries	+	+++	++++
Inefficiency and inequity	-	++++	++++

Note: The estimated importance of each discipline ranges from unimportant ('-') to extremely important ('++++').

For the unfinished agenda of childhood disease, malnutrition and maternal and perinatal health

1. Investors should increase resources for developing and evaluating selected essential packages of interventions, such as the package for the Integrated Management of the Sick Child and the Mother-Baby package, in low-income countries, as potentially highly cost-effective means to achieve massive gains in the health of the poor.

2. A significant portion of the burden of childhood infectious diseases and poor maternal and perinatal health still cannot be addressed by existing tools. New tools are needed—for example vaccines against certain respiratory and diarrhoeal infections, and a wider choice of contraceptive methods. Current efforts, both in strategic research and in new product development, are inadequate to deal with these challenges. Investment in these areas now holds the promise not only of improving health but also of reducing costs.

For the continually changing microbial threats

3. Investors should focus their resources on major microbial threats where technologies for prevention and control are judged to be inadequate for current or projected needs. TB, pneumococcus and malaria require a significant increase in investment at levels appropriate to the scale of the threat from these diseases. Within HIV research, there should be a reallocation of funds from the duplicated testing of therapeutics in the established market economies to the development of affordable, cost-effective interventions in low-income countries, and an expansion of R&D (including vaccine development) working with subtypes of HIV-1 that are predominant in high-prevalence regions. Since untreated sexually transmitted diseases are major factors in the spread of HIV, a modest reallocation of HIV research funds to the development of STD diagnostics could bring a high payoff in reducing the burden not only of STDs, but of HIV as well. Similarly, since worldwide TB is now the leading cause of death in people infected with HIV, some reallocation of funds from HIV research to TB research may help to reduce overall mortality from TB.

4. Investors should support work to sequence the genomes of major pathogens as a means to understand the molecular basis of their pathogenesis, and to identify new immunogens and drug targets. At the population level research should investigate influences on the spread of antimicrobial resistance, approaches to monitoring resistant strains, and approaches to slowing their emergence.

5. Investors should prioritize the development of a set of key products needed to prevent, control and treat these highly significant sources of disease burden. Most require only modest or moderate investment and are expected to bring high returns for health.

6. A Health Product Development Facility or Alliance is proposed as a mechanism to focus and synergise these efforts, concentrating on the key products identified, together with others that may be judged essential for reducing major sources of disease burden. This facility should make full use of the skills, resources and experience of the private sector without excluding other sources of expertise.

For the epidemics of noncommunicable diseases and injuries

7. Faced with rapidly growing burdens of noncommunicable diseases, low-income and middle-income countries should significantly increase their relevant strategic research in epidemiology, behavioural science and health policy with the aim of reliably monitoring the true prevalence and trends of these conditions in their populations, and understanding their determinants. Basic data on mortality, morbidity and disability are currently inadequate in many regions, as are data on the country-specific and region-specific levels and determinants of environmental and behavioural risk factors. Low-cost methods for collecting reliable data, such as the use of disease surveillance points, must therefore be developed. In contrast to the need for epidemiological and behavioural research, biomedical science relevant to these conditions is already comparatively well supported in the established market economies. However, genuine differences in the characteristics of environments and populations will occasionally require additional biomedical research in some regions—as, for example, in seeking explanations for the observed high risk in South Asians of diabetes and heart disease.

8. The development and evaluation of algorithms and policy instruments for the cost-effective prevention, diagnosis, treatment and rehabilitation of noncommunicable diseases is an immediate priority for support by governments and other investors. In particular, policy instruments for effective tobacco control are required, as are efforts to increase health workers' awareness of psychiatric disorders in primary health care so that existing treatments may reach more of those who need them. By contrast, the development of new drugs to deal with noncommunicable diseases should

claim a low priority on the resources of low-income and middle-income countries because of massive investment in this area in the established market economies.

9. Research to respond to the injury epidemic must include an immediate effort to build data sets within countries and for international comparison of the incidence, prevalence and risk factors for different types of injury. Possible links between each type of injury and a range of modifiable risk factors such as alcohol use should be quantified. The development and evaluation of improved strategies for preventing and treating injuries in low-income countries is a priority.

10. To provide the necessary foci for these efforts in R&D on noncommunicable diseases and injuries, the Committee recommends two specific new R&D initiatives. First, we propose the establishment of a Special Programme for Research and Training on Noncommunicable Diseases and Healthy Aging. It should improve the quality and quantity of data on disease burden and mortality from noncommunicable diseases worldwide, with particular emphasis on gaining greater understanding of the risk factors and determinants of these diseases in different settings. It should audit existing treatment strategies in different countries, and—most importantly—invest in the development of cost-effective and sustainable interventions for use in low-income countries. Second, we propose a Special Programme or Initiative for Research, Training and Capacity-Building on Injuries. The initiative or programme should take advantage of growing relevant expertise in Latin America and South Africa. It should coordinate efforts to improve data on the burden of injuries, both intentional and unintentional, particularly those that can be readily prevented. Its aim should be the development of interventions, from products to policy instruments, that can prevent injuries, and the improvement of emergency services to deal with their consequences, especially in low-income countries. Both programmes or initiatives should serve to increase public awareness of the importance of the health problems with which they are concerned.

For research to inform health policy

11. Researchers and governments should agree on the principles for building strong national knowledge bases and data sets that will enable countries to learn from each other's experience. Among the priorities are studies to quantify the impact on health of economic policies and performance, the contribution of investments in health of the poor to their productivity, and the health impact of activities in other sectors, for example education, agriculture and transport; studies of the efficiency and effectiveness of different financial and organizational structures in health systems; measures of health need and the demand for services at household and population level; and measures of health system performance. The development of packages of essential services and the development of measures for assessing quality of care and intervention cost-effectiveness are also priorities.

12. Investors should devote resources to turning research results into action, for example through the development and evaluation of cost-effective instruments of public policy and practical tools for health workers. These may include essential drugs lists, model legislation, priority intervention packages, insurance benefit lists, pricing and taxation policies, practical manuals for use by health workers and summaries of research results for use by health workers and decision-makers.

13. To facilitate the above activities and to assist in providing the information that could guide health policies, a Special Programme for Research and Training on Health Systems and Policy should be established. The programme's agenda might be grouped into three broad domains: (1) generic and comparative issues of research on health systems and health policy, including the interactions between health and economic and social policies, and the outcomes of health system reform; (2) the development of *indicators* to monitor inputs, outcome and process on the demand and supply sides of the health system, together with the development of *tools* such as essential drugs lists and others listed in recommendation 11 above, that help to put policy into practice; and (3) efforts to facilitate national activities in health policy and systems research, such as supporting national capacity-strengthening through training programmes. A linked network of existing institutions might equally well perform these functions, supported by a staffed and adequately resourced independent unit.

For the institutional response to the challenges

14. Governments have much to gain from the development of national agendas for health research, with the active involvement of all relevant actors including scientists, service providers, policymakers and community leaders. Such agendas are likely to be most useful if their focus includes both population health needs and available R&D capacity. Investors may increase the efficiency of R&D by strengthening national and regional re-

search capacity, through, for example, focusing efforts on areas of comparative advantage, on improvements in the quality of training, and on explicit initiatives to translate results into relevant policies and interventions; by offering incentives to reverse the brain drain; by promoting policies that require research posts to be competitive and based on the peer-reviewed allocation of funds; and by making core support for institutions competitive. Additionally, supporting national institutions with a strong international orientation—in funding, staffing and mandate—might have a high payoff. The returns on investment in good standards are likely to be significant, while poor-quality or repetitive research is wasteful and may have adverse consequences for health.

15. Investors may profitably explore the development of new instruments—beyond the current patents system—for engaging the skills and energy of the private sector in the development of vaccines, antimicrobials and other drugs, diagnostic tests, devices and prostheses and equipment for the use of low-income populations. These incentives could include development subsidies, extended patent protection, guaranteed markets, streamlined regulatory requirements, improved market information (including certification of product quality) and contracting for specific tasks. The Health Product Development Facility or Alliance discussed in recommendation 6 is a potentially effective mechanism to focus and synergise efforts—not only for products to combat the major microbial threats, but also for maternal and child health and for the coming epidemics of noncommunicable diseases and injury.

16. A Forum for Investors in International Health R&D should be formed to provide a mechanism for the review of needs and opportunities for global health R&D—making use of analytic data on disease burden, R&D opportunities and the level of ongoing efforts. The forum would bring together the governments of low-income and middle-income countries, the major traditional "donors", and the research community. Analytic work undertaken by and for the forum would provide improved information for decentralized decisions on funding and resource allocation. This in turn should help to focus resources more sharply on completing the highest priority tasks before moving on to others.

17. Given the high returns to R&D in health improvement, a reallocation of health sector resources to R&D is recommended as a means to bring substantial net gains in health, particularly the health of poor populations. Since much of R&D provides an *international* public good, there is a particularly strong case for public sector investors in the established market economies to reallocate their health portfolios to increase R&D funds. The institutional capacity for supporting health R&D that many traditional donors possess strengthens the case for them to increase this form of assistance. The globalization of health problems suggests that sources of investment in international health R&D should be diversified in order to enhance the likelihood of finding appropriate solutions to them. The ministries of health and research councils of high-income countries have much to gain from participating. Governments of low-income and middle-income countries are likely to find increased allocations to appropriate R&D to be both a cost-effective way of improving health in their populations and, potentially, an investment in the infrastructure for productive national industries.

Chapter 1

Introduction

Four major challenges confront human health at the end of the 20th century:

- First, the world's poorest regions are still suffering a heavy—and largely avoidable—toll of premature death and disability from childhood infectious diseases, malnutrition and poor reproductive health. While progress against these old, familiar conditions has been spectacular in recent decades, they still account for more than one-third of the entire global burden of disease.
- Second, all populations are threatened by continually evolving microbes at a time of spreading antimicrobial resistance and greater human mobility. Particular threats include the TB bacterium *Mycobacterium tuberculosis*, pneumococcus, the malaria parasite *Plasmodium falciparum* and the human immunodeficiency virus.
- Third, epidemics of noncommunicable diseases and injuries are fast emerging in the middle-income and low-income countries as their populations age and their exposure to certain risk factors, such as tobacco, increases.
- Fourth, governments are struggling to meet a rising demand for health services in the face of spiralling costs. Yet their task is being hampered by lack of information to guide their policies for disease prevention and treatment. The shortage of data affects both the health sector—which in many countries is pressing ahead with health system reform without knowing how best to provide equitable and efficient services—and other sectors of the economy such as education or employment, whose influences on health may be profound.

Daunting as these challenges appear, there are good reasons to believe that research and development can deliver information and tools that will greatly strengthen the response to them. But, since resources are limited, priorities must be set. Governments and all others who invest in health R&D, such as international organizations and private foundations, must decide how their investments—or how their policies that affect private sector investments—can be put to work most efficiently to bring the greatest possible improvements to human health.

This Report is intended to assist them. It explores how they might inform decisions about resource allocation through a comparatively simple, rational process that takes into account the size of the disease burden linked with a given health problem, the state of the current knowledge base about the problem, the promise of the R&D effort—including the likelihood of developing an intervention that is more cost-effective than any existing ones—and the level of existing R&D investment into the problem. Where a health problem is not restricted to one specific condition but has a broad impact on overall population health—for example, inefficiencies or inequities in a health system—then other measures, such as the percentage of national product consumed by health care, are suggested as means to gauge its severity and assist informed judgement about priorities.

The Report provides much new information on global health status and trends. It contains a major reassessment of current levels of disease burden, new projections of disease burden to 2020 and assessments of the burden attributable to a number of risk factors for disease. It also contains data on current levels of R&D spending; and for selected conditions, analyses of the cost-effectiveness of interventions under development or under consideration for R&D investment. In addition, it provides information on scientists' judgements about development opportunities and strategic research needs. The Committee has identified priorities and suggested some key choices ahead. Our Report points to areas where international efforts in R&D could have a high payoff and proposes limited but important changes in the institutional arrangements for health R&D, including those that affect the private sector that could help to redirect highly constrained resources to bear the greatest fruit.

1.1 The background to this Report

This study was initiated in response to several recent requests for a broad-based review of needs and opportunities for R&D in the health sector. It builds on the World Bank's *World development report 1993: investing in health* (World Bank 1993). The packages of interventions for public health and disease control that were identified by that report—on the basis of disease burden and intervention cost-effectiveness—reasonably reflect the minimum potential of today's technology, and the analysis of health systems and health policy provides an appropriate starting point for country-based plans of action. The World Bank report suggests an approach to assessing priorities for R&D—using information on disease burden, existing interventions and ongoing efforts—that foreshadows the assessments reported here.

The study also draws on the important contributions of the WHO Advisory Committee on Health Research (ACHR) and the strategic orientations, both global and regional, given by the ACHR system. The ACHR's fore-

runner, the Advisory Committee on Medical Research, first suggested criteria for setting WHO's research priorities two decades ago. This Report builds on the ACHR's more recent discussions of a *Health research strategy for health for all by the year 2000* (Advisory Committee on Health Research 1986) and the Technical Discussions on health research at the 43rd World Health Assembly. The report of those discussions states that the setting of priorities for R&D requires "a multidimensional consideration: of the scale and urgency of various problems, of the solutions that are possible or likely to emerge from research as practicable and affordable measures, of possible benefits or detriments to other sectors, and of the different consequential returns achieved by the various possible choices of priorities" (Davies & Mansourian 1992). The report adds that "global interdependence implies that methodological research can be of benefit for all. The search for new objective methods of resource allocation, of determining and ranking priorities, constitutes research of a strategic nature. Strategic decisions are those which derive from a global understanding of a given problem". The present study starts from similar principles.

The Committee also builds on the work of the Commission on Health Research for Development whose report *Health research: essential link to equity in development* (Commission on Health Research for Development 1990) has influenced debate for the past five years. The Commission identified a "gross mismatch" between health needs and research investment in developing countries and found that many countries neglect the research needed to inform decisions on health policy. To fill the gap, the Commission argued for research at the national level for each country to understand its own problems, make the best use of limited resources, improve health policy and management, foster innovation and experimentation, and provide the foundation for a stronger voice from developing countries. In so doing, it developed the concept of Essential National Health Research (see Box 1.1). A growing number of countries are adopting ENHR strategies, facilitated by the Council on Health Research for Development, a nongovernmental body established in 1993.

The Commission argued that national research priorities should be set by: targeting major causes of mortality; taking account also of morbidity; considering the potential effectiveness of interventions that would emerge from the research; taking account of the percep-

Box 1.1 Definitions and explanations of terms used in this Report

Types of health research

Health research: a process for obtaining systematic knowledge and technology that can be used to improve the health of individuals or groups.

Health research provides basic information on the state of health and disease of the population; it aims to develop tools to prevent and cure illness and mitigate its effects; and it attempts to devise better approaches to health care for the individual and the community (Advisory Committee on Health Research 1993). Information about health needs may consist of measurements of conditions, measurements of the relative importance of various risk factors for ill-health, and analysis of the sources of inefficiency in health services which have a direct impact on health.

Health research embraces different types of activity, ranging from fundamental research—whose primary purpose is to advance knowledge—to development and evaluation research—whose primary purpose is to solve specific problems relating to health care and its delivery (see Box Figure 1.1.1).

Each stage of research is to some extent dependent upon others, and a linear model of the different stages of research is unhelpful in understanding the process. The diagonal line in Box Figure 1.1.1 seeks to stress the interrelatedness of each stage and the fact that there is likely to be substantial movement back and forth between stages. Nevertheless, it is generally true that the proportion of the defined research objective that seeks to change practice rather than to advance knowledge will increase with the spread of the dark section towards the left side of the bar.

Fundamental research: research whose purpose is principally to increase knowledge about questions of scientific significance.

Strategic research: research whose purpose is primarily to increase knowledge and understanding of a health problem, with a view eventually to solving or reducing the impact of the problem through further development and evaluation.

The relative importance of the knowledge-gaining component and the problem-solving component will vary depending on the type of project and the nature of the problem. Importantly, the definition of strategic research adopted by this Report *is not purely biomedical but encompasses also the work of behavioural scientists, epidemiologists, demographers and health policy scientists.* Specific examples of strategic research within each discipline might include sequencing the genome of an important pathogen, analysing what proportion of the burden of a given disease can be attributed to a specific risk factor in a specific population, and analysing what effects the decentralization of health services have on the coverage of a given service within a given population.

Development outcomes: products, interventions and policy instruments

Products. These encompass five basic groups of health related material products: drugs, vaccines, equipment including tools for public health, prostheses, and diagnostics.

Interventions. These may be combinations of products, algorithms, information or policies that reduce the risk, duration or severity of an adverse health condition. They may be usefully subdivided as either:

a. ***Public health interventions***—those that are sought of or directed towards entire populations or subgroups, including immunization, mass chemoprophylaxis such as the addition of iodine or medications to salt or the fluoridation of water, and nutritional interventions, such as encouraging women to take folic acid supplements before and after conception;

or

b. ***Personal health service interventions***—those that are provided at facilities and usually to individuals; these include inpatient and outpatient medical treatments, screening and rehabilitation.

Instruments of government policy. These encourage or discourage specific health interventions, e.g. pricing and/or taxing policies on tobacco, pricing policies for health services, essential drugs lists, policies for paying health workers according to the type and range of services they offer.

The health sciences

Biomedical sciences: includes all strategic biological, medical and clinical research, and biomedical product development and evaluation.

Population sciences: includes epidemiology, demography and the behavioural sciences. This category is *not* intended to denote solely that part of health research concerned with fertility, family planning and population control.

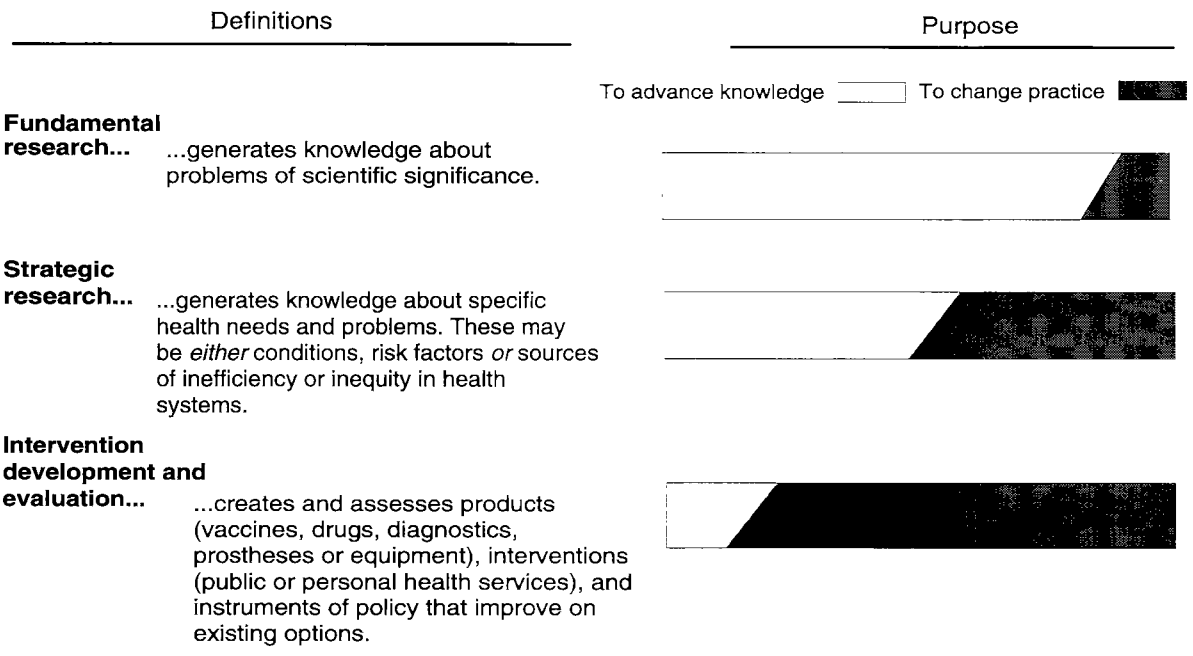
Health policy sciences: includes health policy research, health systems research and health services research.

It is understood that different traditions and institutional cultures may use some of the above terms in other senses than those adopted in this Report.

Essential national health research (ENHR)

This concept, first set out by the Commission on Health Research for Development (1990), aims to achieve equity in health and development. It holds that each developing country should establish and strengthen an appropriate health research base to "understand its own problems; improve health policy and management; enhance the effectiveness of limited resources; foster innovation and experimentation; and provide the foundation for a stronger developing country voice in setting international priorities".

Box Figure 1.1.1 Definitions and purpose of R&D



tions of need held by populations as well as the needs determined by "scientific" analysis; taking account of current R&D efforts; and considering research not only into specific diseases but also into broader health issues. While the Commission recognized the need for some international efforts, its emphasis was on national-level research, with international agendas emerging through consensus between countries.

Our Report emphasizes global priorities, and therefore complements the work of the Commission. However, if assessment is based on rational and quantitative methods, it is likely that global priorities will have much in common with those of individual nations and regional groups. There is already some evidence that such shared concerns are emerging: individual countries' agendas for ENHR identify many priorities similar to those discussed in this Report, including the major childhood infections, problems related to the demand for, and supply of, health services, and problems related to major risk factors for disease such as poor sanitation (Council on Health Research for Development 1995). It is worth stressing, however, that global priorities reach beyond the sum of national ones. For example, the cost of developing an HIV vaccine might be expected to deter any single low-income country from making it a priority. Yet a global assessment of priorities might conclude that the effort was worthwhile because many countries would benefit. Hence, it is essential to complement national assessments with a global one.

1.2 Scope and focus

The focus of this Report is on the needs of people who live in low-income or middle-income countries, since they make up four-fifths of the world's population and suffer most of its ill-health. But the Report's scope is global: in an increasingly connected planet where populations and economies are more and more interdependent, no region can consider itself immune to the problems of others.

Because the scope of this Report is necessarily broad, the Committee's basic assumptions and definitions must be made explicit. First, we should clarify what we mean by *health*. Health has been defined as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" and this definition has also been interpreted as "the ability to lead a socially and economically productive life" (World Health Organization 1978). In the Committee's view, the most important and most practical contribution that the health sector can make to advancing that broad vision of improved health is to reduce the burden of disease and disability. We therefore focus on developing and utilizing quantitative measures of disease burden and the relative cost-effectiveness of different interventions intended to reduce that burden.

We should stress, however, that as a Committee we do not view health as a matter for the health sector alone. It is clear that factors outside the health sector, such as income level and access to education, strongly influence population health. Our Report seeks to advance an agenda for assessing and quantifying those influences so that governments will be able to assess the desirability of devising multisectoral, integrated policies for health—as some, indeed, are already doing.

It is equally important to clarify what the Report means by *health research*. As the definition in Box 1.1 shows, research for health is a process for obtaining knowledge or technologies that can be used to improve human health. Because it involves human subjects, its conduct must always meet ethical standards, and this Committee endorses the guidelines set by the Council for International Organizations of Medical Sciences for that purpose (CIOMS 1993).

Health research encompasses a wide range of activities from fundamental research to product evaluation. Among previous attempts to subdivide the phases of the scientific research process in history, Francis Bacon's 17th-century distinction may be considered among the most useful; he divided "experiments for light" from "experiments for fruit" (*Instauratio Magna*, discussed in Webster 1975). For the purposes of our analysis, we have subdivided the process into three phases: fundamental research, strategic research, and intervention development and evaluation. As Box 1.1 shows, the purpose of fundamental research is mainly "for light"—to increase knowledge—while strategic research seeks knowledge specifically to solve health problems, and intervention development and evaluation put greater emphasis on finding "fruit"—to change practice.

In the Committee's view, these phases are interdependent and equally valuable. However, while we stress in Chapter 2 that fundamental research is the vital base for all other R&D activities, we have excluded it from our assessment of *priorities for resource allocation*. Our task was to consider priorities for R&D to address the practical health problems of populations. We have therefore focused on strategic research and intervention development and evaluation. Fundamental research is driven by many scientific considerations other than the measurement of need and opportunity, and it is therefore beyond the scope of this Report to judge priorities within it.

We have also subdivided the activities of health research into broad disciplinary groupings, to reflect the different levels at which human health problems must be analysed, from the sub-individual level of cells and molecules to the institutional level of health policies. Our three groupings of disciplines (defined in Box 1.1) are: biomedical sciences, population sciences, and health policy sciences. Each is to some extent dependent on the others for the information that sets their respective research agendas on particular health problems. In the case of malaria research, for example, biomedical researchers have studied the immune response of individuals to malaria parasites at the molecular level and have used the knowledge to develop candidate vaccines. Population scientists (epidemiologists) work with their bio-

medical colleagues to carry out trials of the vaccines and other interventions, such as insecticide-impregnated bednets. Sociobehavioural researchers, meanwhile, study the factors that determine whether people use bednets or other protective devices or not, economists study the pricing and policy factors that determine whether people should be asked to buy their own bednets or have them provided free, and health policy researchers study the advantages and disadvantages of different approaches to organizing the prevention and treatment of malaria.

We have sought to determine the balance of disciplinary effort that is most relevant for each of the four identified health challenges. Table 1.1 provides suggestive results; they are of interest not for being a specific guide to disciplinary priority but, rather, for indicating the need for a broad mix.

In our assessments of current resource allocation we have usually considered health R&D as a segment within the health sector, rather than health R&D as a segment within all R&D. This is because other components of the health sector such as disease control, health promotion and clinical services are intimately linked with strategic research and intervention development. None the less, individual countries conducting analyses of investment in health R&D may consider it appropriate to look at resources in the overall R&D context as well as in the health sector.

1.3 Approach and methods

The Committee has taken a comparatively simple approach to assessing needs and opportunities for research and development. In thinking about the claims on R&D resources that a particular problem might make, there are clearly certain criteria to consider. Is the problem big? (The world lost 70 times as many years of healthy life from TB as from lymphatic filariasis in 1990.) Do we already have good and cost-effective tools for dealing with the problem? (The availability of multidrug therapy—MDT—for leprosy weakens the case for investing in development of a leprosy vaccine.) Is the science base good? If so, one might proceed rapidly to product development and testing (as with the candidate conjugate pneumococcal vaccines); if not, strategic research to develop the knowledge base might be required (as with HIV vaccines). Are the high-income countries already spending a lot on the problem? (R&D money available to low-income and middle-income countries could add little to what is already being spent by rich countries to study atherogenesis or to develop new drugs for controlling hypertension or hyperlipidemia.)

In the case of problems that cut across specific diseases or risk factors—such as the rising costs of health care—we again suggest measuring the scale of the problem, for example in terms of the percentage of GDP consumed; assessing the reasons for the persistence of the problem through the informed judgement of experts; assessing the extent of existing knowledge about the problem; and the probability of developing policies or interventions that will provide cost-effective solutions to it.

Few would disagree that decisions about resource allocation within health R&D should, in some way, take the above considerations into account. Yet the Committee has been struck by how often these considerations are ignored: R&D money goes to diseases of little epidemiological significance while major killers, such as TB, are neglected; attention goes to marginal improvements in already good products while major opportunities are missed (e.g. work on heat-stable polio vaccine continues while countries with heavy disease burdens from infections such as *Haemophilus influenzae B* or pneumococcus must wait for trials of available vaccines). This Report argues, simply, that investors in R&D should attempt to take these factors into account as quantitatively, explicitly and systematically as possible. The degree to which this is possible will vary and the Committee considers its approach to be part of an ongoing process. The knowledge that the process yields can only inform—not determine—resource allocation decisions. Even where quantitative information is excellent, the approach should not be prescriptive.

This Report contains summaries of the assessments of disease burden for 1990 and projected for 2020 (Annex 1) and the burden attributable to selected risk factors (Annex 2). The full data from which these summaries are drawn, including separate assessments of mortality, years of life lost and years lived with disability, are published in the companion volumes to this Report (Murray & Lopez 1996 and forthcoming). In general, the Committee has used the disability-adjusted life

Table 1.1 R&D to address major health challenges: the role of different disciplines

	Disciplines		
Broad health challenge	**Biomedical science**	**Population sciences**	**Health policy sciences**
Childhood infections, malnutrition and poor reproductive health	++	++	++++
Evolving microbial threats	++++	++	++
Noncommunicable diseases and injuries	+	++++	+++
Informing health policy	-	++++	++++

Note: The estimated importance of each discipline ranges from the unimportant ('-') to extremely important ('++++').

Box 1.2 Measuring the burden of disease

This Report uses the disability-adjusted life year (DALY) as its main unit of currency for measuring the burden of disease. Unlike traditional mortality statistics, the DALY allows researchers and health policy-makers to assess the nonfatal consequences of ill-health and injuries and can thus reveal the extent of health problems that mortality statistics fail to capture. For example, the number of *deaths* from psychiatric and neurological diseases in 1990 was about 1% of the world total. Measured in terms of disability-adjusted life years, however, this group of diseases accounted for more than 10% of the total global disease burden (Annex 1).

Each DALY indicates the loss of a year's healthy life—that is, the time lived with a disability or the time lost through premature death. Years of life lost through premature death are calculated as the difference between the actual age at death and the age to which a person could have expected to live at birth in an advanced industrialized country—that is, 82.5 for women and 80 for men. Disability is assessed in terms of its expected duration and its severity. The total number of DALYs in a population in any given year indicates that population's disease burden: the higher the total, the greater the burden. The advantage of this currency is that, as a single indicator, it provides a comparable measure of the outcome of health interventions—in terms of DALYs averted—for a wide range of health problems and diseases.

The value choices incorporated into the DALY continue to be debated (see, for example, Morrow & Bryant 1995). An extensive discussion of these issues is contained in the companion volumes to this Report (Murray & Lopez 1996 and forthcoming), which present disease burden estimates in detail and also include sensitivity analyses. The Committee took the decision to use the DALY as its main indicator of disease burden for four reasons. First, the reality is that decision-makers allocate resources in part on the basis of aggregated measures of disease burden, implicitly if not explicitly. Second, it is important to have a unifying measure that enables assessment of both the burden of disease and the cost-effectiveness of different interventions. Third, the DALY has been developed through collaboration between different sectors and has helped to strengthen the foundations for a multisectoral approach to health which, the Committee believes, should continue. Fourth, the explicit nature of the assumptions underlying the DALY enables them to be debated and modified.

By 1995 some 28 countries were using the DALY in some form to assist them in the measurement of population health needs.

year (DALY) to measure disease burden and assess health need (see Box 1.2). In addition, wherever possible, we have considered other indicators, such as the percentage of GDP consumed by health care in individual countries and the level of R&D investment into particular health problems. Our methods are set out below. We suggest five steps to inform decision-making about the allocation of R&D resources to and within a problem area (e.g. TB or malnutrition or tobacco use).

1. Calculate the burden of the condition or risk factor

We have used the DALY as our main unit. Annexes 1 and 2 provide details of how burdens are calculated for conditions and risk factors respectively.

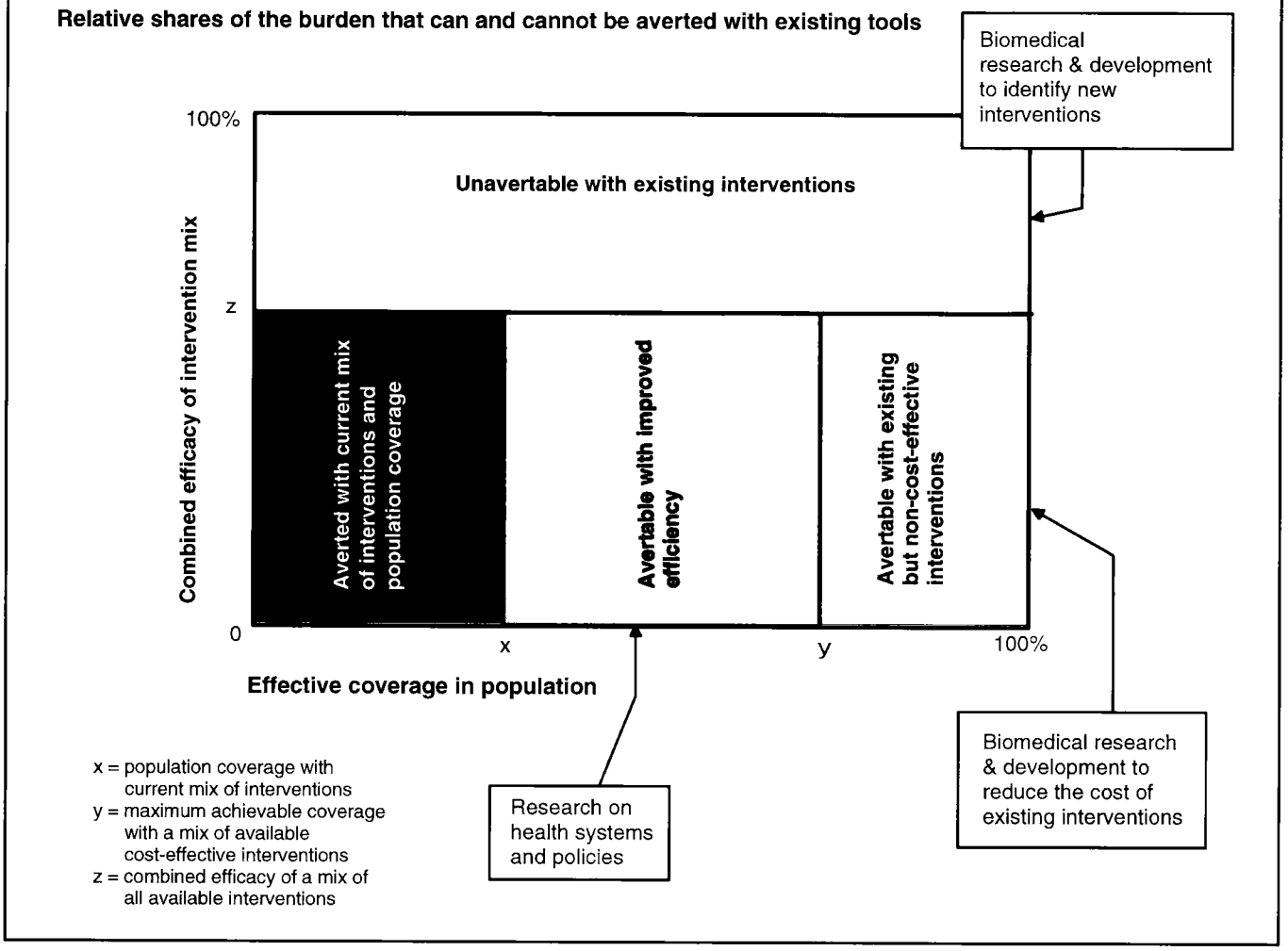
2. Identify the reasons why the disease burden persists

This requires an analysis, essentially, of whether the problem persists mainly because of (a) a lack of knowledge about the disease and its determinants, (b) a lack of tools, or (c) failure to use the existing tools efficiently. Of course, more than one factor is likely in each case. Where possible, this analysis can be quantitative. Figure 1.1 indicates the analytical approach applied. Using data on the efficacy of the available cost-effective interventions, and consulting the judgement of field experts on the proportion of the population receiving effective interventions, it is possible to estimate:

- what portion of the total burden of each disease or condition is now being averted;
- what could be averted now with better use of existing cost-effective interventions;
- what could be averted now, but only with interventions that are not cost-effective; and
- what cannot be averted with existing interventions but requires new ones.

The analysis is intended to identify where the greatest needs lie, and thereby guide assessment of the priorities for different types of research. The unit of currency employed for this analysis is, once again, the disability-adjusted life year. While such analyses are not intended to suggest that some spurious precision can be achieved in the analysis of need, they do indicate a sense of the *relative* distribution of the effort required.

Figure 1.1 Analysing the burden of a health problem to identify research needs



The whole square in Figure 1.1 represents the total estimated disease burden (in DALYs) from a given condition, such as diarrhoeal disease, globally or for a particular region. The horizontal axis represents the extent to which effective treatment is reaching the population—that is, how far into the population a mix of interventions is penetrating. The vertical axis represents the combined efficacy of this mix. The subdivisions within that square represent different portions of the burden: (1) that which is being averted now by the existing mix of cost-effective interventions among the people that the intervention is reaching, (2) that which could be averted if the existing interventions were used more efficiently, (3) that which could be averted with existing tools, but not cost-effectively, and (4) that which is not avertable with existing interventions. Calculations of the relative share occupied by each subdivision can help to spell out the priorities for research. For example, where it is calculated that a large portion of the total burden of a certain disease cannot be averted with the existing cost-effective tools, then there is a strong case for R&D to develop new ones. Where it is calculated that a large portion of the burden could be averted if existing tools were used more efficiently, there is a strong case for research into the needs and behaviours of users and the behaviour of providers, to learn how coverage could be increased and efficiency maximized. The methods used to conduct this form of analysis are described in more detail in Annex 1.

3. Judge the adequacy of the current knowledge base

This undertaking relies on the subjective judgement of informed scientists. If the knowledge base is adequate to support development of specific interventions, then the estimated cost-effectiveness of those interventions relative to those currently available can be assessed. The desirability of an intervention will then depend on its cost, the estimated probability of success and the ex-

tent to which it is better than available alternatives. If the knowledge base does not yet allow the development of new interventions—judged to be attractive in the way indicated—there is a suggestion that strategic research is desirable to strengthen the base. Clearly, the analysis will sometimes conclude that multiple approaches are desirable—particularly if the relevant disease burden is large.

4. Assess the promise of the R&D effort

This can be divided into two subsections:

a. ***The expected cost-effectiveness of the potential intervention.*** Provided certain data are available, calculations of the likely cost-effectiveness (in dollars per DALY averted) of a desired intervention can be undertaken and the results compared with the cost-effectiveness of existing interventions. Thus, for example, as we discuss in Chapters 3 and 4, a malaria vaccine could be highly attractive compared with other available preventive strategies while, by contrast, a schistosomiasis vaccine would be unlikely at present to compete with the available interventions. A broad guide to what counts as cost-effective is shown in Table 1.2; in essence, anything that costs less than US$ 25 to US$ 30 per DALY averted in low-income countries is highly attractive, and anything that costs less than US$ 150 is attractive. In middle-income countries, interventions that cost less than US$ 100 per DALY averted are highly attractive and those that cost less than US$ 500 attractive.

While there are undoubted uncertainties in the assessment of intervention cost-effectiveness, these should be kept in perspective. The range of cost-effectiveness is extremely large: some interventions in low-income countries cost less than US$ 15 per DALY averted while in industrialized countries specialized treatments for myocardial infarction may cost well above US$ 10 000 per DALY averted (Mark et al. 1995).

b. ***The probability of successful development.*** In most instances, there will be an ongoing R&D effort with one or several tools in the pipeline. The probability of success will depend in part on the knowledge base that underlies the development of the tools. For example, a candidate drug's probability of success is likely to be higher if the drug target is known to be essential to the organism, and if the mechanism of action is understood. Obviously, the closer the product is to application, the higher its chances of success, the lower will be the required investment and the shorter the time required before completion.

5. Finally, assess the adequacy of the current level of effort

Annex 5 reports the Committee's attempts to describe ongoing levels of resource allocation to R&D into particular health problems. We find that some important health problems receive extraordinarily little R&D investment. While the amount of funding devoted to a health problem cannot and should not be expected to be directly proportionate to the scale of the health problem, the particularly severe mismatches that have emerged from this study indicate a misjudgement of priorities. In light of what is now being spent, and of the attractiveness of development and strategic research possibilities identified in step (3), judgements about appropriate changes in the level or composition of resources allocated to the problem area can be made. A shortage of available data makes this effort a difficult one; additional attention is required on an ongoing basis.

The Committee's approach builds on earlier efforts to inform resource allocation in a number of specific ways. First, we explicitly consider disease burden and the burden attributable to selected risk factors, using a unit of measure that incorporates morbidity as well as mortality. Previous discussions have in practice considered mortality only, and none has attempted to quantify the burden attributable to risk factors. Second, we have attempted explicit analyses of the reasons for the persis-

Table 1.2 Good buys: examples of attractive health interventions in low-income and middle-income countries

	Attractive interventions (US$ per DALY averted)	Highly attractive interventions (US$ per DALY averted)
Low-income countries	**<150** Primary prevention programmes to reduce STD transmission through behaviour change	**<25** Measles immunization; breast-feeding promotion; targeted mass anthelminthics; smoking prevention or cessation programmes; treatment of pneumonias with antibiotics
Middle-income countries	**<500** Treatments with medication for schizophrenia and bipolar affective disorder; secondary prevention of stroke or angina by behaviour change and appropriate medication	**<100** Improved antenatal care; use of oral rehydration solutions; promotion of improved weaning practices

Source: Jamison 1993

tence of disease burden in selected areas, where previous discussions have left these analyses implicit. Third, we have made a limited number of estimates of the cost-effectiveness of desired interventions, where earlier efforts have made no such explicit estimates.

The Committee views this systematic approach to informing decision-making as a way of informing judgement—not replacing it. Our experience in applying the approach suggests that neglecting one or more of the above steps is frequent and distorts resource allocation; hence our conclusion about the desirability of more generally adopting a systematic approach. So far, the Committee has been able to apply the process with full rigour only to selected health problems and for others, where good data are not available, has relied more heavily on expert judgement and qualitative analysis. As such our work has made only a start, and further advances will require a continuing effort. It is hoped that this Report will help to stimulate a wider and ongoing systematic process.

Table 1.3 illustrates, with examples, the approach taken by the Committee. The first two examples show conditions where, in our view, the information clearly points to the need for R&D investment. The third example (leprosy) shows a condition where, in our view, R&D investment in a vaccine is less easy to justify.

Table 1.3 Steps to inform resource allocation: selected examples

Condition or risk factor	Need	Opportunity: promise of R&D effort					Investment requirement
	Disease burden (rank, of 96 causes)	Primary reasons for persistence of burden	Current knowledge base/R&D capacity	Desired intervention/ estimated likely cost-effectiveness (in US$)	Probability of success	Current effort, additional cost (in US$)/ time frame	Conclusion
Pneumonia	High (1)	Failure to use existing tools efficiently	Good	Package for integrated management of the sick child: Very high (<US$ 50 per DALY gained)	High	Current investment relatively small; required further costs and time frame: modest (US$ 15 million over 3 years)	High priority for investment
Malaria	High (11)	Lack of tools	Moderate to good	Malaria vaccine: Very high (<US$ 30 per DALY gained and <US$ 15 in some circumstances)	High	Current investment relatively small; required further costs and time frame: moderate (US$ 50 million over 10 years)	High priority for investment
Leprosy	Low (95)	Failure to use existing tools efficiently	Good	Leprosy vaccine: Low (US$ 2 453 per DALY gained compared with <US$ 50 for MDT treatment based on passive case finding and treatment, or US$ 42–US$ 2 700 based on active case finding	Moderate	Not assessed	Low priority for investment

Chapter 2

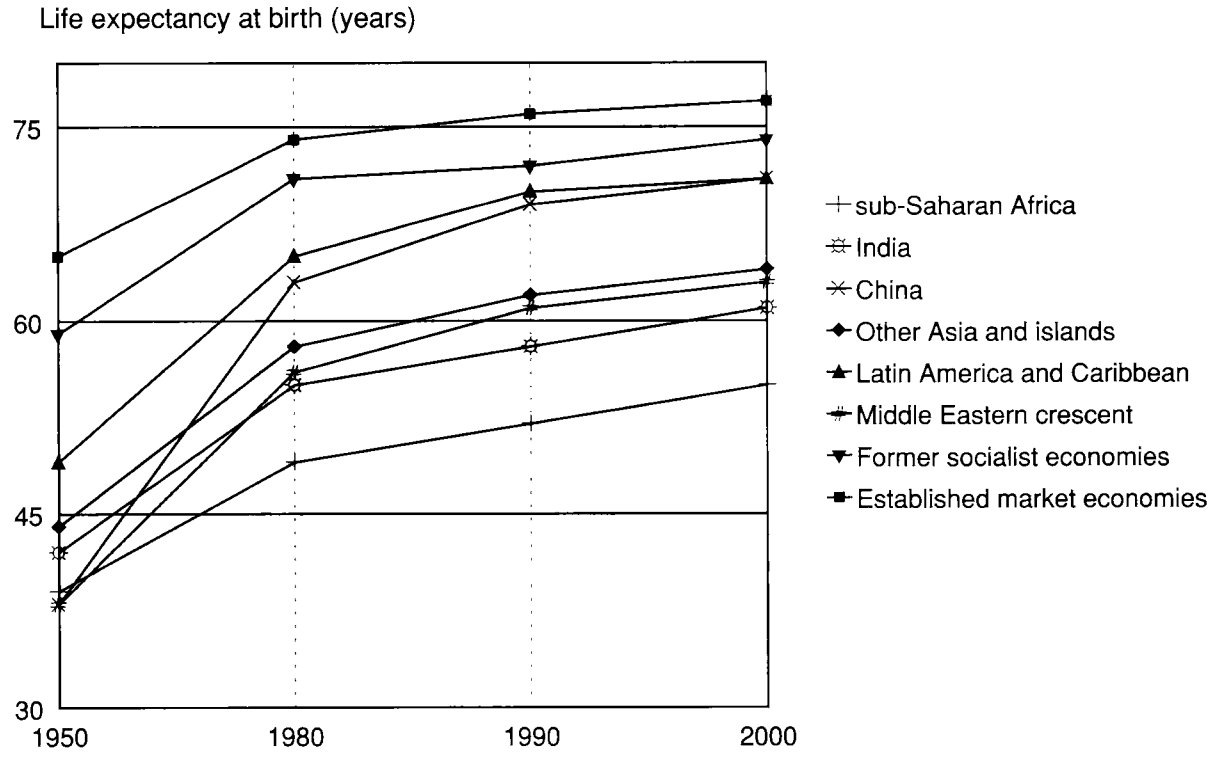
Why invest in health research? Historical experience and the promise of science

The health of the world's peoples has improved more in the past four generations than in the whole of their history. In China in 1950, the odds that a child would not live to reach school age were as high as one in three. For those children's children, just 30 years later, the odds had fallen to about one in 15, and they are expected to reach one in 28 by the year 2000 (World Bank 1993).

The scale and pace of the change are unprecedented. In the middle-income and low-income countries overall, life expectancy at birth has risen sharply from 40 years in 1950 to 63 years in 1990 (Figure 2.1) and the trend is still upwards. Even in sub-Saharan Africa, where the improvement has been slowest and smallest, the gain has been greater over the past four decades than it was over a comparable period in Europe in the 19th century.

The reasons for the dramatic improvement are complex. The rise in per capita incomes through the 20th century has been closely linked to the rise in life expectancy, with the steepest increases occurring at the lowest income levels (Figure 2.2). As people's incomes grow, they are able to buy more food, live in better housing and reach a higher level of education. And as a population grows more affluent, the proportion of people with access to safe water and better sanitation increases. All of these consequences of higher income have helped to improve health. But income growth alone cannot explain all of the improvement. As Figure 2.2 shows, the life expectancy of people in every income bracket has shifted steadily upwards over the past century so that a given income buys better health now than it did at equivalent levels 30 years before. Therefore, other factors must help to explain the trend since 1900.

Figure 2.1 Trends in life expectancy, 1950–2000



Source: World Bank 1993:203

2.1 The scientific underpinnings of past health improvement

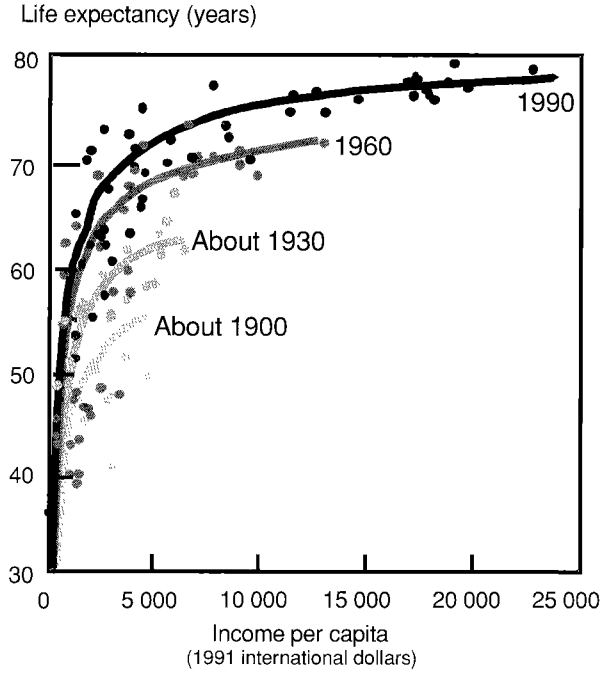
One vital—and perhaps underestimated—factor has been the impact of scientific research. Research has led to tangible improvements in two ways: by bringing knowledge that people use daily in their homes to maintain their health, and by producing direct technical interventions such as vaccines, treatments and public health measures.

2.1.1 Everyday knowledge as a product of research

The importance of household knowledge for health may only now be gaining recognition. On the basis of studies of the U.S. census for 1900, Preston and Haines (1991) have shown that neither household income nor education made much difference to children's chances of survival until scientific knowledge about the sources of ill-health became available. The work of Pasteur, Koch and others from the 1850s onwards established the germ theory of disease and, as people began to understand about infection towards the end of the 19th century, the differences in child mortality between affluent, educated households with access to that knowledge and poorer, uneducated households without it widened sharply. The implication is that the educated households were able to acquire and use the new knowledge more rapidly to adopt healthier behaviours, such as boiling water for infants, washing their hands regularly, and quarantining sick children. These actions strongly enhanced their chances of survival.

Studies of present-day populations support the idea that people are more likely to be healthy if they have access to accurate information. In many low-income countries today, the strongest determinant of children's survival is their mother's level of education, even after the household's income and access to health services have been taken into account. In general, educated women are more likely to limit their family size, and children born into smaller families have better survival chances than those born into large ones. Educated parents are more likely to make the best use of health information to adopt safe behaviours, avoid unsafe ones and seek the help of health workers when their children are unwell. Studies in high-income countries also suggest that, while income remains a strong determinant of health, access to information may also play an important role. Immigrants, for example, who may be disadvantaged by language differences, tend to suffer poorer health irrespective of their income level; and even where access to health services is not restricted because the services are provided free, inequalities in the health of households persist.

Figure 2.2 Life expectancy and income per capita for selected countries and periods



Note: International dollars are derived from national currencies by assessment of purchasing power, not by exchange rates. This measurement returns relatively higher incomes for poorer countries.
Source: World Bank 1993: 34. Also see Table 30 in this source for a fuller explanation of the derivation of per capita income.

2.1.2 Technical interventions

Research has also brought technical interventions such as vaccines, drugs, diagnostics, public health tools such as water treatment methods, therapeutic equipment, and algorithms for clinical procedures, whose impact on health has been profound. In many sub-Saharan African countries, child mortality has fallen steeply over a period of little economic growth, suggesting that these technological interventions must account for a large part of the improvement. Safer water supplies and improved sanitation, themselves the products of research, have reduced the spread of diarrhoeal disease, especially in urban areas. Vaccines against a handful of common childhood diseases have played a particularly significant role: without them, it has been estimated, the total burden of disease in children under the age of five would rise by almost a quarter. Improved education has also played a major role in health improvement, largely because it has enabled people to make good use of the preventive and therapeutic interventions available to them.

A brief review of the history of research over the past century shows how information has increasingly been applied to achieve better health. The greatest of the tangible advances since the 1880s has been against communicable diseases, beginning with the demonstration of the microbial origins of infections. From this discovery flowed two main approaches to treating infection: che-

motherapy and immunoprophylaxis, or the use of vaccines.

The great flowering of chemotherapy dates from the late 1930s with the production of the sulphonamides, the outcome of a pharmaceutical company's research, and then penicillin, discovered earlier by Fleming and developed by Florey and Chain in academic laboratories within the public sector. Subsequent discoveries have also come from varied origins, with both streptomycin and cephalosporin originating in university laboratories and other antimicrobials emerging from the private sector. During the Second World War, the benefits of this research were powerfully demonstrated when antibiotics and antimalarials transformed the prospects and the morale of the Allied troops, bringing a sharp reduction in the proportion of losses that were due to disease compared with those due to enemy action.

The development of vaccines against human diseases began 200 years ago with Jenner's inoculation against smallpox. The past century has seen the introduction of effective vaccines against polio, diphtheria, pertussis, tetanus and measles which now reach eight out of ten children worldwide. Newer vaccines, for example, against *Haemophilus influenzae* and hepatitis B, are also gaining more widespread use.

Beyond the assault on communicable diseases, there have been many more tangible benefits of R&D. Anaesthesia has evolved from a relatively crude process to become a highly sophisticated technology. With the discovery of insulin the effective treatment of diabetes began; with X-ray, the first of the scanning technologies, which is now complemented by ultrasound, positron emission tomography and magnetic resonance imaging, non-invasive diagnosis became possible for a wide range of conditions. Since epidemiologists established the link between tobacco and lung cancer in the 1950s, governments have gradually introduced policy changes to restrict smoking and millions of individuals have chosen to quit the habit. The development of hormonal contraception has given women greater control over their fertility, and the treatment of diarrhoeal disease has been revolutionized by oral rehydration therapy. The development of the randomized clinical trial has enabled physicians and researchers to assess the efficacy of interventions in a rational manner. Meta-analysis of many trials enables researchers to detect the benefits—and disadvantages—of interventions whose effects are comparatively modest but which may be of great importance in the treatment of common diseases.

Health research goes much further than the biomedical sciences, however. Researchers in health economics and epidemiology have developed measures of the cost-effectiveness of interventions that enable governments and other authorities to plan the best use of health care resources and, at a much broader level, integrate health into their development policies. Health policy research has been instrumental in enabling governments to improve safety standards and increase efficiency. For example, studies have demonstrated the effects of taxing alcohol on reducing the rate of motor-vehicle crashes and investigated the potential of different incentive systems to encourage physicians to use cost-effective treatments. Health services researchers have begun to answer important questions about the most effective approaches to treatment for a wide range of conditions—such as whether community care is appropriate for severely mentally ill patients in specific settings, or which routinely provided obstetric interventions are actually beneficial. Such research has also demonstrated that programmes of primary health care and nutrition in poor rural areas can be highly cost-effective in reducing infant and child mortality. Systematic reviews of clinical research, such as those now being produced by the Cochrane Collaboration, and the dissemination of research findings to practitioners, are enabling health workers to base their practice on evidence.

Behavioural research has also led to improvements in health care. For example, in Kenya and Ghana researchers learned that parents often believe that their sick children's convulsions are caused by spirits. Rather than seek treatment for malaria—the likely cause—they seek charms from traditional healers. The studies have prompted health workers to produce information and education packages for women to enable them to make more informed choices about treatment. Research into the behaviours and beliefs of health care providers has helped to show why, for example, health workers sometimes miss opportunities to immunize children, physicians sometimes prescribe inappropriate treatments for diarrhoea, and general practitioners sometimes fail to administer aspirin immediately after diagnosing acute myocardial infarction. These findings have resulted in better training for health workers and, ultimately, better services to patients and greater efficiency.

2.2 The value of research and the fundamental science base

While the impact of research on health is relatively well known, its economic value to society may be less widely appreciated. Data from the United States demonstrate that many products of R&D, such as vaccines and treatments, have produced significant savings by averting disease, reducing health care costs and enabling greater productivity (National Institutes of Health 1995). The fluoridation of water is estimated to save US$ 4 billion a year in the United States by averting the costs of treating dental caries. The vaccine against *Haemophilus influenzae B* is estimated to save that nation US$ 400 million a year. Research into drug addiction has resulted in treatment programmes that for every US$ 1 invested in them bring a return of between US$ 4 and US$ 7 in reduced drug-related crime, criminal justice costs and theft. When savings related to health care are included, total savings can exceed costs by 12 to 1. Research has also helped to reduce the costs of alcohol abuse, a major risk factor for disease and injuries worldwide which

costs the United States alone an estimated US$ 98.6 billion per year in lost productivity, treatment, damage to property and crime. After researchers demonstrated that an increase in the minimum legal drinking age in the various states of the United States from 18 to 21 would reduce the number of road-traffic incidents and related fatalities significantly, all states imposed a minimum age of 21 years, saving up to US$ 600 million per year.

There have been few analyses of the payoff from specific R&D investments, and the lack of data on resource flows is striking. However, where data exist, they suggest that very high returns are possible. For example, a sputum test for *Pneumocystis carinii* pneumonia, an important opportunistic infection in HIV disease, was developed through R&D that cost around US$ 440 000. The test is now estimated to save about US$ 50 million per year in the United States by overcoming the need for more expensive invasive diagnostic procedures. Also in the United States, studies have confirmed that it is not necessary to screen all the nation's donated blood for HIV antigens—a much more expensive and laborious process than the routine screening for antibodies to the virus that is practised currently. The studies, which cost US$ 500 000, enabled the Federal government to save up to US$ 49.4 million per year by avoiding the purchase of a costly antigen test kit.

But besides these economic gains, research brings another kind of wealth to society. The culture of research has provided a rational, knowledge-based framework for progress in health. Both medical practice and health policy have been the prey of ineffective remedies and fashions in policy for centuries, and a scientific framework has provided as much for eliminating the irrational and ineffective as it has for developing new ways to improve health. At the heart of that rational framework lies the fundamental science base—the underpinning of all the knowledge, products and practical applications that have emerged since the 19th century.

The development of vaccines, recognized as one of the most cost-effective of all medical interventions, provides an informative example of the role of fundamental science in the development of practical medical interventions. From the end of the last century until the middle of this, vaccines were produced by identifying the pathogenic agent, inactivating it by formaldehyde or attenuating it by prolonged culture. These almost entirely empirical procedures yielded vaccines for smallpox, polio, measles, BCG, pertussis, diphtheria and tetanus. Today it may be argued that the easy vaccines have been made, and that far greater understanding of the complexities of pathogenesis and the mechanisms of immunity will be required for many vaccines in future.

Modern molecular biology has provided a powerful set of methodologies and a new approach to developing vaccines. But the foundations of this new biology were basic scientific inquiries that were totally unrelated to practical application. In the words of Robert Oppenheimer: "It is a profound and necessary truth that the deep things in science are not found because they are useful; they are found because it was possible to find them" (Rhodes 1986). The original questions that led to the key findings could not, at face value, have appeared less relevant to practical applications, and were often ridiculed by politicians (see Box 2.1).

Clearly, strategic and applied research depend critically on the continuing pursuit of fundamental knowledge. Without that knowledge, no matter how important the practical problems society would like to have solved, there may be no tools to solve them. Lord Porter has argued that "there are only two kinds of science—applied science, and not-yet-applied science" (Lord Porter, personal communication to the Committee). The familiar linear model of science, which begins with the very "basic" and moves steadily towards the "applied" is no longer accepted dogma. Today, a real reciprocity between fundamental and more applied science has emerged. For example, clinical studies of people with immunologic disorders and cancers have led to fundamental insights into the immune system and regulation of normal cell growth and development. And basic inquiry into fundamental biological questions has continued to yield practical products, including drugs and vaccines. Interdisciplinary connections will be increasingly important in all of science as the pace of discovery and the amount of available information grows, but most particularly in biomedical sciences.

2.3 Looking ahead: research tools for the future

Because opportunities arise from unanticipated experimental findings, it is impossible to predict with any certainty what the major breakthroughs in science will be over the next two decades. Nevertheless, there are a number of developments that are likely to be critical to the direction that biomedical science will take. Some are research technologies; others are conceptual and experimental advances in biology. A few of these are discussed briefly here. The list is by no means comprehensive, but it should provide a sense of the possible consequences of new knowledge to improve the productivity of the R&D enterprise itself.

2.3.1 Technologies for health R&D

- **Recombinant DNA technology.** This has made it possible for scientists to manipulate genes in the test-tube and within cells and living organisms. It is now possible to identify, amplify, clone and mutate many genes from lower organisms, and some from humans. The techniques for gene amplification allow scientists to produce millions of copies of a gene in a matter of hours, and have led to effective and affordable new diagnostics. The proteins encoded by genes can be pro-

duced and harvested in bulk, enabling scientists to understand their structure and biological activities. This technology is rapidly becoming more affordable and is already available to many middle-income countries and some low-income countries.

- **Structural biology.** Now that even rare proteins can be produced in large quantities, researchers can crystallize key biological molecules and determine their structures. From the structure, scientists can learn the molecular basis for the biological activity of the protein or enzyme and, using computer modelling techniques, design drugs with specific characteristics to mediate that activity.
- **Combinatorial chemistry.** In the past, the discovery of new drugs was a labour-intensive and nonrational process that involved screening thousands of compounds over a period of months or years, and then making derivatives from lead compounds. With this method, pharmaceutical companies could test at most several thousand compounds a year. By a new process, companies and even smaller research units can synthesize up to 1000 new derivatives in a week. Rather than manipulate specific chemicals, the process makes random derivatives, then active compounds from within the pool are selected by sophisticated biological assays. This technology makes it possible for many more compounds than before to be tested for biological activity both quickly and relatively cheaply. It will almost certainly increase the capacity of the pharmaceutical industry in developing countries.
- **Computer and data analysis technologies.** The rapid development of faster computers and the sophisticated software available to individuals with personal computers has revolutionized the analysis of medical and scientific data and information. Databases containing information on genes from humans and microbes are available to anyone with a personal computer, a modem and a telephone. International links enable countries to share data for analysis of the efficacy and effectiveness of medical interventions, and to study vaccines and drugs in post-marketing surveillance. Powerful data analysis technologies have enabled scientists to conduct meta-analyses of clinical trials and epidemiological surveys that determine the importance of particular risk factors in diseases.
- **The communications revolution.** E-mail, the Internet and dedicated health telecommunications services, such as SatelLife, are enabling growing numbers of researchers to access and share informa-

Box 2.1 Fundamental questions that brought unexpected health benefits

Fundamental research is driven not by health need, but by curiosity. Yet without it, many health problems could not have been addressed. Here are three examples of apparently "irrelevant" questions that biologists have asked—and found out more than they expected to from the answers.

- "Do bacteria have sex?" If evolution were to derive only from random small mutations, it would be difficult to see how complex traits and organisms could ever have evolved, since most mutations are clearly deleterious. The work of Lederberg established that it is possible to exchange genes and whole pieces of chromosomes in bacteria, and led to an understanding of recombination as a rapid evolutionary mechanism. The process can be observed, for example, in the rapid transfer of some markers for antibiotic resistance across genera. Not only has this discovery been vital in understanding the basis of antimicrobial resistance, but it has also led to the development of recombinant DNA technology and provides the knowledge base for the biotechnology industry.
- "Do tumour cells inhibit the specialized functions of differentiated cells?" Köhler and Milstein were concerned with discovering whether tumour cells suppress normal, differentiated cells, such as the white cells of the immune system, and prevent them from performing their usual functions. In learning that the answer was, generally, yes, they also discovered that when tumour cells of the lymphoid series are fused to antibody-producing white cells, antibody production is not inhibited, and the antibody-producing cells become immortalized. The resulting antibodies, known as monoclonal antibodies, derive from a single cell that can be grown to infinite number. Today, they are used worldwide for diagnostics and for protein purification.
- "Why are some bacteria 'immune' to infection by particular phages?" A number of physicists in the 1940s believed that biology was an exciting new scientific frontier, and to obviate the enormous complexities of studying living mammals, chose instead to study the simplest possible organisms, viruses called phages that infect only bacteria. From that work came the discovery of restriction enzymes that cut DNA, the molecule that carries genetic information, at very precise locations. This has led to the possibility of cloning defined pieces of DNA containing genes of interest for health research, and to DNA fingerprinting, which is useful in molecular epidemiology and studies of genetic traits.

tion regardless of their location. The technology will improve the opportunities for countries to coordinate epidemiological information, such as surveillance networks for infectious diseases. Research journals are also beginning to publish their papers on line and an increasing number of scientists use electronic peer review (see Box 2.2). Physicians and surgeons are beginning to use communications technology to consult each other for information and advice, for example in diagnosing complex or rare conditions. A digitized image, for example from a CT scan, may be transmitted electronically from the treating physician to another thousands of miles away for comments. While so far such technologies have had little impact on the health needs of people in low-income countries, their promise for geographically remote and medically underserved populations in both rural and urban areas is now gaining increasing recognition. The technologies also offer the prospect of distance learning and continuing training for health care providers and health managers. With the costs of international telephone calls expected to fall in the near future, the information revolution may be expected to gather pace in low-income countries.

2.3.2 Promising areas of biomedical research

Since the 1970s, biomedical research has moved forward rapidly and the outlook for the future suggests that this pace is likely to continue. Here, we focus on three areas of research whose outcomes are expected to help address important health problems.

- **The Human Genome Project.** This international collaborative effort aims to map and sequence all human genes and understand their functions. The genome contains between 50 000 and 100 000 genes, of which scientists so far know the function of only about 3 000. One-third of these have already been associated with disease. The project is a key investment for, with growing knowledge of human genes and of the complex interplay between genes and environment, it will become possible to predict the probability that an individual will develop a particular disease over that person's lifetime. This may enable more effective strategies for disease prevention and risk aversion. As well as studying human genes, researchers are mapping and sequencing the genomes of several other organisms, including some that provide useful models for studying development. There is now grow-

Box 2.2 A peer review network for biomedical science

The future of international health and medicine may be shaped by two recent innovations: a global revolution in electronic communication, and a worldwide extension of organized processes of scientific self-criticism for evaluating medical science and practice. Through critical peer review, experts in a particular field (peers) assess the validity and merit of research produced by others in the field. This process of self-criticism and quality assurance has been thus far based in medical journals. While there are thousands of journals, the extent to which they use peer review varies. Research published in peer-reviewed journals helps shape the clinical decisions made by physicians and other health professionals, the kinds of therapies and technologies used, and the strategies adopted by nations to promote health and prevent disease. A science of peer review is emerging at the same time that new communication technologies have extended the reach of information and reduced the costs of its dissemination.

The potential impact of the digital information age on the science and practice of medicine, and particularly on extending the culture of science through the practice of peer review, is well recognized by organizations that promote health internationally and by medical journals. In many regions a scientifically robust medical profession is maturing or just emerging. Participation in self-critical scientific dialogue and peer review promotes a professional culture in medicine that may be as important to sustainable improvements in clinical practice and public health as the delivery of medical education, technology and supplies. Access to the world medical literature and identification with peer review (as a journal reader, author or reviewer) may contribute substantially to increasing professional self-identity and the development of professional institutions and culture. Decreasing scientific isolation by bringing more scientists and clinicians into the world biomedical community is key to achieving change.

A consortium of medical journal editors, led by the *Journal of the American Medical Association* and the *British medical journal*, in partnership with Project HOPE, a nonprofit nongovernmental organization, are now planning a global dissemination of biomedical information through new technologies. This effort was launched at a meeting in Bellagio, Italy, in April 1995 that brought together editors of major medical journals from the high-income, low-income and middle-income countries. A lasting system of communication between medical scientists and practitioners across national boundaries and diverse cultures, based on access to peer review literature and publishing but evolving to other telemedical and tele-distance learning applications, is envisioned. The goal is to improve worldwide access to biomedical peer review systems and information and the practice of peer review in all elements of health care from research to clinical care. The next major step will be a Congress on Global Biomedical Communication to be held in Prague in 1997 to launch a worldwide electronic biomedical peer review network.

ing interest in sequencing the genomes of important disease-causing organisms as a step towards understanding the molecular basis of pathogenesis. Such studies should provide urgently needed information, for example, about potential new targets for antimicrobial drugs and about potential immunogens for the design of new vaccines.

- **Developmental biology.** The power of molecular biology and genetics have begun to reveal clues to the fundamental question in developmental biology: that is, how are the events that lead to the development of specialized organs within a complex individual programmed into the single cell of the fertilized egg? Using simple model organisms that can be readily genetically manipulated—a small roundworm and the fruitfly *Drosophila*—many of the early functions of the developmental programme are now becoming clear. For example, scientists can now understand the development of the eye and other organs, and the determination of head and tail, in terms of molecules produced by specific cells at a precise time in development. The ability to make mutations in these lower animals that mimic human genetic diseases will allow a much greater understanding of the nature of these diseases and allow more rapid research on interventions to prevent or ameliorate them.

  In the course of these fundamental studies on development, researchers have learnt that alterations in many genes critical for normal development can lead to a genetic imbalance that in turn triggers the development of cancer. From these fundamental studies, they have identified a number of oncogenes—mutated or altered genes that are aberrantly expressed in specific human tumours. Scientists have continued to elucidate the role of these oncogenes in the complex web of normal development, learning how changes of even just one amino acid in the proteins they encode can start the neoplastic process. Such work is likely to result in new diagnostic tools for detecting cancer cells at an early stage, and it could lead to new therapies to prevent or correct the aberrant and unregulated growth of cells.

- **Neuroscience.** The human brain remains the ultimate intellectual challenge for biomedical research. But in recent years, studies of its mechanisms have begun to bear fruit. From molecular genetic studies in model organisms, scientists are discovering genes that are critical to neurological development. Fundamental questions about, for example, the ways in which particular nerves home to particular anatomical regions, or how different kinds of stimuli and neurotransmitters evoke responses from specific nerves, are becoming amenable to experimental study. Already knowledge of signalling neurotransmitters and their receptors has led to the development of drugs that are playing an increasingly important role in the treatment of mental illness. Studies using scanning technologies have, for the first time, provided physical evidence of biochemical changes in the brain related to vision, thought and emotion. While it is premature to anticipate what the practical consequences of this knowledge will be, it is anticipated that new treatments and preventive therapies for neurological and psychiatric diseases, such as Alzheimer disease, will be among them. The search for practical responses and affordable preventive strategies for neurological and psychiatric diseases has acquired a new urgency in the light of the worldwide projected epidemic of these diseases.

The question of paramount importance, however, is to what extent these technologies and the knowledge that they are yielding will be engaged to address the health problems of people in low-income and middle-income countries, who make up four-fifths of the world's population. In some respects, there are grounds for optimism. Recombinant DNA technology and monoclonal antibodies are just two examples of advances that have enabled the development of highly cost-effective diagnostics in low-income countries; and combinatorial chemistry is, as we have argued, likely to lower the costs of drug screening dramatically. As these technologies become more widely available, their impact is likely to increase.

But there are also grounds for serious concern. In 1992, no more than 5% of the total spent on health research worldwide was devoted to problems that overwhelmingly burden developing countries. Assessments of R&D spending for this Report have revealed stark imbalances in the allocation of research resources, with some of the most important sources of global disease burden—such as diarrhoeal disease or childhood pneumonias—receiving less than half of one per cent of all health research funds (Annex 5). As we show in Chapter 7, there is also disturbing evidence that even the meagre share of funds that are allocated to the health problems of low-income countries may now be declining, due mainly to shrinking budgets for bilateral official development assistance from the governments of the established market economies. It is of concern, too, that investment by the pharmaceutical industry in R&D on antimicrobials has declined in recent years. If the dividends of research are to be shared equitably by the world's populations, intensive work lies ahead. The challenges of coming decades will not be met unless resources are used rationally and equitably to serve the health needs of the majority. Indeed, given the scale of these challenges, there is a risk that some of the gains of the past could be jeopardized. A key responsibility for researchers and investors in health research is to improve the collection and dissemination of data on the important sources of disease burden and the relative distribution of resources into R&D. With more informed decision-making about the priorities for health research, countries can hope to consolidate the health improvements of the 20th century and achieve new progress in the 21st.

2.4 Chapter summary

Life expectancy has risen steeply throughout the 20th century. While rising incomes and education have been key factors in the massive health gains of recent decades, health research has also played an important, and possibly underestimated, role. Health research has brought knowledge that people can use to adopt healthier behaviours and technological solutions such as vaccines, drugs and treatment algorithms for a range of pressing health problems of the low-income and middle-income countries. Advances in biology and in the technologies of research promise further advances in future. But in order to hold on to the improvements of the past and to build on them in future for the benefit of all populations, investors must maintain a strong science base and build assessment of global health needs into their decisions about resource allocation for strategic and applied research.

Chapter 3

An unfinished agenda: improving maternal and child health

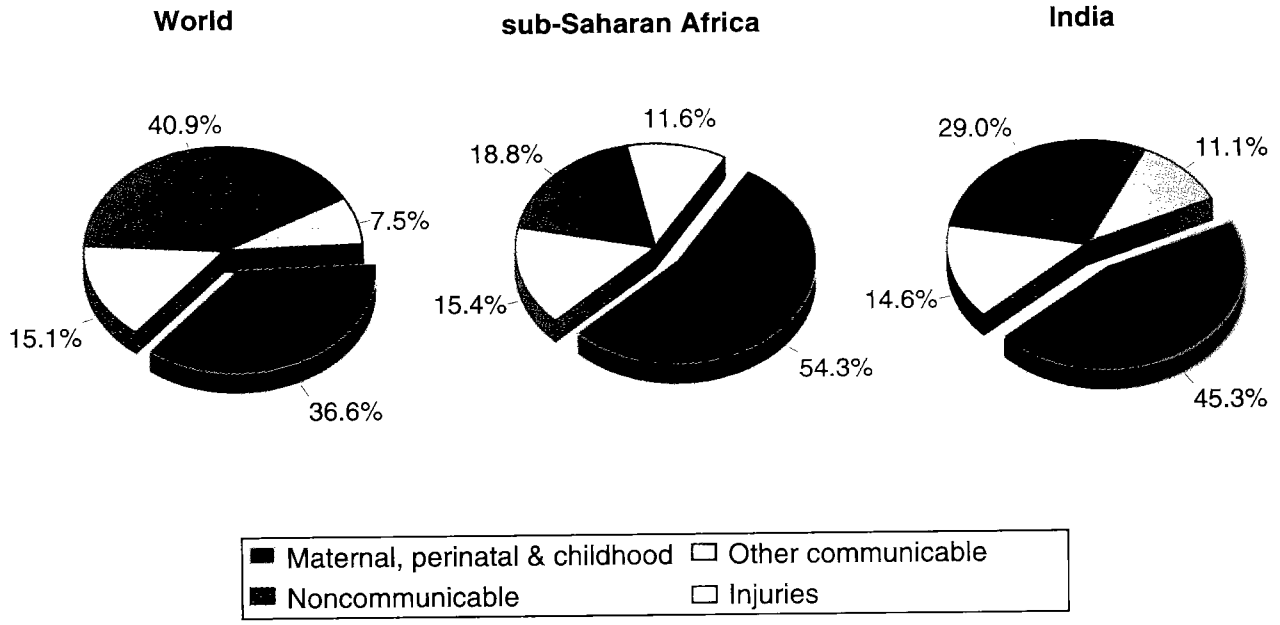
The world's poorest populations live under the shadow of a group of old enemies which, despite decades of progress and an arsenal of weapons to prevent and treat them, still kill more than 12 million children and almost half a million women a year. They are responsible for more than half of the disease burden in sub-Saharan Africa, almost half of it in India and—even though they are virtually unknown in the rich countries—more than a third of the entire global burden (Figure 3.1). They are:

- the communicable diseases of childhood—such as pneumonia, diarrhoeal diseases, malaria, measles and the other vaccine-preventable infections, and intestinal parasitic infestations;
- malnutrition; and
- poor reproductive health—the consequences of unwanted pregnancy and the complications of pregnancy, childbirth and the first week of life. These conditions make up only a subset of the massively important cluster of reproductive health needs, which we return to elsewhere in the Report.

In this chapter, the first of four focusing on the major health challenges identified in this Report, we ask how research and development can tackle this group of conditions. We discuss them as a group because they often occur together, because the reasons for their persistence are largely shared, and because efforts to address them must overlap.

Poverty increases people's vulnerability to most diseases, but its link with this group of conditions is particularly strong. The childhood infections, malnutrition,

Figure 3.1 Traditional enemies: percentage of the burden of disease attributable to maternal, perinatal and childhood conditions (in DALYs), 1990



Source: Annex 1

and maternal and perinatal conditions are borne almost exclusively by poor populations. Not only is poverty a predisposing factor for these conditions, it is also a consequence of them. As incomes have risen and health technologies have improved, there has been significant progress against them, but that progress has not gone far enough. As long as they persist, hundreds of millions will be trapped in a cycle of underdevelopment, prevented from reaching their potential at school, in the workplace, in the household and thus in the economy.

The persistence of these old foes in the face of effective means to avoid or control them—such as vaccines, drugs and algorithms for safe care in pregnancy and delivery—must be blamed in large part on inaction. Governments have failed to invest in the health of poor people by providing essential, responsive and equitable health services, and the pharmaceutical industry has too few incentives to develop promising new candidate vaccines, drugs or other products for their needs. But action is not all that is required. Many of the existing interventions fall short of their potential today because no one knows how to make the best use of them. Operational research is needed to make existing interventions more responsive to people's needs and to increase their effectiveness. And, where existing tools are inadequate, new ones need to be developed.

The case for renewed effort is strong on humanitarian grounds alone. But there is also a strong economic rationale for pursuing greater equity. Most of the existing interventions against childhood diseases and maternal conditions are, in principle, highly cost-effective and, in poor countries where these conditions are highly prevalent, the potential health gain from using them properly is massive. All can be delivered for less than US$ 50 per year of healthy life that they gain, and some for less than US$ 30 (Bobadilla et al. 1994). In recent years, attention has focused on the idea of putting interventions together into *packages*. Briefly, this means grouping services to make the best use of patients' and carers' time, treating an individual instead of the individual's diagnosis, bringing prevention and treatment activities together, and reducing the costs of providing the services by sharing resources. Health workers and operational research teams have shown, for example, that it makes good sense to examine a mother and her newborn baby together, rather than make them both attend a clinic twice. Or that, when a child is likely to be affected by several conditions at once, it makes sense to diagnose and treat them together rather than separately. Some packages, such as the group of vaccines delivered by the Expanded Programme on Immunization (EPI), are already well established. Others, such as a package for the care of sick children, have been developed and are ready for implementation. Still others, however, are little more than theoretical concepts.

According to health economists' estimates, developed with data from low-income countries, a set of these packages of essential services, including family planning, immunization, the care of sick children, school health programmes, and the care of women in pregnancy and childbirth, could be delivered for less than US$ 12 per head per year. Together, put to best use, these packages could lift around one-third of the burden of premature mortality and disability from the populations of low-income countries. Figure 3.2 shows the potential impact of the essential packages on total disease burden in both low-income and middle-income countries.

The incentive for making these packages of essential interventions work is therefore exceptionally high. As yet, however, few have been evaluated in real populations, although efforts are now underway to do so, for example in Tanzania (Box 3.1). A key question for research is to establish *how* to achieve this effective use of packages. In the following sections, we investigate the health needs of children and mothers in low-income countries in more detail, and discuss how research and development could improve existing interventions and produce new ones where needed.

3.1 Responding to children's needs

3.1.1 The magnitude of the burden

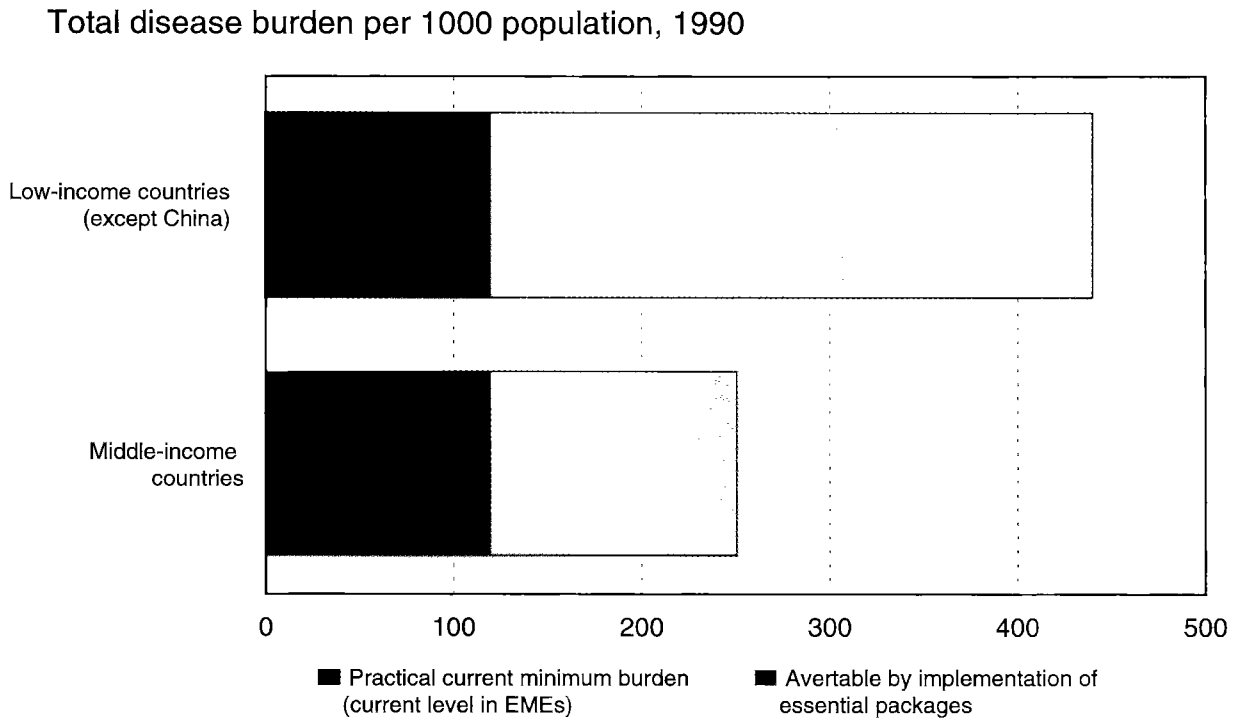
More than a quarter of the entire global disease burden is caused by conditions that primarily affect children in low-income populations (Table 3.1).

Of these conditions, pneumonia, diarrhoeal disease, malnutrition, measles and malaria are dominant. Together, these five conditions are responsible for seven out of every ten deaths among under-fives in low-income countries and the vast majority of the disease burden. As Figure 3.3 shows, they frequently overlap and interact with each other.

Pneumonia, the most frequently suffered disease worldwide, kills four million children under the age of five every year and ranks first among all causes of disease burden. Disease-specific mortality rates from pneumonia are between 10 and 50 times higher in low-income countries than in the established market economies (Stansfield & Shepard 1993). Most deaths are in children under the age of two years and more than 60% are caused by two bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae,* with the remainder caused by a variety of bacteria and viruses including respiratory syncytial virus and adenovirus. Pneumonia can also be a complication of infection with measles virus or with pertussis. Children are most vulnerable to die of pneumonia if they are poor, undernourished, weighed less than average at birth, are not breast-fed and live in crowded homes. Indoor air pollution from cooking stoves may be an additional risk. Children whose mothers received an adequate education are less likely to die than those whose mothers are uneducated.

Diarrhoeal disease kills another three million under-fives and ranks second among all causes of disease burden worldwide. There are three broad types of diar-

Figure 3.2 Much to gain: the potential impact of the essential packages



The two horizontal bars show, for low-income and middle-income countries respectively, the total disease burden per 1000 people in 1990, measured in years of healthy life lost (DALYs). The black segment shows the lowest level of burden that could practicably be achieved if all countries had as little ill-health as the established market economies. The grey segment, to the right, shows the amount of the total burden that could be removed if the essential packages were fully implemented.

rhoeal disease: acute watery diarrhoea, persistent diarrhoea—lasting more than 14 days—and dysentery. About half of all deaths are caused by acute watery diarrhoea, with rotavirus the single biggest cause. Babies who are not breast-fed are eight or more times more likely to die of diarrhoeal disease than breast-fed babies. In addition, low birth weight, undernourishment and lack of maternal education all increase children's vulnerability. Unsafe water and sanitation, and poor personal hygiene, are important risk factors for diarrhoeal disease (Table 3.2). It should be noted, however, that diarrhoeal disease is not the only consequence of unsafe water and poor sanitation. These risk factors also increase children's vulnerability to waterborne parasites and other pathogens, such as polio virus, and poorly drained areas also provide opportunities for disease-bearing mosquitos to breed.

Malaria is a major threat to health in sub-Saharan Africa, where it accounts for almost a tenth of the total burden. Worldwide, the disease currently accounts for just over 2% of the burden. Children whose immunity to the malaria parasite has not yet developed are more liable to suffer severe and complicated malaria than adults, and 90% of deaths from the disease are among the young. Malaria is discussed in more detail in the following chapter, but is included here because its epidemiology, diagnosis and treatment are closely linked with the other major childhood killers.

The vaccine-preventable childhood infections—polio, diphtheria, pertussis, tetanus and measles—together still account for about 5% of the global burden and 10% of the burden in under-fives. Half of this is due to measles virus, which is linked with the deaths of about one million children a year and ranks as the eighth greatest cause of disease burden worldwide. Measles is most likely to kill undernourished, underweight children and is a particular threat in populations suffering from enforced migration and famine. Every year, half a million babies die of neonatal tetanus because their mothers are not immunized with tetanus toxoid, and more than 110 000 children are still crippled by polio virus.

Helminth infestations. Every year, between 170 million and 400 million children become infected with

Box 3.1 The Tanzanian Essential Health Intervention Project

The development of a common currency for measuring the global burden of disease and the cost-effectiveness of interventions has, in principle, enabled countries to establish health intervention priorities. However, the adoption and implementation of an essential package of health interventions entails some difficulties, such as a health system's capacity to effectively plan and implement the package, and the availability of the information needed in the planning process. To assess the feasibility and impact of such an approach at district level, Canada's International Development Research Centre (IDRC) supported the creation of the Essential Health Interventions Project (EHIP). It is EHIP's hypothesis that health intervention prioritization and resource allocation should be made on the basis of burden-of-disease and cost-effectiveness analysis carried out at the district level. EHIP has identified several steps as necessary for achieving this end:

- assess "the District Health Management Teams' capacity to establish priorities and plan the allocation of resources according to local estimates of burden of disease and knowledge of cost-effectiveness";
- determine the extent to which district health plans can be translated into effective delivery of and use of the essential health interventions;
- assess the cost as well as impact of the essential health intervention package on the burden of disease.

In an effort to promote the implementation of EHIP, the International Development Research Centre and the Tanzanian Ministry of Health organized a 12-day workshop in summer 1995 in Morogoro, Tanzania, with representatives from WHO, the World Bank, and from the districts of Morogoro Rural and Rufiji, where the project will be implemented. The objectives were: to give all participants a basic understanding of the project's objectives; to identify potentially cost-effective essential packages based on disease burden data currently available in Morogoro and Rufiji; and to develop and plan activities for the first year of the project.

Six interventions were costed: the Integrated Management of the Sick Child, the Mother-Baby package, EPI-Plus (that is, an augmented form of the Expanded Programme on Immunization with selected additions of antigens and micronutrients), STD control, impregnated bednets, and tuberculosis management. The simulations provided some comparisons of costs between districts and at the national level.

The research component of the project aims at investigating supply and demand aspects of the health system. It hopes to determine the current health system capacity and to identify those areas that need capacity-building. Its two main components are health system research and demographic and epidemiological research. The research component of Tanzania's EHIP aims at strengthening the districts' information base so as to assist the District Health Management Teams establish priorities and plan the allocation of resources based on local burden of disease estimations, cost-effectiveness, system capacity, and community preferences.

The EHIP steering committee is chaired by the IDRC and includes representatives from Tanzania and several international donors. However, the IDRC is committed to establishing full intellectual partnership with the recipient country and leaves all in-country management and planning to the host country.

one or more of three common types of intestinal nematodes: giant roundworms, hookworms and whipworms. Schistosomiasis, caused by trematodes, affects almost 100 million school-aged children each year and onchocerciasis, caused by nematodes, also affects children. Unsafe water and poor sanitation are of course risk factors for waterborne parasites. The combined burden from these parasites is comparatively small at around 1% of the total, but their impact on children is profound. Not only do worms cause anaemia and reduce growth, they also affect cognition, reducing the usefulness of precious time in school. Intestinal helminths also contribute to malnutrition.

Malnutrition is a massive, and in some respects neglected, health problem. Its causes are complex and its name misleading. In fact, this condition results not only from inadequate dietary intake, but also from repeated infections and parasitic infestations (see Box 3.2).

Malnutrition is usually identified by indicators of reduced growth, such as low weight for height or low weight for age, and by specific micronutrient deficiencies. As many as one-third of children under the age of five in developing countries are underweight, with the prevalence reaching almost 60% in South Asia. Malnutrition affects not only physical development but also cognitive performance and educability.

More than 40% of women of reproductive age in developing countries are regarded as underweight, again with the greatest concentration by far in South Asian countries. Women who are underweight when they become pregnant are more likely to give birth to underweight infants, and underweight infants are themselves at greatly increased risk of death in childhood. It now appears that they may also face higher-than-average risks of certain noncommunicable diseases in later life, at least in some circumstances.

Some 13.8 million children have reduced eyesight be-

Table 3.1 The burden of childhood disease

Condition	Burden (as % of total DALYs), 1990		
	World	Sub-Saharan Africa	India
Childhood communicable diseases			
Lower respiratory tract infections (pneumonia)	8.2	10.2	11.4
Diarrhoeal diseases	7.2	10.9	10.2
Vaccine-preventable childhood infections*	5.2	10.3	6.4
Malaria	2.3	9.2	0.4
Bacterial meningitis and meningococcaemia	0.5	0.3	0.5
Intestinal nematodes	0.4	0.2	0.3
Malnutrition (direct effects only)	3.7	3.2	4.2
Total burden from these conditions	27.5	44.3	33.4

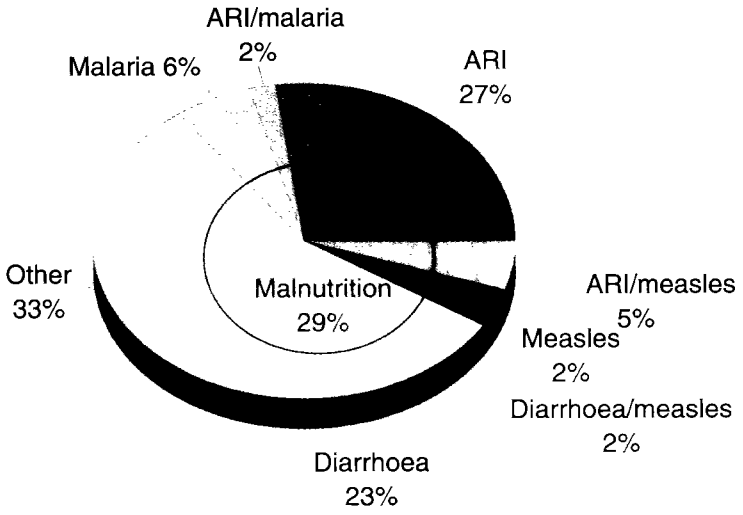
*Diseases preventable with the vaccines currently available through the Expanded Programme on Immunization: diphtheria, pertussis, tetanus, polio, measles.

Source: Annex 1

cause of vitamin A deficiency, of whom up to half a million lose their sight every year. More than 25 million people are mentally retarded as a result of iodine deficiency. Iron-deficiency anaemia affects about four in every ten women of reproductive age in developing countries.

The complex and interactive relationship between inadequate food intake and infection in causing malnutrition is of tremendous importance to public health. But its significance is often underestimated because traditional mortality statistics usually attribute deaths to one cause only and those involving infectious diseases are usually described in terms of the infection only. Similarly, the burden of disease that can be *directly* attributed to malnutrition—estimated to be about 3.7% of the global total—underestimates its overall impact on health. Since malnutrition predisposes people to infections and may produce long-term disability, it is a powerful risk factor and the *indirect* cause of

Figure 3.3 Distribution of 12 million deaths among children less than 5 years old in all developing countries, 1993



Notes: 1. Although less than 4% of deaths under age five are directly attributable to malnutrition (i.e. to being underweight or short for age or anaemic, etc.) a much larger percentage of deaths are associated with malnutrition in the sense that they occur in malnourished children and may, in part, be caused by their malnutrition. This figure points to 29% of deaths associated with malnutrition; recent studies and ongoing work suggest that the association is higher still.

2. Much of malnutrition is itself caused by the infections indicated; hence *inadequate food intake* would be associated with a (perhaps substantially) smaller percentage of deaths.

Source: Modified from material provided by the WHO Division of Diarrhoeal and Acute Respiratory Disease Control

Table 3.2 The burden of disease avoidable if access to safe water and sanitation were universal

Region	Disease burden attributable to unsafe water and sanitation (as % of total DALYs), 1990
Established market economies	0.1
Former socialist economies	0.2
India	9.5
China	2.0
Other Asia and islands	7.4
Sub-Saharan Africa	10.1
Latin America and Caribbean	5.3
Middle Eastern crescent	8.8
World	6.8
EME and FSE	0.1
Developing countries	7.6

Source: Annex 2

a much greater burden. Almost one-sixth of the entire global burden in 1990 can be attributed to malnutrition; in sub-Saharan Africa, the proportion is as much as one-third and in India, more than one-fifth (Table 3.3).

3.1.2 Current R&D investment

Research spending has been assessed for the two main childhood killer diseases—pneumonia and diarrhoeal diseases. The results indicate clearly the broad mismatch between activity and need. In 1992, total funding for *all* health research worldwide—from basic science to health policy research—reached almost US$ 56 billion. But assessments based on annual averages for three years from 1990 to 1992 indicate that each year just US$ 32 million was spent on R&D on diarrhoeal diseases relevant to the needs of low-income and middle-income countries. This is far below a tenth of one per cent of the 1992 world total. R&D expenditure on acute respiratory infections relevant to the needs of low-income and middle-income countries was estimated at between US$ 48 million and US$ 68 million (Annex 5). These amounts are insignificant compared with the size of the global burden from these conditions. And, even though the research financed by these investments was directed at low-income and middle-income countries, the outcomes of that research have often been enjoyed disproportion-

Box 3.2 Malnutrition: why hunger is only half the story

The search for solutions to the global problem of malnutrition begins with a better understanding of the relationship between its two contributing factors—inadequate food intake and infection—and their relative importance in different populations.

The dietary component of malnutrition takes several forms. An inadequate overall intake of food results in a condition frequently called protein-energy malnutrition (PEM), which is usually measured in terms of growth failure in children and underweight in adults. A number of specific micronutrient deficiencies—most importantly vitamin A, iodine and iron—also contribute to malnutrition. Other micronutrients, such as zinc, potassium, sodium, magnesium and phosphate may be important, but full data are not available. In reality, micronutrient deficiencies may also contribute to growth failure alongside PEM.

Children who are sick tend to lose their appetite, or have food withheld from them by well-meaning carers. When they do eat, their absorption of nutrients may be impaired, their energy requirements increased, and symptoms of diarrhoeal disease may lead to direct loss of nutrients. In turn, inadequate dietary intake adversely affects mucosal immunity and increases children's susceptibility to infections. As understanding of this interaction has grown, researchers have established that it is not merely additive, but synergistic and multiplicative: as a child loses weight, the risk of death climbs not in a simple additive fashion but more and more steeply. If two children begin life with the same birth weight and are exposed to the same frequency of infectious diseases, but one is better fed and cared for, the better-fed one will suffer shorter overall periods of illness and will recover and regain weight more rapidly afterwards. The less well-fed and less cared-for child will be ill for longer periods, lose more weight, and will take longer to regain it. This child is more and more likely to die.

Children who are starving clearly need more food to grow. But for children whose diet is barely adequate, the treatment of infection may be as important as getting more food. Treatment for infectious and parasitic diseases has been shown to have an important effect on weight and growth, and, in the absence of diarrhoea, there is little difference in the growth of children up to the age of three years, despite significant differences in energy intake (World Bank 1993). Mass chemotherapy to reduce intestinal worm infestation has been shown to lead to significant weight gain in a number of different populations.

Understanding the conditions under which malnutrition can be less expensively addressed through control of infection than through increasing nutrient intake is a clear research priority: resource constraints and efficiency considerations typically preclude the possibility of proceeding with a range of approaches.

Table 3.3 The burden of disease that could be avoided if malnutrition were eliminated

Region	Disease burden attributable to malnutrition (as % of total DALYs), 1990
Established market economies	0.0
Former socialist economies	0.0
India	22.4
China	5.4
Other Asia and islands	14.5
Sub-Saharan Africa	32.7
Latin America and Caribbean	5.2
Middle Eastern crescent	11.0
World	15.9
EME and FSE	0.0
Developing countries	18.0

Source: Annex 2

ately by the populations of the industrialized countries—for example, vaccines and drugs designed to protect business travellers and holidaymakers.

Our findings underscore the degree to which researchers—and those who fund them—have neglected two of today's most important global health problems. While the relationship between the size of a health problem and the amount of R&D investment cannot be expected to be proportionate, a mismatch of this degree strongly suggests a serious misjudgement of priorities and the need for reallocation of resources.

3.1.3 Assessment of research needs

A key step towards assessing needs and opportunities for R&D on this unfinished agenda is to analyse the reasons *why* poor maternal and child health persist in a population. As we set out in Chapter 1, we have identified three broad reasons to explain the persistence of a disease in a population: (a) a lack of knowledge about the disease and its determinants, (b) a lack of tools and (c) failure to use the existing tools efficiently. This tripartite analysis is a means of guiding decisions about the *types* of research and development that are most likely to pay off and the probable balance of effort that should be devoted to each of them. For example, a lack of knowledge about the disease calls primarily for strategic biomedical and epidemiological research. Lack of tools calls for biomedical research and development, and may also require the development of instruments of policy (such as essential drugs lists, pricing policies and the like) by health economists and other health policy researchers. Failure to use the existing tools efficiently calls for research and policy development to achieve either or both of the following: (1) greater *technical* efficiency, obtained through behavioural research to understand the reasons for current failures and operational research to improve the delivery of services; and/or (2) greater *allocative* efficiency, obtained by targeting resources to the problem.

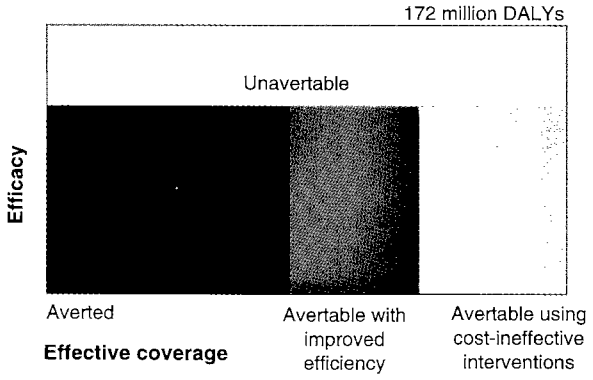
Here, we assess the relative importance of the three reasons for the persistence of the major childhood diseases. In the case of the two most significant diseases, pneumonia and diarrhoea, we have conducted quantitative analyses.

Pneumonia. The causes of lower respiratory tract infection are generally understood and the existing interventions—primarily case management with antimicrobials—are generally effective. In low-income countries, options for preventing infections are much more limited: vaccines against the two principal microbial agents, *S. pneumoniae* and *H. influenzae*, are not available. Recently, antibiotic-resistant strains of *S. pneumoniae* have emerged and, if these become widespread, control prospects could be worsened—a situation we discuss in Chapter 4. At present, however, it appears that pneumonia's persistence in the low-income countries is due to a combination of reasons (b), i.e. lack of tools, and (c) failure to use the existing tools efficiently in the population at risk.

We have further analysed the pneumonia disease burden to quantify the relative importance of each of the three reasons for its persistence. As set out in Chapter 1, the Committee used published data on the efficacy of the mix of currently available existing interventions, together with estimates provided by specialists in each field of the approximate proportion of the population that receives these interventions. These data were used to assess what proportion of the burden could be averted with better use of the existing cost-effective interventions, what proportion could be averted only with interventions that are not cost-effective, and what proportion cannot be averted now but requires new interventions (Figure 3.4). The relative size of each of these subdivisions of the burden aids decision-making about the broad types of research that are most appropriate to tackle the remaining burden.

Figure 3.4 Analysing the burden of pneumonia to identify research needs

Relative shares of the burden that can and cannot be averted with existing interventions



Note: The total DALY figure represents the number for this condition in 1990 plus an estimate of the number then averted through existing interventions.

As Figure 3.4 shows, around one-fifth of the remaining burden of pneumonia could probably be removed by more efficient use of the existing tools—for example, by making appropriate case management widely available and reducing the *inappropriate* use of antimicrobials. About another one-fifth could be averted today only with approaches that are not yet cost-effective, such as treatment with expensive antimicrobials or in tertiary facilities. Beyond these avertable parts of the remaining burden, more than a quarter of the total cannot be averted by any existing approaches.

Diarrhoeal disease is rarely fatal in the industrialized countries. Its causes, like those of pneumonia, are well understood, and effective treatments exist. In ideal conditions, oral rehydration therapy (ORT) can successfully treat 90% of cases of acute watery diarrhoea, which accounts for about half of all deaths from diarrhoeal disease. ORT could substantially reduce the disease burden if more health workers used it instead of mistakenly prescribing inappropriate antimicrobials and other drugs, and if more mothers and other carers knew when and how to use it. However, some additional tools would help: for example, there is so far no licensed vaccine against rotavirus, the principal causative agent of this form of diarrhoea in low-income countries. The burden that persists in low-income countries therefore appears to be due once again to (b) a lack of tools and (c) failure to use the existing tools efficiently.

As with pneumonia, we have analysed the burden due to acute watery diarrhoea in an attempt to quantify the relative importance of these reasons. Whereas in the case of pneumonia the results were split between the need for more efficient use of existing tools and the need for more tools, the results for this form of diarrhoeal disease show a different balance. Figure 3.5 shows that more than half of the remaining burden could be lifted now with more efficient use of existing tools—for example, through better use of ORT.

However, acute watery diarrhoea accounts for only half the total burden of diarrhoeal disease. Persistent diarrhoea requires careful dietary management, while dysentery must be treated with an effective antibiotic. Most cases of dysentery are caused by *Shigella* bacteria and as yet there are no effective vaccines to protect against these extremely common infections. Worryingly, an increasing number of strains of *S. dysenteriae* are becoming resistant to antimicrobials and the need for effective vaccines is becoming more and more pressing. Thus, while the broad reasons for persistence of the disease burden still lie mainly in a failure to use existing tools efficiently, new tools are also needed in some areas.

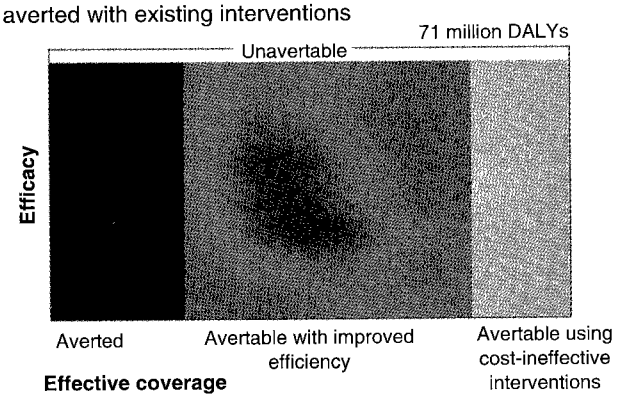
Malaria is a more complex problem. There are some important gaps in researchers' understanding of the disease process and an undoubted shortage of tools—subjects to which we return in the next chapter. However, among the principal victims of the disease—young children in rural sub-Saharan Africa—there is little doubt that case-fatality rates could be substantially lowered today with more efficient use of the existing tools, for example, through more rapid diagnosis and appropriate treatment with the affordable, first-line antimalarials.

The vaccine-preventable childhood infections. The impact of immunization on children's health has been dramatic. As a result of the Expanded Programme on Immunization, vaccines against measles, diphtheria, pertussis, tetanus and polio averted almost 3 million deaths and 138 million cases of disease in low-income and middle-income countries during 1994. When the Programme began work in the 1970s, only some 5% of children in these countries were immunized. Twenty years later about 80% of infants under the age of 12 months are being immunized against polio, diphtheria, pertussis and tetanus, and about the same percentage of infants under the age of 2 are being immunized against measles. Without these efforts, the burden of disease among under-fives would be 23% greater than it is today.

But the Programme has not yet reached its potential. Immunization coverage is still relatively low in sub-Saharan Africa—around 54% on average. In some countries, coverage is falling and in 18 countries is below 50%. The vaccine-preventable childhood infections remain, primarily, not because of a lack of understanding of the disease processes or their causes, but because of a failure to extend coverage to these groups. In practice, coverage of 100% is unlikely to be achievable, but a target of 90% has been set. Reasons for the failure to reach 90% to date are essentially due to (c) failure to use the existing tools efficiently. Among the inefficiencies are inadequate resources, administrative failures, failure to target those least likely to be immunized and most likely to become infected, missed opportunities to immunize children through health workers' misjudgements, and failure to engage with local communities. In addition,

Figure 3.5 Analysing disease burden of acute watery diarrhoea to assess research needs

Relative shares of the burden that can and cannot be averted with existing interventions



Note: The total DALY figure represents the number for this condition in 1990 plus an estimate of the number then averted through existing interventions.

there are technical failures in the service, including breakdown in the cold chain and problems with poor-quality vaccines.

But there are also some areas of need where new tools are desirable. A significant proportion of deaths from these infections occurs in very young babies below the age at which vaccines are recommended. Alternative approaches, such as immunizing pregnant women to enable them to transmit passive immunity to their newborn infants, should be explored. In addition, there are important diseases, such as hepatitis B, for which vaccines of proven efficacy exist, but which are not yet incorporated into the EPI in many countries.

Helminth infestations remain a source of disease and disability even though mass chemotherapy has proven to be effective and among the most cost-effective interventions available. Failures in the design and administration of programmes, and particularly failure to target those at greatest risk, including school-age children, account for much of the burden. High reinfection rates are an additional problem. However, the burden that remains can be attributed mainly to (c) failure to use existing interventions efficiently.

Malnutrition. This condition persists in part for the obvious reason that too many people have an inadequate food intake, but also for less obvious reasons. First, the existing interventions have not been used as well as they might. For example, the efficacy of vitamin A supplementation is clearly established and the success of breast-feeding promotion programmes has been demonstrated in a range of settings, but these interventions do not reach all those who might benefit from them. Secondly, a significant part of the burden may remain because of important gaps in the knowledge base. For example, the relative contributions of interventions to control infection and inadequate dietary intake in different epidemiological environments are not known. Likewise determinants of the relative efficacy of interventions to increase *quality* of dietary energy intake (through increased proportions of protein and fat) relative to *quantity* of intake remain to be well understood. These are some of the reasons why the wide variation in rates of underweight between different populations (for example, between South Asia and sub-Saharan Africa) are not fully explained. The importance of certain micronutrients such as zinc remains unclear, and the impact of low weight in utero and in infancy for adult health in low-income environments has not been fully assessed. Thus, in clear contrast to the other childhood conditions, malnutrition appears to persist at least in part because of reason (a), lack of knowledge of the disease process and its determinants.

Table 3.4 summarizes the above assessments and points towards broad priorities for R&D.

For pneumonia, diarrhoeal disease, the vaccine-preventable infections and helminth infestation, we conclude that the knowledge base is adequate to proceed with the development and evaluation of interventions. Efforts should, in our view, focus mainly on making existing interventions more efficient in the populations at risk through behavioural and operational R&D. For malaria, some new knowledge is needed, but the primary requirement in the currently vulnerable population is again more efficient use of existing interventions. In the case of malnutrition, even though better food supplies and more efficient use of the existing interventions to control infection and enhance micronutrient intake are of course desirable, more knowledge is also needed, suggesting that strategic epidemiological and biomedical research are priorities. In parallel, however, efforts to increase the efficiency of existing interventions should be maintained with equal intensity.

3.1.4 Opportunities for intervention development and evaluation

As set out in Chapter 1, the process of assessing opportunities for developing and evaluating interventions should consist of specifying the nature of the desired interventions, estimating their probable cost-effectiveness relative to existing approaches, and then further assessing how much it is likely to cost to develop them, how long it will take, and how likely they are to succeed. Obviously, the process can indicate interventions that are *unlikely* to be cost-effective as well as those that are attractive. (For example, the Committee has calculated that in the current epidemiological situation, development of a vaccine against one parasite—*Schistosoma mansonii*—is not likely to be a profitable investment of R&D funds as long as the drug praziquantel remains active against the par-

Table 3.4 Broad reasons for the persistence of disease burden from the five major childhood killers

Condition/risk factor	Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools efficiently
Pneumonia		++ +	+++
Diarrhoeal disease		++	++++
Vaccine-preventable childhood infections		++	++++
Malaria	+	++	+++
Malnutrition	+++		+++
Helminth infestations		+	+++++

Note: The estimated rating ranges from little importance ('+') to extremely important ('+++++'). A blank means not significant.

asite, *unless* the vaccine were to give exceptionally long-lasting protection [Supplementary paper 2].) The extent to which this type of assessment can be quantified, and how much it will, or should, continue to rely on subjective judgement, are matters for debate.

In the Committee's view, a selected small group of desirable interventions could dramatically reduce disease burden among children in low-income countries if they were applied widely. We therefore conclude that R&D should focus on them. We discuss them here, with information on their likely cost-effectiveness, the probability of their success and the necessary costs and time frames for development where available. Our selection has been informed by review of the available data, consultation and informed judgement. An ongoing effort will be needed to make the process systematic, and this list can be no more than a preliminary step.

The desired interventions are of two distinct types: packages of essential interventions, and tools to improve the content of those packages.

Highly attractive packages

- *Refine, implement and evaluate the package for the Integrated Management of the Sick Child*

  Since pneumonia, diarrhoeal disease, malaria, measles and malnutrition share many common risk factors and may be found together in the same child at the same time, researchers have argued that they may be most effectively addressed as a group rather than singly. A package of clinical services for sick children, known as the Integrated Management of the Sick Child (IMSC), has already been developed by research organizations including WHO. So far, guidelines for outpatient care have been completed but their effectiveness needs to be evaluated in the field. In addition, further guidelines for inpatient care have yet to be developed. In the view of the Committee, the enormous potential of the package to reduce disease burden, and its outstanding cost-effectiveness, are solid grounds for investing substantially in operational research to evaluate the outpatient component of the package and to develop the inpatient component in specific settings.

  In the current package, treatment guidelines for outpatients have been developed to cover the most common potentially fatal conditions, enabling health workers to focus on the whole child rather than on specific diseases. The health worker assesses every child for a set of signs and symptoms, including cough or difficulty in breathing, diarrhoea, fever, and ear problems, and assesses the child's nutrition and immunization status. Depending on the findings, the health worker can then allocate the child either for urgent referral, or specific medical treatment and advice, or simple advice for home treatment. The guidelines for the IMSC are printed in wallcharts and booklets for use in health care settings. Health workers are trained in their use.

  Properly implemented, this package could, in principle, reduce the global burden of disease by more than any other (World Bank 1993). Like other packages, it is likely to be more cost-effective than the sum of the separate services that it contains when these are given singly because, in principle, it exploits the shared use of inputs and reduces the cost to patients of obtaining services. As yet, however, the potential of this package has not been met—otherwise the burden from these conditions would not be as great as it is now. The key to maximizing the effectiveness of the package may lie in operational research.

  Table 3.5 summarizes the existing estimates of cost-effectiveness of the package in different settings. This kind of information can help to clarify how, and in what settings, this desired intervention is most likely to pay off, and where it is not worth developing. The IMSC has been estimated to cost less than US$ 50 for every DALY averted in low-income countries. By comparison, in middle-income countries, where child mortality rates are relatively low, this intervention is still cost-effective but less so than in low-income countries, at US$ 50 to US$ 100 per DALY averted (Bobadilla et al. 1994). This suggests that the package would not be cost-effective in countries where child mortality is very low, and that efforts should focus on its implementation and refinement in low-income countries.

  The development of the IMSC represents a highly attractive investment to research investors. Not only is its potential to reduce disease burden exceptionally high, it is also at an advanced stage of development. It is judged that the R&D needed to develop and evaluate the package in different settings can be achieved in a relatively short time, probably under five years,

Table 3.5 Comparisons of the likely cost-effectiveness of the package for Integrated Management of the Sick Child in different settings

Setting	Cost/ beneficiary (US$)	Cost / capita (US$)	DALYs averted per 1 000 population	Effectiveness*	Cost / DALY (US$)
Low-income countries	9	1.6	184	0.25	30-50
Middle-income countries	8	1.1	21	0.25	50-100

*Calculated by multiplying efficacy, diagnostic accuracy (when applicable) and compliance.

Source: Bobadilla et al. 1994:175

and at a cost of about US$ 15 million. Investment and effort should be focused on these tasks, including assessments of the cost-effectiveness of the package in different local settings.

- *Evaluate an immunization package augmented by additional important immunogens and selected micronutrients*

The Expanded Programme on Immunization is highly successful. However, at least two existing interventions, vitamin A supplementation and hepatitis B vaccination, could in principle be added to the existing schedule for marginal cost and potentially significant health gain. Limited experience is already being accumulated in some countries under the name EPI-Plus. The Committee views this as an attractive opportunity for wider development and evaluation.

It has been calculated that an augmented EPI that includes hepatitis B vaccine, yellow fever vaccine and micronutrient supplementation with vitamin A, and iodine where required, could be delivered for no more than US$ 17 per DALY averted in low-income countries (World Bank 1993). In middle-income countries, the cost would be slightly higher, at between US$ 30 and US$ 50 per DALY averted, but still a very good "buy" for health. The opportunity to develop and evaluate such an augmented programme is excellent: costs are likely to be low and the time needed for development is probably less than five years. Some limited trials to assess the safety of administering vitamin A at the same time as immunization should be incorporated.

In addition, as we discussed earlier, alternative approaches to preventing severe infectious diseases (such as pneumonia) during the first three months of life should be investigated. Possibilities include the immunization of pregnant women, or women of childbearing age, to protect newborn infants through the transfer of antibodies from mother to child, as currently practised for the prevention of neonatal tetanus.

Packages for further investigation

Work should also continue on evaluating the potential of packages for which little information is currently available, but which appear to merit R&D investment because they are expected to provide cost-effective ways of reducing disease burden. For example:

- *A Healthy Schoolchild package*

This would focus on reducing the levels of helminth infestation—including those that cause schistosomiasis and onchocerciasis—in children of school age. Although the disease burden from these helminths is comparatively low, the cost-effectiveness of existing interventions is exceptionally high. Mass chemotherapy delivered annually to schoolchildren is estimated to cost less than US$ 25 per DALY averted in low-income countries. By reducing the burden of helminth infestation, governments may be able to invest in their countries' human capital by improving children's cognitive performance and educability. Additionally, some micronutrient supplementation might be feasible.

- *A Healthy House package*

Improved shelter, safe drinking water and proper sanitation together form the pillars of preventive child health programmes. A package of interventions might emerge from collaboration between the health sector and others (e.g. municipal engineering departments, community groups) to design and modify the *physical* environment of homes for maximum health, for example through demonstrating latrine construction, water source protection and the provision of soap, and interventions to reduce indoor air pollution, as well as reimpregnation of bednets and some other modest vector control activities. Much is known about the risks of unsafe water and poor sanitation and shelter, but appropriate technologies for reducing those risks need to be identified at national and local level. These might include small-scale water disinfection systems, further improvements in latrine design and cost-effective approaches to providing proper shelter. If this R&D were to pay off in making homes safer, households could see significant reductions in diarrhoeal disease and other childhood infections.

Tools to improve package content

- *Develop and promote wider use of insecticide-impregnated bednets*

Bednets, used properly, have been shown capable of reducing child deaths from all causes by one-quarter in areas where mortality is high. If a programme of bednet use is to be worth developing, however, it is desirable to demonstrate that it can at least compete with or supersede existing interventions. Comparative cost-effectiveness estimates for bednets and another existing preventive intervention against malaria, chemoprophylaxis, have been performed for this Report. In this case, there are data from The Gambia for at least some of the intervention types compared and additional studies in Burkina Faso, Ghana and Kenya. Analyses based on those data show that in a high-mortality area, impregnated bednets would be much more cost-effective than chemoprophylaxis, buying years of healthy life for approximately half the price of chemoprophylaxis. Obviously, the cost-effectiveness depends on a number of factors, such as how dependably householders use bednets as intended. A range of different scenarios are set out in greater detail in Supplementary paper 2. As the sum-

Box 3.3 Best buys for R&D for child health

Strategic research

- Understand the relative importance, in different environments, of increased nutrient intake and controls on infectious disease as means to reduce malnutrition.

Package development and evaluation

- Evaluate and refine the package for the Integrated Management of the Sick Child.

New tools to improve package content

- Evaluate the efficacy and optimal dosage of candidate rotavirus vaccine in low-income countries.
- Evaluate the efficacy of candidate conjugate pneumococcal vaccine and existing Hib vaccine in low-income countries.
- Develop and evaluate ways to increase efficiency in the Expanded Programme on Immunization by simplifying delivery and maximizing use of opportunities for immunization.
- Evaluate promotion of insecticide-impregnated bednets, possibly for inclusion in a future Healthy House package.

mary data presented here show, however, the cost-effectiveness remains surprisingly high even in far from optimal conditions (see Table 3.6).

The payoff from developing this intervention in high-mortality settings is clearly great. It is considered that development work in assessing the actual efficacy and cost-effectiveness of selected different kinds of programmes could proceed in under five years and for very modest costs.

- *Complete trials in low-income countries of appropriate vaccine against rotavirus*

The analysis of research needs for acute watery diarrhoea suggested that existing interventions, such as oral rehydration therapy, could remove much more of the burden of diarrhoeal disease than they currently do. However, in the judgement of public health researchers, the existing mix of interventions is unlikely to eliminate the problem even under optimal conditions. A further desirable intervention, in the view of the Committee, is to complete trials of candidate rotavirus vaccines in low-income countries. A vaccine which gives 80% protection against severe rotavirus diarrhoea in trials in the United States has so far shown much lower efficacy in developing countries. Trials at higher doses are currently under way. A key requirement for further R&D is to establish, in addition to safety and efficacy, the optimal dose and the potential for delivering the vaccine within the Expanded Programme on Immunization. If 80% efficacy were achieved, the estimated cost-effectiveness would be exceptionally high: around US$ 10 per DALY averted. Since more than one candidate vaccine is already in advanced development, and others based on equally promising approaches are under earlier stages of development, the likely payoff is high, the time frame short and the investment requirement relatively low.

Clearly, a vaccine against *Shigella dysenteriae* is also highly desirable and becoming more urgent with the spread of antibiotic-resistant strains. However, rotavirus vaccines are at a more advanced stage of development and therefore, according to the criteria adopted by the Committee, they are a more promising R&D investment at this time.

- *Complete trials in low-income countries of existing appropriate vaccines against* Haemophilus influenzae *and* Streptococcus pneumoniae

Since the licensing of conjugate vaccines for *H. influenzae* in the United States and many northern European countries, the infection has all but disappeared as a public health problem in those countries. The high efficacy of Hib vaccines appears to have been confirmed in Chile, and a trial in The Gambia is now nearing completion, with results expected in late 1996. Although cost-effectiveness estimates in low-income countries are not yet available, the Committee considers this intervention is likely to be cost-effective in areas where child mortality from pneumonia is high. Trials should be continued and if the vaccine's

Table 3.6 Comparisons of the likely cost-effectiveness of two malaria interventions

(Cohort analysis, 10 000 newborns)

Option	Cost (US$)	DALYs averted	Cost per DALY (US$)
Impregnated nets (government distribution, 50% compliance)	143 000	10 400	14
Chemoprophylaxis (government distribution)	79 000	2 800	28

Source: Supplementary paper 2. Based on cohort of 10 000, followed from birth to age 5, West Africa model life tables. Cost of nets US$ 9.77; costs of government bednet programme including insecticide and reimpregnation, and costs of chemoprophylaxis programme, taken from Picard et al. 1993. Assume 2 children sleeping under each net. Further assumptions (e.g. on efficacy of each intervention) detailed in Supplementary paper 2.

efficacy is confirmed, further studies should investigate the potential cost-effectiveness of delivering it as part of the EPI in a range of different countries.

New conjugate vaccines for *S. pneumoniae* are currently under development and trials in low-income countries are expected soon. A more detailed discussion of these vaccines can be found in Chapter 4.

- *Increase the efficiency of the Expanded Programme on Immunization*

The vaccines given within the EPI are among the most cost-effective of all interventions. Measles vaccine buys years of healthy life for less than US$ 10. Polio, diphtheria, pertussis and tetanus together cost less than US$ 25 for each DALY averted. If health workers made use of all opportunities for immunizing children, and if the delivery of vaccines were made simpler, this already excellent set of interventions could be made even more cost-effective. At present, five contacts are required between health worker and child. If there were only one (i.e., if all immunization requirements could be met at once), costs could be cut by as much as 70% (World Bank 1993). Steps towards improving the technical content of the package could include reducing the number of doses of vaccine required (and ensuring that any new antigens incorporated into the programme can be given at the same time as those already incorporated). In the longer term, the possibility of potential "one-shot" vaccines and other initiatives deserves investigation. Although the time frame and costs of such activities are more difficult to estimate, the expected payoff in reducing costs of the EPI programme are so great that a relatively large investment is merited.

3.2 Achieving safe motherhood

In traditional public health circles, women are often discussed only in relation to their role as reproducers. Women are more than mothers, however, and have the right to good health in their own right—including the right to *avoid* unwanted children. However, the particular risks that many women face through their reproductive role form a major barrier to their overall health. In the Committee's view, R&D that results in better reproductive health for women will enhance their health overall. While each chapter of the Report is concerned equally with men and women and their risks for all types of disease, in this section we focus on women's reproductive health needs.

Good reproductive health is about more than avoiding disease. According to the definition adopted by WHO, it is also about the ability to have a safe, responsible and fulfilling sex life and the freedom to decide if, when and how often to have children (Khanna, Van Look & Griffin 1994). Among the necessary conditions for this good reproductive health are the right of men and women to learn about and obtain safe, effective, affordable and acceptable methods of family planning, and the right of women to have appropriate health services to enable them to go through a safe pregnancy and birth. Yet all too few women in the poorest countries find these services within their reach. The immediate consequences are unacceptably high rates of unwanted pregnancies, unsafe abortions, complications of pregnancy and delivery, and infants dying in the first week of life. In the longer term, children born to women in these circumstances also suffer poorer health. In addition, HIV/AIDS and other STDs are important causes of poor reproductive health: they are discussed in the next chapter.

3.2.1 The magnitude of the burden

Only some of the effects of poor reproductive health can be quantified in terms of disease burden, death or other measures of mortality and morbidity. These include the number of women who die in delivery, the number of babies who die in the first week of life, deaths resulting from ectopic pregnancy and deaths resulting from unsafe abortions. Excess fertility may result, indirectly, in a measurable burden of ill-health to children: those who are born either too soon after an older sibling, or into a family where there are already more children than can be reasonably fed, cared for and educated, are at greater risk for a number of diseases. It is much more difficult, though, to quantify the impact of other distressing outcomes of poor reproductive health. For example, women may become permanently incontinent as a result of a bad delivery, or may suffer fistulae in the reproductive tract that not only interfere with sexual intercourse but bring social stigma. Equally, it is difficult to quantify the benefits to couples of contraception that not only "averts a birth" but also improves quality of life for the entire household. Table 3.7 summarizes the burden of those conditions that can be measured in terms of DALYs.

Excess fertility. An estimated 120 million fecund women are not using contraception even though they want to avoid becoming pregnant. Surveys within individual countries suggest that most women want smaller families than the current average family size in their country, even though in some countries, particularly in sub-Saharan Africa, the gap between desired and actual family size is small. In addition, an estimated 300 million couples are not satisfied with the methods of contraception available to them. In part because of this dissatisfaction, many couples stop using their contraceptive method or do not use it properly. Up to 30 million unintended conceptions occur every year among people using contraception.

In the poorest countries, the capacity of the services is inadequate to meet need. In many sub-Saharan African countries, for example, family planning services are able to meet less than a third of the potential demand. As well as desiring fewer children, many couples want to

space their births better. Evidence suggests that babies born within 24 months of an older sibling are more likely to suffer ill-health or to die before they reach five years of age.

Unwanted pregnancies not only carry heavy emotional and practical costs to women and their families; they may also be dangerous and impose a heavy economic burden on the population as a whole. Worldwide, it is estimated that 25 million of the 55 million abortions performed each year are done under unsafe conditions. The complications kill some 70 000 women. A study in Tanzania found that symptoms diagnosed as likely to be due to the complications of abortion were the most common reasons for admission to gynaecological wards.

Complications of pregnancy and childbirth. Having a baby carries risks in the healthiest populations, but the difference in the degree of risk to women in developed and developing countries is among the starkest of the global gaps in health. In the established market economies, there are just 7 maternal deaths for every 100 000 births. In low-income countries there are more than 500. Girls and young women are at particularly high risk. Maternal complications include haemorrhage, sepsis, hypertensive disorders of pregnancy, eclampsia and obstructed labour. The death of a woman puts her surviving children at risk, too: such children are 50% more likely to die before they reach age five than had their mother lived.

Perinatal complications, which are inextricably linked to those affecting the mother, include birth asphyxia, birth injuries, sepsis and prematurity. In the assessments conducted for this Report, this category also includes low birth weight. Perinatal complications can also include a number of communicable diseases acquired during pregnancy or delivery, including STDs, neonatal tetanus and hepatitis.

Together, maternal and perinatal conditions account for 9% of the global total, and about 12% of the total in India and in the Middle Eastern crescent.

3.2.2 Assessment of research needs

Couples—and women and girls outside stable relationships—continue to suffer all these effects of poor reproductive health despite the existence of a number of methods of contraception and effective algorithms for the management of safe pregnancy, childbirth and care of infants in the first week of life. As above, we have analysed the reasons for the persistence of the burden as a step towards identifying the probable balance of R&D that is likely to bring results. We have analysed each condition separately.

Excess fertility. Inefficient use of the existing tools is a major part of the problem. Too few women who want contraceptives have access to them, either because of shortages of supplies or inadequate services. Many women and girls lack access to information about how to avoid pregnancy and many health workers lack the training to meet their needs. In addition, the available range of methods for family planning offers couples inadequate choice. In particular, there is much unmet demand for a wide choice of long-term methods, postcoital methods for both emergency and regular use, and male methods.

These reasons point to two overall types of R&D: research aimed at improving the efficiency of existing services in family planning, and the development of new and acceptable methods of contraception. The need for new knowledge is relatively small, except in two areas. Behavioural strategic research is needed to better understand perceived needs in different communities. Secondly, some strategic biomedical research is required, both into mechanisms of spermatogenesis, sperm maturation and fertilization that would lay the foundations for developing a wider choice of male contraceptives, and also into mechanisms of implantation which would lay the foundation for developing postcoital methods for emergency and regular use.

In general, however, the knowledge base is adequate to enable most of the relevant intervention opportunities to be assessed. Some selected interventions are discussed below, in section 3.2.3.

Table 3.7 The burden of maternal and perinatal ill-health

Condition	Burden (as % of total DALYs), 1990		
	World	Sub-Saharan Africa	India
Maternal conditions (obstructed labour, abortion, maternal sepsis, maternal haemorrhage, hypertensive disorders of pregnancy)	2.2	3.2	2.6
Perinatal conditions (birth asphyxia, birth trauma, low birth weight)	6.7	6.5	8.8

Note: A background paper to this Report (Jamison, Jamison & Shibuya, forthcoming) presents an alternative methodology for constructing DALYs that would add in DALYs from late fetal death but have the overall effect of markedly *reducing* DALYs arising from perinatal conditions relative to maternal conditions.

Source: Annex 1

Maternal and perinatal complications. The gap between maternal mortality rates in the industrialized countries and in the low-income countries indicates that knowledge about how to deliver a baby is not the problem. Once again, inefficiencies in the use of existing interventions, such as algorithms for the early detection of complications of pregnancy and for safe delivery, must be held to account. Essential obstetric services, such as a referral plan for home deliveries, are also lacking in many communities. In addition, there is a shortage of *appropriate* tools to facilitate safe and convenient obstetric practice in low-income populations.

Table 3.8 summarizes the discussion above.

As with the childhood conditions, the Committee concludes that the predominant effort in R&D should therefore be directed at operational research to develop, evaluate and improve the efficiency of the existing interventions for family planning and maternal health in low-income populations. In addition, a significant amount of effort needs to be devoted to the development of new tools.

Box 3.4 Best buys for R&D on maternal and perinatal health

Package development and evaluation

- Develop, evaluate and refine the Mother-Baby package for pregnancy, delivery and neonatal care.
- Evaluate the implementation of a range of family planning packages offering a wide choice of methods.

New tools to improve package content

- Develop new contraceptive methods, particularly to widen the choice of long-term but reversible methods, postcoital methods for regular and emergency use, and methods for men.

3.2.3 Opportunities for intervention development and evaluation

As before, the Committee has identified a small number of key interventions that have the potential to reduce disease burden and improve the quality of life for millions of women and their families.

- *Develop and evaluate a package of services for mother and infant for antenatal care, delivery and the first week of life: the "Mother-Baby package"*

For safe motherhood, the priority is to develop existing services into an integrated form that can reach all who need them at the highest level of quality possible. The World Bank has estimated that the extension of prenatal, delivery and postpartum care to 80% of the world's population would reduce by 40% the burden of disease associated with unsafe childbirth. In low-income countries the cost-effectiveness of such a package is expected to be high at between US$ 30 and US$ 50 per DALY averted (Bobadilla et al. 1994). However, although WHO has identified the desirable contents of such a package, their cost and effectiveness in different administrative environments remains to be evaluated. And while researchers have good overall knowledge of what constitutes good, essential care in the delivery and the postpartum period there is much less understanding of the types, and degree, of intervention that are essential in antenatal care. Indeed, research in the EMEs is only now evaluating the outcomes of different programmes of antenatal care and has only recently established which obstetric practices benefit patients and which do not.

The Mother-Baby package which is now being developed by WHO incorporates the provision of information and services for family planning, antenatal care, including the diagnosis and treatment of STDs, and the detection of any pregnancy complications; the ensuring that all birth attendants have the necessary skills, knowledge and equipment to perform a clean and safe delivery and to give essential postpartum care to mother and baby; and the provision of essential obstetric care for all high-risk cases and emergencies. Properly implemented, the package could avert about half of the maternal deaths that occur each year (World Health Organization 1995). Communities should be involved in developing, implementing and evaluating the services provided.

Among the R&D priorities identified by WHO for the development of the package are: studies of the delivery of services to women and girls with the aim of identifying targets for improvements in the quality of care; the assessment of appropriate technologies,

Table 3.8 Broad reasons for the persistence of the burden of poor reproductive health

Condition	Inadequate knowledge of the physiological processes	Inadequate tools	Failure to use existing tools efficiently
Excess fertility	+	+++	++
Maternal complications		+	+++++
Perinatal complications		+	+++++

Note: The estimated rating ranges from little importance ('+') to extremely important ('+++++'). A blank means not significant.

such as a simple partograph, that can be used to monitor labour outside the hospital environment or the adaptation of simple sterile pre-loaded injection capsules to enable health workers to give oxytocin in stage III of labour, with the aim of reducing postpartum haemorrhage and minimizing the risk of sepsis; and ultimately, the development of guidelines for health workers. The expected costs and time frame of developing the package are moderate.

- *Evaluate the practical implementation of alternative family planning packages, particularly those offering a wider choice of contraceptive methods*

A package of existing family planning interventions, including information on sexual health, access to contraceptive methods and regular monitoring where appropriate, can be delivered for US$ 20 to US$ 30 per DALY averted in low-income countries. Since good reproductive health has wider benefits to women and families, however, this assessment may underestimate the value of such services to human well-being and economic development. To improve the availability and choice of family planning, development and evaluation of services are needed, not only at the level of policies to increase the availability of contraceptives themselves, but also to make improvements in the interactions between service providers and clients. Efforts should focus on developing acceptable and effective services for particularly vulnerable groups, including teenage girls. Once again, local communities' views should be made central to this research.

R&D efforts are needed both for developing male methods of contraception and for better and more acceptable female methods. The aim should be to increase the choice of cost-effective options to people in *low-income countries*, particularly for those who want long-term but reversible contraception. The cost-effectiveness of such interventions is difficult to estimate because the benefits they bring go much further than simply averting disease burden. However, it is likely that the development of methods that are accessible and acceptable would prove an excellent investment, given that inadequate choice or dissatisfaction with a particular method has been shown to lead to reduced use and thus increased risk of excess fertility. There is a strong case, therefore, for continued investment in the development of products already at advanced stages of development, such as postcoital contraceptive methods for regular as well as emergency use, and alternative injectables with reduced side-effects.

3.3 Chapter summary and recommendations

The infectious diseases of childhood, malnutrition and poor reproductive health are massive burdens on the people of low-income countries and thus on global health. They account for well over one-third of total disease burden, and more than half of the burden in sub-Saharan Africa. A set of packages of existing essential health interventions, such as the package for the Integrated Management of the Sick Child, could in principle avert more than one-third of the burden of ill-health among children in low-income countries for less than US$ 12 per head per year. R&D efforts on this unfinished agenda should concentrate on developing and evaluating certain packages of essential services in low-income countries to increase the efficiency of existing interventions. This will involve mainly operational research and behavioural studies. In addition, a lesser, but significant, degree of investment is needed to develop new tools to improve the content of some packages. This will call for primarily biomedical research. Finally, the health sector must assess the potential for collaboration with other sectors such as education and agriculture in reducing risks and enabling people to take greater control of their health.

Recommendations

1. Investors should increase resources for developing and evaluating selected essential packages of interventions, such as the package for the Integrated Management of the Sick Child and the Mother-Baby package, in low-income countries, as potentially highly cost-effective means to achieve massive gains in the health of the poor.

2. A significant portion of the burden of childhood infectious diseases and poor maternal and perinatal health still cannot be addressed by existing tools. New tools are needed—for example, vaccines against certain respiratory and diarrhoeal infections, and a wider choice of contraceptive methods. Current efforts, both in strategic research and in new product development, are inadequate to deal with these challenges. Investment in these areas now holds the promise not only of improving health but also of reducing costs.