# 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*

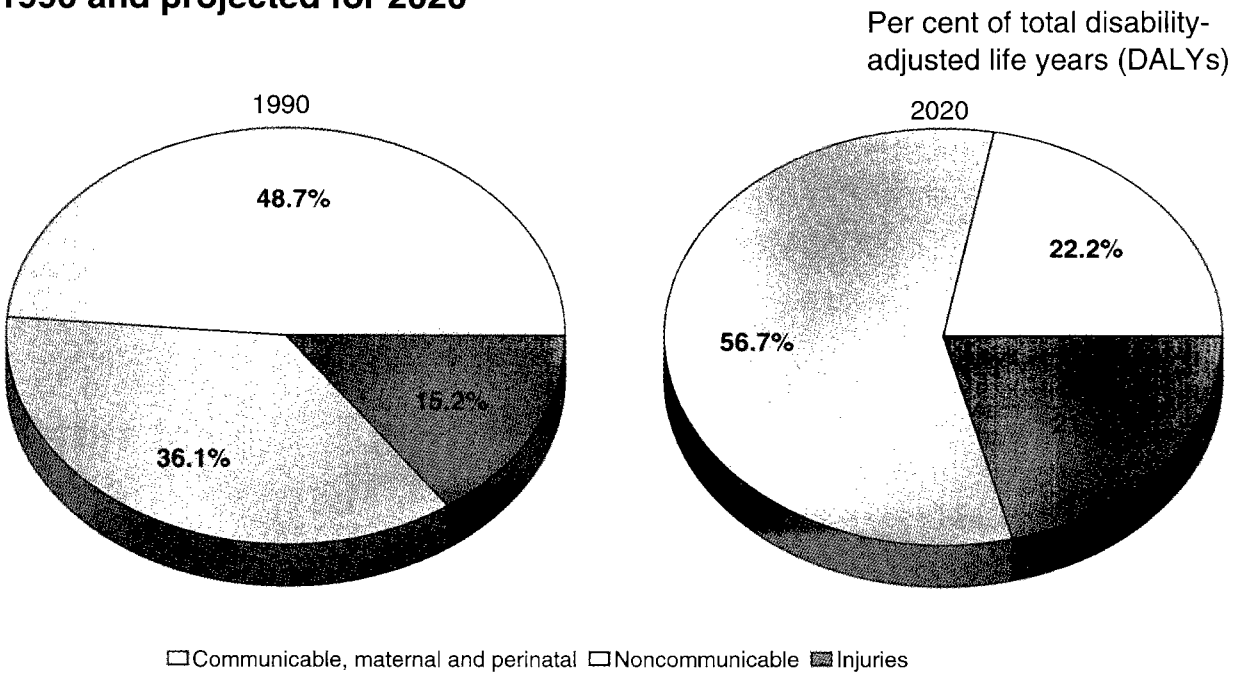
Millions of people are still denied adequate health care, and population health needs are growing more complex. Governments in both rich and poor countries are struggling to meet a rising demand for services in the face of spiralling costs, yet their task is being hampered by a lack of information about 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*

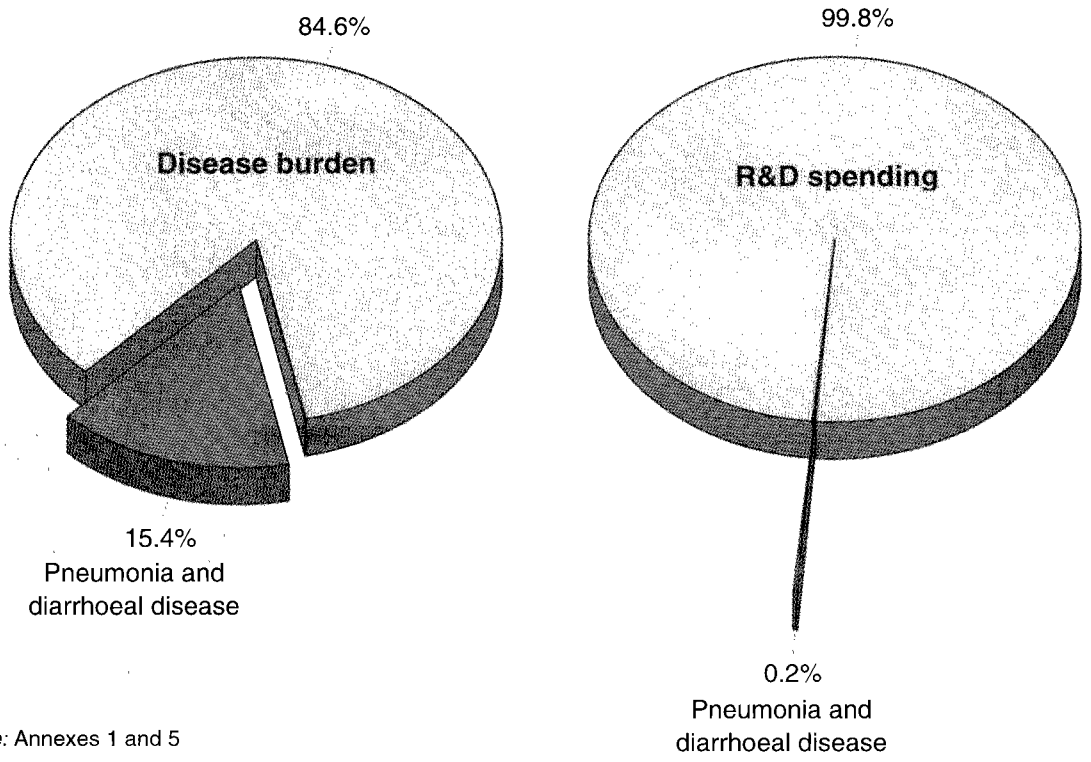
In principle, the world already knows what to do about most childhood infections and about making pregnancy and childbirth safe. Considerable suffering, waste and loss of life could be avoided now with existing interventions, often at low cost, and with striking potential gains for global health. But 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*

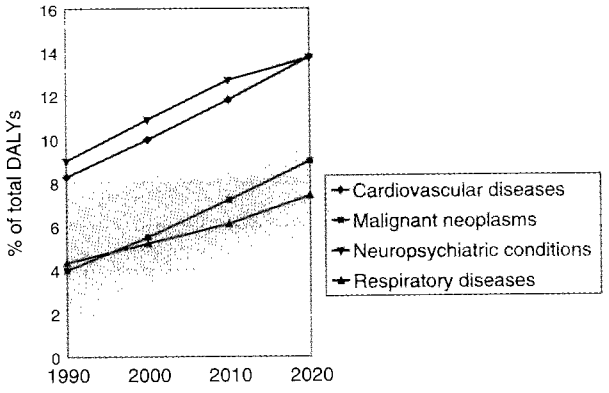
In 1990, noncommunicable diseases accounted for just over 40% of the total loss of healthy life worldwide. By 2020, their share is expected to reach about 60%, with the brunt of the increase being borne by the low-income and middle-income countries. In India, the burden of all noncommunicable diseases 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.

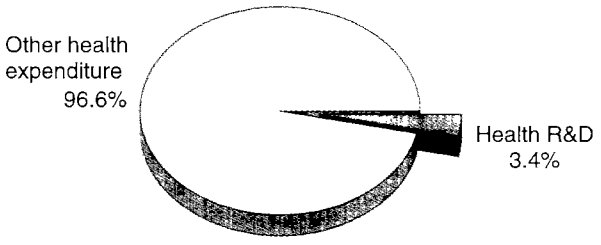
**The untapped strength of the private sector.** The international health system has failed to engage the capacity and skills of the private sector in working to improve the health of poorer populations. The private sector's traditional contribution to health lies in the development of new drugs, diagnostics, 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.