Chapter 4

The continually changing threat of infectious disease

From the Second World War until the late 1970s, the health community perceived infectious diseases as a receding threat. The development of antimicrobial drugs, immunization programmes and the better nutritional status enjoyed by the populations of the industrialized countries made it appear, for a short while, as if human progress over microbes might be inexorable. But the events of the 1980s and 1990s have quashed this optimism. The emergence of HIV/AIDS, the spread of drug-resistant strains of organisms such as *Mycobacterium tuberculosis, Plasmodium falciparum* and *Staphylococcus aureus*, and the resurgence of once-controlled diseases, such as diphtheria in the former Soviet Union, have combined to deliver an unwelcome message: many battles may have been won, but not the war.

The relationship between humans and microbes has always been a dynamic one. Either through genetic changes in a microbe that alter its relationship with its host, or demographic and behavioural factors that offer the microbe new opportunities (see Table 4.1), the balance of power shifts continuously. For all the current intense public interest in "emerging and re-emerging" diseases—a broad term that covers everything from newly identified infections to the resurgence of old enemies—there is nothing new about this continuous flux.

At the end of the 20th century, however, two factors have coincided to cause particular concern. The first is that widespread use and misuse of antimicrobials since the 1940s has led to the emergence and spread of growing numbers of drug-resistant pathogens. The second is that demographic changes have been rapid and on a massive scale. The global trends towards urbanization, higher-density settlements, and mass, rapid intercontinental travel are just some examples of the ways in which humans have changed their interactions with

Table 4.1 Factors in the emergence and re-emergence of infectious diseases

Broad factor	Examples of specific factors	Examples of diseases
Microbial adaptation and change	Antigenic drift; plasmid transfer; response to specific selection pressures in environment.	Antigenic drift in influenza; subtype divergence in HIV-1; emergence of antibiotic resistance in, for example, *Streptococcus pneumoniae, Mycobacterium tuberculosis, Shigella dysenteriae, Staphylococcus aureus, Neisseria gonorrhoeae*; emergence of drug resistance in *Plasmodium falciparum.*
Human demographics and behaviour	Societal events: population growth and migration (especially urbanization); war or civil conflict; urban decay; sexual behaviour; changing eating habits and technologies for food processing and bulk food preparation; intravenous drug use; use of high-density facilities; international travel; illegitimate trade.	Spread of HIV and other STDs; spread of TB, malaria, Lassa; spread of leishmaniasis in Sudan, India; cholera in refugee camps; increase in microbial food poisoning in the industrialized countries.
	Health system failures: breakdown or curtailment of prevention/treatment /vector control programmes; inadequate laboratory facilities, infection control measures or health care capacity.	Spread of drug-resistant strains of bacteria and malaria parasites; nosocomial transmission of microbes; resurgence of tuberculosis in the established market economies; resurgence of diphtheria in Russia and Ukraine; resurgence of African trypanosomiasis in Zaire; measles epidemics in the Americas.
	Changes in land use: e.g. agriculture; dams; changes in water ecosystems; deforestation/reforestation; famine.	Schistosomiasis; malaria; Argentine haemorrhagic fever; Hantavirus pulmonary syndrome; *possible* factor in emergence of Ebola virus.

Note: Categories are not mutually exclusive: several factors may contribute to the emergence of a disease.

Source: adapted from Satcher 1995:10

Table 4.2 Major microbial threats

Condition	Burden (%), 1990
Pneumococcal disease	3.5*
Tuberculosis	2.8
Malaria	2.3
STDs excluding HIV	1.4
HIV	0.8

*Based on a conservative estimate of the proportion of all DALYs caused by acute respiratory infections that can be attributed to pneumococcus.

Source: Annex 1

land, other species and with each other, setting the scene for different patterns of transmission of microbes.

In Chapter 3 we argued that much of the burden from communicable diseases could be removed through better use of existing interventions. There is, however, an important caveat: what works today will not necessarily work tomorrow. Some of the existing interventions, such as antimicrobials for pneumonia, may fail in the future if the severity and extent of drug resistance increases. This disturbing possibility underscores the need for continued efforts in the surveillance of infectious diseases and in the ongoing search for new technologies to control them.

The projections of disease burden to 2020 generated for this Report are based on simple econometric variables such as income per capita and human capital (Annex 1). With the exception of HIV, where historical data are inadequate and a separate projection model has been used, they are based on trends observed over the past few decades. They assume that the general decline in communicable diseases that has been observed since 1950 will continue as a function of rising income, increased education and technological development. As yet, there is little unequivocal evidence that the spread of drug-resistant strains of important microbes is causing an increase in case-fatality rates from the diseases that they cause, and therefore the projections have not taken into account any scenario in which drug resistance leads to higher death rates. However, the possibility of such scenarios cannot be ruled out, particularly if technological development fails to keep pace—as it has in the recent past—with the selection of resistant strains. In those frightening circumstances, the gains of recent decades could be halted or even reversed.

Vigilance against microbial threats therefore remains necessary as a basic insurance policy against the unexpected. How, though, should researchers be expected to decide which microbes deserve special attention? While disease *control* authorities and health service providers can to some extent prepare for the arrival of unexpected epidemics, for example by training capacity in microbiological surveillance and in infection control techniques, it is unlikely that health *researchers* can prepare cost-effectively to respond to all potential microbial threats. However, researchers can make it their business to monitor trends, maintain capacity in microbiology, and to research and develop new tools for *known* microbes:

a) whose contribution to disease burden is already significant, and
b) whose impact in future may reasonably be expected to worsen, for specific reasons, if new tools to prevent, control or treat them are not made available. Those reasons might include: the existence, anywhere, of drug-resistant strains of those microbes; a lack of effective vaccines, drugs or other control measures; and/or evidence that demographic and/or behavioural trends are likely to favour their spread.

This chapter focuses on four communicable diseases or disease clusters whose causative organisms constitute, in the view of the Committee, serious threats to global health in coming decades for one or more of the reasons listed above. They are:

- tuberculosis;
- pneumococcal disease (caused by *Streptococcus pneumoniae*, commonly called pneumococcus);
- malaria; and
- sexually transmitted diseases (STDs) including HIV/AIDS.

It will be clear that there is some overlap between Chapters 3 and 4. As Chapter 3 showed, pneumonia and malaria both are primarily threats to children and much of the current burden from these conditions could be avoided with better use of the existing interventions against them. Equally, sexually transmitted diseases are a major cause of reproductive ill-health in women in low-income countries, and, once again, their burden could be sharply reduced by better use of existing interventions. Despite this obvious overlap with the unfinished agenda of maternal and child health, the Committee has chosen to focus on specific microbes in greater detail here because they display particular characteristics that threaten the prospects for maintaining control of them in future, and therefore require additional R&D responses. (See Table 4.2.)

4.1 Tuberculosis

4.1.1 The magnitude of the burden

Among infectious diseases, tuberculosis is the single biggest killer of adults, and is responsible for more than a quarter of avoidable adult deaths. At any one time around the world, some 20 million people are sick with TB and, over the next decade, an equal number are likely to die because of it. One-third of the world's population is infected with the causative organism, *Mycobacterium tuberculosis,* and in some regions and age groups the proportion is even higher. In South Africa, for example, more than half of all adults aged between 20 and 59 are estimated to be infected (Sudre, Ten Dam & Kochi 1992). Because TB is primarily an adult disease, its impact on

productivity is more profound than that of most other communicable diseases. TB ranks seventh among all causes of disease burden worldwide and alone accounts for almost 3% of the total burden. Only one other single microbe, pneumococcus (see below), plays such an important role in global ill-health, and none features so large in adult ill-health. As the adult proportion of the population increases with the demographic transition, the proportion of the total disease burden attributable to TB is likely to increase too.

People are more likely to develop TB disease if they live in poor housing, overcrowded conditions, and are undernourished. Individuals infected with both *Mycobacterium tuberculosis* and HIV are about 30 times more likely to develop TB disease than those infected with *M. tuberculosis* alone. In 1994, an estimated 5.6 million people were infected with both pathogens and TB is now the leading cause of death among HIV-infected people.

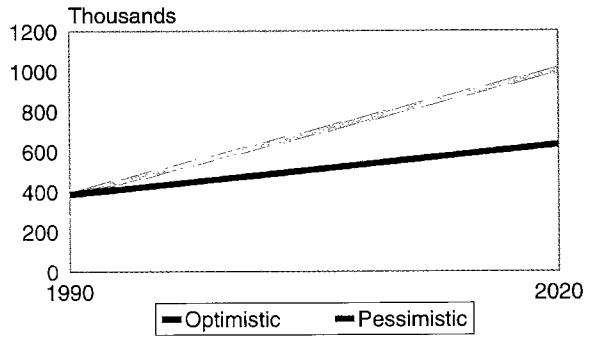
The emergence and spread of multidrug-resistant (MDR) strains of *M. tuberculosis* in New York and other urban U.S. centres during the 1980s and early 1990s caused widespread concern. MDR strains have also been recorded in European countries, the former socialist economies and South Africa and there are reports of high rates of resistance in certain Asian countries. Worldwide, the prevalence of MDR strains is not known, but WHO estimates that more than 50 million people are already infected with such strains.

The resurgence of TB in the United States has stimulated renewed efforts to speed up diagnosis, improve the delivery of therapy and reduce transmission. The systematic practice of *directly observed treatment, short-course* (DOTS), combined with other efforts, appears so far to be improving cure rates and reversing the epidemic in New York. However, the potential threat from MDR strains, not only in the United States, but more particularly in low-income and middle-income countries where the prevalence of TB and HIV are much higher, remains extremely serious. The cost of treating a case of multidrug-resistant TB in New York City is more than 100 times higher than the cost of treating a drug-sensitive case: US$ 250 000 compared with about US$ 2000.

Projections to 2020 indicate that the burden from TB in sub-Saharan Africa will double from its 1990 level of 3.4% of the region's total DALYs to reach almost 7% by 2020. In India, where TB currently accounts for nearly 5% of the burden, there will be a less precipitate, but significant, rise to around 7%. It should be noted that these figures cover only HIV-negative cases of TB. HIV-positive cases are accounted for under HIV; but the caseload in HIV-negative people will also increase because the growing burden in people infected with HIV will increase the opportunities for wider transmission of TB.

In addition to the projections of disease burden, projections of deaths have also been generated, under a range of optimistic and pessimistic assumptions about income and human capital (Annex 1). Under the optimistic scenario, deaths from TB in sub-Saharan Africa will increase from 386 000 in 1990 to 632 000 in 2020.

Figure 4.1 Tuberculosis deaths in sub-Saharan Africa: alternative projections



Source: Murray & Lopez 1996 and forthcoming

Under the pessimistic scenario, the total could climb to just over one million (Figure 4.1) (Murray & Lopez 1996 and forthcoming).

4.1.2 Current investment

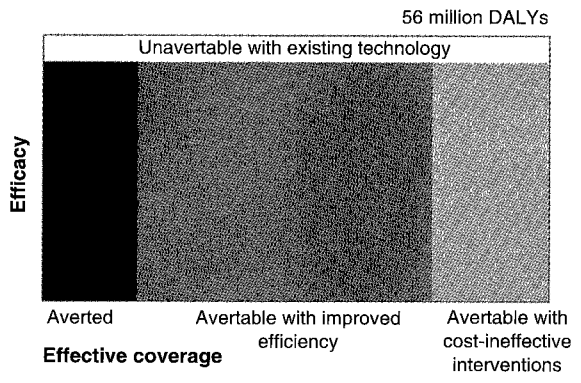
The Committee has assessed spending on R&D directly related to TB. Based on averages for three years between 1990 and 1992, we estimate that R&D on TB received between US$ 19 million and US$ 33 million per year. This is less than 0.1% of the total spent on health research in 1992 (Annex 5). Moreover, much of this money is dispersed in very small allocations from a mass of small granting bodies to a large number of small implementing institutions. As with the major childhood infectious diseases, this sum represents a severe mismatch between need and activity—particularly given the expected impact of HIV on TB. While the relationship between the magnitude of the disease burden and the amount of R&D investment in it cannot be expected to be proportionate, a mismatch of this degree once again strongly suggests a serious misjudgement of priorities.

4.1.3 Assessment of research needs

In order to identify priorities for R&D on the massive problem of TB, we have analysed the reasons for its persistence. Once again, we have grouped reasons under three broad headings: (a) lack of knowledge of the disease or its causes, (b) lack of tools to prevent or treat it, and (c) failure to use existing tools efficiently.

The cause of TB and the factors that predispose individuals to develop disease are largely known. The reasons for its persistence on such a scale must therefore lie either in (b) a lack of tools or (c) inefficient use of existing tools—or both. The existing tools can be highly effective: directly observed treatment, short-course (DOTS), the preferred treatment option, can achieve cure rates of greater than 90%. But only a small proportion of the eight million cases of TB diagnosed annually receive

Figure 4.2 Analysing the burden of tuberculosis to assess research needs



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

DOTS. Worse, health systems in many countries are still not using short-course therapy at all, but instead attempt to impose on their patients a 12-month course which is difficult to comply with, and therefore ultimately less cost-effective. In some countries, a plethora of different treatment regimens, many of them inappropriate, coexist. For all these reasons, cure rates in some countries are as low as 40%. It is clear that more efficient use of DOTS would reduce the burden of tuberculosis considerably.

However, it seems unlikely that, even in perfect conditions, DOTS alone could eliminate TB. Some of the burden that remains today must be attributed to (b) a shortage of tools. First, there are technical shortcomings with DOTS itself in its current form. The current treatment regimen requires patients to take different types of pills on alternate days for two months (isoniazid, rifapentine, pyrazinamide and ethambutol), and then two types of pills (isoniazid and rifapentine) three times a week for a further four months. This is inconvenient, may be a factor in reducing compliance and may thus contribute to the emergence of drug-resistant strains. Improved formulations that required fewer administrations of the drugs, and fewer contacts between health workers and patients, would make DOTS more widely achievable.

Improved versions of the existing strategies are unlikely to be enough, however. New tools are needed on several fronts. While DOTS itself is an effective method of preventing the transmission of TB, additional methods for prevention are highly desirable. The current vaccine, BCG, is useful in preventing some childhood forms of the disease but ineffective in adults. Vaccines with greater and broader efficacy than BCG could play an important part in interrupting transmission, but none is yet available and there is still a considerable requirement for new knowledge before one can be developed. In certain circumstances chemoprophylaxis (i.e. drug therapy for infected individuals not currently ill) can play a useful role, alongside DOTS, in preventing the spread of infection—particularly among vulnerable groups (e.g. HIV-positive people). However, current chemoprophylactic tools and regimens are rarely cost-effective and their misuse may encourage the selection of drug-resistant strains. In addition, there are other important technological gaps in the arsenal against TB. For example, the current diagnostic technologies are limited, as are tools for the testing of drug sensitivity.

We have conducted a preliminary quantitative analysis of the disease burden from TB to identify research needs. As before, our method uses existing data on the efficacy of the current mix of cost-effective interventions, plus assessments of the degree to which those interventions currently reach the population in need, to analyse what proportion of the burden (in DALYs) can and cannot be averted with existing interventions (Figure 4.2).

This analysis shows that less than a fifth of the estimated total burden (that is, the burden that would exist if there were no effective interventions) is currently averted. Although the efficacy of DOTS is high, the proportion of the population receiving it is low. With a massive improvement in the proportion of the population receiving effective DOTS, more than half of the burden could be averted now. Such an improvement could be achieved, in principle, through improvements in technical efficiency and greater resource commitment.

However, even if the most optimistic scenario with the best use of DOTS were achieved, another one-third remains avertable either only with cost-ineffective interventions, or not avertable at all with the currently available tools. For a disease of the epidemiological significance of TB, this is a huge loss of healthy life. If the selection of multidrug-resistant strains outpaces the development of new treatment strategies, meanwhile, the unaverted portions of the burden could increase further still. The Committee concludes that the reasons for the persistence of TB lie mainly in a shortage of tools and failure to use the existing tools efficiently (Table 4.3). Obviously, the shortage of tools will become more acute still if drug resistance begins to have a major impact on treatment.

We therefore conclude that R&D efforts need to be divided between biomedical research to devise new interventions and operational research to make existing interventions more efficient. Before the full range of new interventions can be developed, however, there will be some need for strategic biomedical research to broaden the knowledge base, for example in finding new molecular targets for drug action.

4.1.4 Priority areas for strategic research

TB research has suffered from neglect of the disease during the 1970s and 1980s which has led to a fall in R&D capacity. However, there has been considerable ef-

Table 4.3 Broad reasons for the persistence of tuberculosis

	Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools efficiently
1990	+	++	+++
Future scenario with severe drug resistance	+	+++	++

Note: The estimated rating ranges from little importance ('+') to extremely important ('++++').

fort during the 1990s to begin rebuilding capacity through direct R&D initiatives within both the public and private sectors (see, for example, Box 4.1). In the Committee's view, there are important areas of strategic research that will be required to build up the knowledge base to re-equip scientists to develop new tools and, in the process, strengthen capacity. These include:

- Further epidemiological surveys of the prevalence of MDR strains in different countries and the factors associated with their spread; and
- Further sequencing of the genome of *M. tuberculosis*, enabling laboratories to rapidly screen new potential immunogens and molecular drug targets.

The costs of gaining this knowledge may be lower than expected, particularly in relation to the size of the potential payoff in terms of averting disease burden. For example, it is estimated that the bacterial genome can be sequenced for as little as US$ 1.5 million. The rate at which such sequencing can be done is accelerating rapidly because of technological improvements.

While these areas of strategic research will be vital, it is not necessary—or wise—to wait for them to be completed before work begins to develop and evaluate certain interventions. There is already an adequate knowledge base to enable researchers to assess some opportunities. For example, the efficacy and the cost-effectiveness of short-course chemotherapy is known. As a result, some desirable future interventions can aleady be identified.

4.1.5 Opportunities for intervention development and evaluation

The Committee considers that three interventions could significantly reduce the global disease burden from tuberculosis. These have been selected according to the criteria set out in Chapter 1: that is, the knowledge base to develop them exists already; they are expected to be cost-effective relative to other interventions; and the expected costs and time frames for their development are judged to be reasonable. In our view, development efforts should focus on these.

- *Develop effective strategies to extend coverage of directly observed treatment, short-course (DOTS) for TB and increase its applicability and acceptability*

This emerges as an excellent target for R&D investment. Short-course chemotherapy given under direct observation can cure up to 95% of patients and, at as little as US$ 3 to US$ 5 per DALY averted in low-income countries, represents one of the most cost-effective interventions for any health problem. It would be still more cost-effective if it could be extended at low cost to a larger proportion of the affected population and thereby reduce not only the prevalence of the disease but also transmission. Examples of the types of improvement that are feasible include:

(a) new formulations of the existing chemotherapeutic agents to combine at least some of them and thus reduce the number of pills that people must take;
(b) longer-acting injectable formulations that reduce the number of needed contacts between health workers and patients, and reduce the risks of noncompliance; and
(c) community-based systems for delivering DOTS so that patients do not necessarily need to travel to a clinic or be visited frequently by a health worker, but can still have directly observed therapy.

- *Develop improved diagnostics and clinical algorithms for the detection of smear-negative infection*

Better methods are needed for detecting *M. tuberculosis* in smear-negative individuals, particularly those who are HIV-positive and at high risk.

- *Develop a new prophylactic intervention*

A vaccine is desirable and, while it constitutes a long-term investment, the potential payoff could be extremely high. Advances in strategic research on *M. tuberculosis* in recent years have made it possible to manipulate the genome of the microbe, increasing the prospects for producing attenuated strains. However, additional options must be investigated. One such option would be to develop mass chemoprophylaxis using a long-acting injectable agent (long-acting rifapentine) that can be administered to people on a single occasion. The potential of such tools to control the spread of infection is good, and their development is judged to be technically feasible, although great care would be required to avoid administering such chemoprophylaxis to anyone with active disease.

Box 4.1 Action on tuberculosis: an international collaboration

The global emergency created by the tuberculosis epidemic has already triggered some innovative R&D responses. A key example is the ACTION TB programme set up by the pharmaceutical company Glaxo (now Glaxo Wellcome) in 1993, with an investment of around US$ 18 million over five years. ACTION TB combines the efforts of researchers in different countries and involves both the public and the private sectors in a search for efficient, reliable and safe treatments for the disease. The focus of the programme's research is on:

- the molecular and cellular biology of tuberculosis;
- the immunological response to tuberculosis infection; and
- the identification of novel drug targets.

The programme's collaborating scientists are based in the United Kingdom, Canada and South Africa. South Africa was chosen because the country has high rates of tuberculosis; HIV infection is widespread and increasing; multidrug-resistant strains of *Mycobacterium tuberculosis* are present; and the country has suitable infrastructure and—most importantly—motivated and qualified researchers. The South African Medical Research Council facilitates the initiative there, with five separate teams in molecular biology, immunology, bulk production, biochemistry and pharmacology, and operational research.

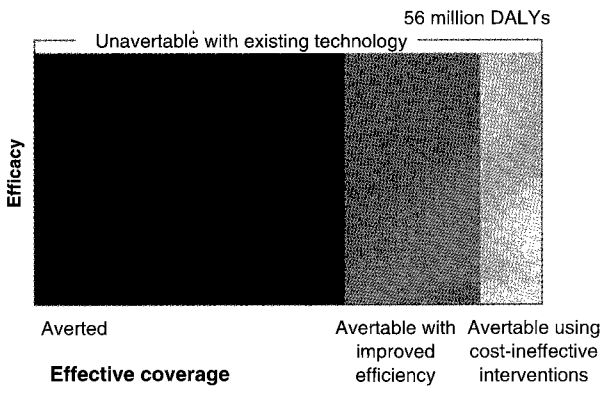
Two years after the programme began, research is progressing well and some suitable targets for drug screening have been identified. International links are proving helpful and stimulating, and the participants are learning the factors needed for success in such a collaboration—factors that may apply to many similar ventures elsewhere. A "champion" is needed to ensure both the start and the continuation of the programme. The sponsoring company must play an active part and not act purely as a donor. All parties must have something to contribute, and participating scientists must be allowed a measured degree of freedom in their work.

To ensure success, the relationship between the company and the research council should be one of complete trust. The involvement of the research council facilitates the collaboration, but should never absolve the council from its responsibilities to fund research in the area covered by the private-sector initiative. In order to remove some of the disincentives to interaction, the often rigid bureaucracy of a government research council may need to be adapted to the norms of industry and management.

The Committee has modelled the expected impact of one of these hypothetical new prophylactic interventions on the total disease burden of TB. (See Figure 4.3.) This approach is useful partly because it shows how much of the burden could be averted by interventions of varying efficacy and coverage.

To generate this diagram (Figure 4.3), we assume that the new intervention brings the combined efficacy of the total mix of interventions up to 95% and that 80% of the population receive it. With this addition to the mix of available interventions, more than half of the burden would become avertable immediately, and most of the remainder would become avertable with more efficient use of the mix of interventions. Obviously, these proportions would vary depending on the level of coverage and the efficacy of the new preventive intervention.

Figure 4.3 Tuberculosis: impact of a hypothetical prophylactic intervention



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

4.2 Pneumococcal disease

4.2.1 The magnitude of the burden

Of an estimated four million child deaths in developing countries each year from pneumonia, almost half (1.9 million) are caused by a single organism, *Streptococcus pneumoniae* (Schwartz et al. 1996). The lack of public attention to this organism, commonly known as pneumococcus, is sharply at odds with its impact on world health, which is at least comparable with that of the TB bacterium both in terms of death and of disease burden. As well as causing pneumonia, S. *pneumoniae* also

causes meningitis, septicaemia and potentially disabling ear infections.

Effective treatment for pneumococcal disease exists, in the form of case management with antimicrobials. In low-income countries, however, the case-fatality rates for pneumonia are 10 to 50 times higher than in the established market economies, due in part to poor access to treatment. Pneumococcus is most likely to kill poor, undernourished babies whose mothers are uneducated.

The spread of drug-resistant strains of *S. pneumoniae* worldwide is a cause for serious concern. Rates of resistance have been associated with overall antimicrobial use. For example, in Spain as the use of macrolides—the class of antibiotics that includes erythromycin, clarithromycin and azithromycin—has increased, the prevalence of isolates resistant to macrolides has also risen. Individuals who have been treated with antimicrobials in the past are at increased risk of becoming infected with resistant strains, and people who have been hospitalized are also at greater risk. In South Africa, a recent study found that 40% of invasive isolates acquired in the community, and 95% of invasive isolates acquired in hospital, were resistant to penicillin. Of these penicillin-resistant isolates, 9% were also resistant to chloramphenicol, 4% to erythromycin, and 21% to cefotaxime. In Europe and Asia, the rates of resistance vary with penicillin usage.

It is not clear that the efficacy of antimicrobial treatment for pneumonia caused by *S. pneumoniae* is lowered when a patient is infected with drug-resistant strains. Most studies to date have shown that, with moderately resistant strains at least, the efficacy of the drug is not reduced. However, higher levels of resistance may be more difficult to treat; this is already the case when resistant strains cause meningitis. Most researchers are concerned by the possibility of reduced antimicrobial efficacy in future.

4.2.2 Assessment of research needs

Here we analyse the reasons for the persistence of illness and deaths from pneumococcus on such a massive scale, despite the availability of effective treatment. As Chapter 3 argued, lack of action and inadequate commitment play a large part in the failure to address the conditions that overwhelmingly burden low-income countries. However, as before, the Committee considers that lack of action alone cannot explain the persistence of the disease. We have once again sought to determine how much of the burden can be ascribed to (a) inadequate knowledge of the disease or its causes, (b) inadequate tools to prevent or treat it, and (c) failure to deliver the existing interventions efficiently.

It seems unlikely that reason (a), inadequate knowledge of the disease, can account for much of the existing burden when effective treatments exist and mortality rates are low in the industrialized countries. Rather, the fault seems to lie with reasons (b) and (c). (See Table 4.4.)

Table 4.4 Broad reasons for the persistence of pneumococcal disease

Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools efficiently
+	++	+++

Note: The estimated rating ranges from little importance ('+') to extremely important ('++++').

Vulnerable groups are not receiving the existing effective interventions and there are technical failures in the delivery of services. The health sector has not invested adequately in behavioural research to determine households' needs or the factors that predispose some households to seek care sooner than others, nor made adequate efforts to develop more effective algorithms, nor done enough to translate R&D findings into practice through evaluation research and staff training. Reason (c) therefore appears to be significant.

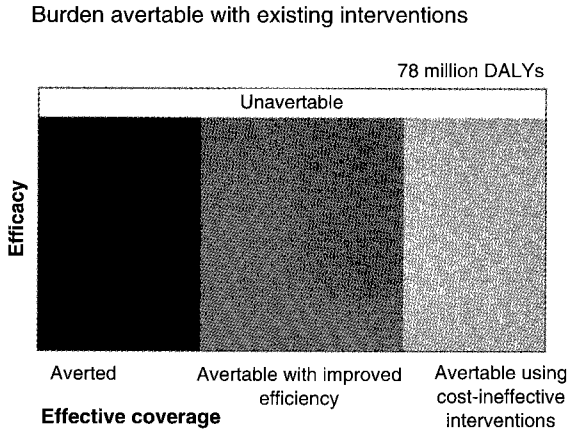
However, the Committee believes that (b), a lack of tools, is also playing a major part. Currently, the control of pneumococcus relies very heavily on case management. There is no vaccine against pneumococcus that is suitable for young children in low-income countries. An existing pneumococcal vaccine licensed in the United States is based on polysaccharide antigens from 23 of the 90 known serotypes of *S. pneumoniae*. While it offers some protection to older children and adults by stimulating antibody responses, it does not stimulate a strong immune response in infants. Also, around one-fifth of the invasive infections in children in low-income and middle-income countries are caused by serotypes not represented in the licensed vaccine.

We have used available data on efficacy and assessments of coverage to estimate what proportion of the burden of pneumococcus could be averted with more efficient use of existing interventions, what could be averted but only with cost-ineffective interventions, and what is judged to be currently unavertable. Figure 4.4 shows the current situation.

With case management, just over one-quarter of the total burden (that is, the burden that would exist were there no effective treatment) is averted. A further one-third could be averted if case management were made available to a wider population through greater efficiency in the allocation of resources. Another quarter could be averted now, but only with interventions that are not currently cost-effective, such as expensive alternative antimicrobials and tertiary care. In principle, only 10% is unavertable. This analysis is broadly comparable with the general analysis for all childhood pneumonia outlined in Chapter 3: it shows that a large part of the remaining burden could be averted by putting existing interventions to better use but that new tools, such as a vaccine, are needed to achieve complete control.

The assessment of likely future needs is, of course, more complex. As long as the efficacy of existing antimi-

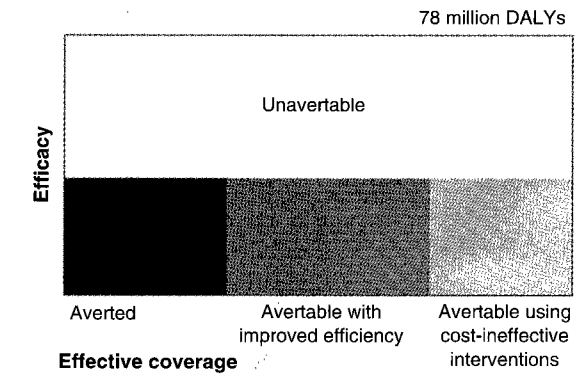
Figure 4.4 Analysing the burden of pneumococcus to identify research needs



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

crobials remains high, they are likely to remain the mainstay of treatment. If, however, drug resistance were to lower their efficacy, then disease burden would climb no matter how efficiently they were used. In that case, new antimicrobials would no longer be merely desirable; they would be essential. And the need for a vaccine would become even greater. The hypothetical scenario in Figure 4.5 illustrates this possibility in an heuristic manner. It assumes that 50% of the pneumococcal isolates found are multidrug-resistant, while case management remains the only cost-effective treatment. In this extreme scenario, we assume that treatment would fail in half of the cases where it now works. This would mean that the proportion of the burden that is averted would fall by half, as would the proportions that could be averted with more efficient use of case management and with cost-ineffective treatments. As a result, more than half of the total burden would become unavertable.

Figure 4.5 Pneumococcus disease: scenario 1



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

Whatever the real future, the current heavy reliance on case management is clearly not sufficient on its own to meet all needs. In the Committee's view, the overall size of the current burden, the shortcomings of present treatment strategies, and the threat of reduced efficacy in future point strongly towards a need for new tools, both for prevention and for treatment.

4.2.3 Priorities for strategic research

The Committee considers that there are two priority areas where the knowledge base needs to be increased in order to enhance the prospect for developing improved treatments. Strategic research should focus on efforts to:

- Identify ways to reduce the inappropriate use of antimicrobials with the aim of slowing the selection of resistant strains. This is likely to involve behavioural studies of the attitudes and practices of health workers to identify the reasons for inappropriate use. In addition, in the longer term, sequencing the bacterial genome to identify new molecular targets for drug action may enable the development of alternatives to antimicrobials. This effort may also help to identify new antigenic epitopes and, eventually, alternative cost-effective approaches to immunization beyond the immediate priorities discussed below.
- Understand the clinical relevance of antimicrobial resistance. This research will overlap with, and be informed by, clinical trials to determine the significance for treatment of strains of *S. pneumoniae* that show resistance to antimicrobials in the laboratory.

4.2.4 Opportunities for intervention development and evaluation

While strategic research continues to pursue these objectives, the current knowledge base is adequate for two highly desirable interventions to be developed. These are listed below. Both are expected to be cost-effective interventions, and achievable with reasonable costs and time frames.

- *Trials of candidate conjugate pneumococcal vaccines in selected low-income countries*

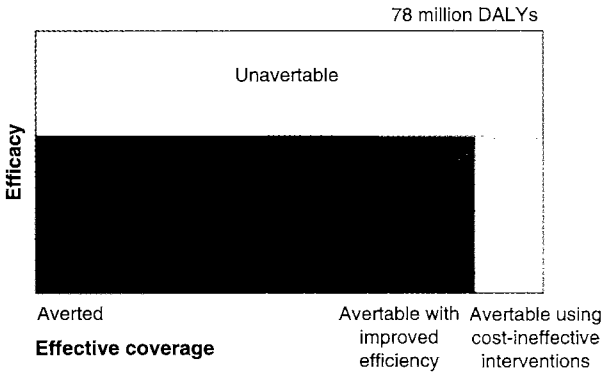
  An immediate priority is to demonstrate the safety and efficacy of vaccines suitable for young children in low-income countries. Three candidates are currently under development, based on capsular antigens conjugated to protein carriers, which stimulate a T-dependent immune response and are likely to be suitable for infants. The ideal vaccine should match as closely as possible the mix of serotypes that cause most invasive infections in low-income countries. A seven-valent conjugate vaccine has been developed

by a manufacturer in the United States with support from the National Institutes of Health, and two further vaccines are also at advanced stages. If safety, immunogenicity and efficacy are confirmed, the feasibility of delivering the vaccine within the existing schedules of the Expanded Programme on Immunization should also be assessed. The expected cost-effectiveness of a pneumococcus vaccine in low-income countries is between US$ 80 and US$ 140 per DALY averted, making it a very attractive investment; the time and funding required to complete trials is estimated to be modest, at around US$ 6 million over five years. Although the unit cost of the proposed pneumococcal conjugate vaccine is likely to be relatively high, its *cost-effectiveness* nevertheless makes it a highly attractive buy for global health. In the longer term, additional, even more cost-effective, approaches to immunization may be found but these should not deter investors from acting now to avert a massive disease burden.

The Committee has modelled the impact of such a vaccine on future disease burden to demonstrate its likely payoff in terms of reducing disease burden. The hypothetical scenario 2 shown in Figure 4.6 once again assumes 50% antibiotic resistance. It further assumes that an effective vaccine is widely available through the Expanded Programme on Immunization (EPI). In this situation, the vaccine could be expected to increase considerably the proportion of the burden averted over the relatively low levels seen in scenario 1 (where there is 50% antibiotic resistance but no vaccine). Note, however, that relatively little gain could be achieved with more efficient use of this mix of interventions. Even with the improvements resulting from the vaccine, just over one-third of the burden would still remain unavertable. Clearly, with a burden as big as that from pneumococcus, this gain is well worth having. However, the analysis also demonstrates the limitations of relying exclusively on one tool for disease control. With 50% resistance, even an effective vaccine would not be enough.

Figure 4.6 Pneumococcus disease: scenario 2

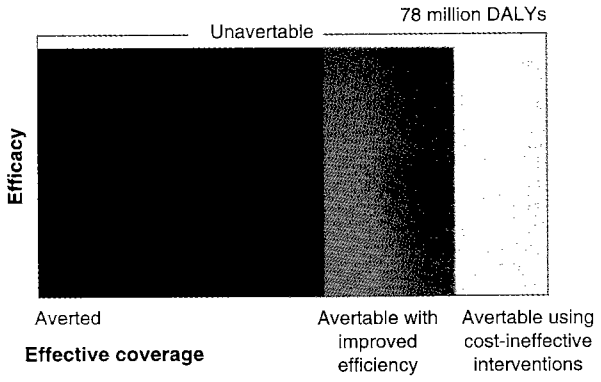
Burden avertable given 50% antibiotic resistance and a new conjugate vaccine



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

Figure 4.7 Pneumococcus disease: scenario 3

Burden avertable with effective case management and a vaccine



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

Figure 4.7 models the combined impact of continued case management and a new vaccine in an environment where drug resistance has not emerged as rapidly as anticipated, or has been overcome by use of alternative antimicrobials. Under this hypothetical scenario 3, the proportion of the burden averted doubles to more than half. A further quarter is likely to be avertable with efficient use of the combined interventions and the unavertable portion shrinks further. The payoff from combining the two interventions in these circumstances is therefore extremely high and the case for testing a candidate vaccine strong.

- *Develop and evaluate combined antimicrobial therapies and improve case management*

As the analyses show, better case management will continue to be essential. As one possible means to slow the emergence of resistant strains, combined formulations of antimicrobials should therefore be developed and evaluated.

4.3 Malaria

4.3.1 The magnitude of the burden

Every year, worldwide up to 500 million people fall sick with malaria, 90% of them in Africa. In 1990 there were around 856 000 deaths from the disease, some 731 000 in sub-Saharan Africa (Annex 1). Outside Africa, more than two-thirds of reported cases are concentrated in South and South-East Asia and the Amazon region of Latin America. In 1987, the direct and indirect costs of

malaria to Africa annually were estimated at US$ 800 million; by 1995, they were expected to exceed US$ 1.8 billion. In 1990 malaria alone accounted for 9% of sub-Saharan Africa's disease burden, and claimed 2.3% of the global burden—almost three times as much as diabetes mellitus worldwide (Annex 1). If parasite resistance becomes more widespread and new drugs fail to keep pace, its impact could worsen significantly.

Twenty years ago, malaria had been eradicated from 37 countries. While sub-Saharan Africa continued to suffer the lion's share of all cases and deaths, the number of cases elsewhere had fallen after an intensive eradication effort based largely on spraying houses with insecticide (Annex 7). Reasons for the gradual comeback of the disease in South and South-East Asia, and in Latin America, are complex: they include the cost of eradication efforts, a loss of motivation in the face of a seemingly declining threat, and the development of insecticide resistance by the vectors and drug resistance by the parasites.

Today malaria is undoubtedly a major threat to world health, mainly because of the emergence and spread of drug resistance but also because of important demographic factors. Drug-resistant strains of malaria parasites have become increasingly prevalent, particularly in South-East Asia in Cambodia, Thailand and Myanmar, and in the Brazilian rain forest where mining and changing land use is exposing non-immune adults to areas of high risk and intense transmission. Chloroquine resistance is becoming increasingly important in eastern and southern Africa and some resistant isolates have also been reported in west African countries. The principal vector has also evaded various control strategies. Malaria has thrived on uncoordinated and rapid economic development, rapid urbanization and mass migration. It is a significant problem in countries where wars have destabilized communities: Ethiopia, Cambodia, Sudan, Somalia, Rwanda, Iraq, Afghanistan and Djibouti. A rising number of travellers from the industrialized countries are also being exposed to malaria.

4.3.2 Current investment

In common with other diseases that afflict mostly people in low-income countries, malaria is seriously underfunded in relation to its importance as a source of disease burden. Analyses performed for this Report indicate that spending on R&D in malaria was around US$ 58 million a year for the period 1990–92, out of almost US$ 56 billion spent on all health research worldwide. The sources of funding for malaria appear to be highly dispersed across a handful of major sources and a mass of much smaller ones. Whether this is an efficient use of resources is questionable.

4.3.3 Assessment of research needs

As Chapter 3 argued, the reasons for the persistence of malaria are a combination of (c) failure to use existing tools efficiently and (b) inadequate tools. Better use of existing tools could avert a significant element of the remaining burden of malaria in those who are worst affected—children in Africa—today. Yet the malaria parasite's own complexity makes it a moving target that needs continuous attention. The list of drugs available to treat malaria is short. *P. falciparum* rapidly develops resistance to drugs, particularly under conditions of poor compliance. As little as five years after mefloquine was introduced, for instance, strains resistant to that drug emerged. In some parts of South-East Asia there are now parasites resistant to all the major traditional drugs. Even the benefits of the Chinese drug artemisinin must be tempered by the need to limit its use as a safeguard against emerging resistance. Complexities in the life cycle of the parasite, and the human immune response to it, have made vaccine development difficult too, and there are currently no vaccines licensed. New tools are clearly needed now and are likely to become critical in the near future. (See Table 4.5.)

Thus the priority is for biomedical development and evaluation to continue work on the existing candidate vaccines and the small number of candidate drugs currently in the pipeline. To enable this, strategic biomedical research will remain a priority to increase the knowledge base.

4.3.4 Priorities for strategic research

In the Committee's view, there are a number of areas in which strategic research is likely to bring high payoffs. They are:

- Sequence the genome of *P. falciparum*. The biggest single advance in molecular biology to aid malaria research in recent years is a project to map the malaria parasite genome, supported by the Wellcome Trust. The cost of *sequencing* the entire genome is expected to be around US$ 10 million; the payoff is likely to be

Table 4.5 Broad reasons for the persistence of malaria

	Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools efficiently
1990	+	+++	++
Future scenario with severe drug resistance	+	++++	+

Note: The estimated rating ranges from little importance ('+') to extremely important ('++++').

Table 4.6 Comparisons of the likely cost-effectiveness in fighting malaria of insecticide-impregnated bednets and a vaccine

Intervention	Total cost (US$)	Total DALYs averted	Cost/DALY (US$)
Impregnated nets: government purchase and distribution, compliance between 50% and 100%, 25% reduction in all-cause mortality in children below age 5 years.	142 896	10 385–20 768	7–14
Hypothetical vaccine (a): 30% reduction in all-cause mortality in children below age 5 years: EPI delivery, protection lasts 1–5 years, cost between US$ 1 and US$ 7.50 per child per year.	7 768–229 127	21 123	0.40–11
Hypothetical vaccine (b): as for (a) but no EPI delivery, protection lasts 1 year, cost US$ 15 per child per year.	497 094	21 123	24

Note: Modelled for a cohort of 10 000 children from birth to age 5 assuming expected deaths age 0–4 without intervention, from West Africa model life tables. The further assumptions on which these calculations are based are explained in full in Supplementary paper 2.

Source: Supplementary paper 2

an unprecedented improvement in the opportunities for developing drugs and vaccines.

- Continue the use of nucleic acid technology to screen in animal models sequences from the genome in the search for new candidate molecules for vaccines and new targets for drugs.
- Further investigate the potential for genetic engineering to make the mosquito vector *Anopheles gambiae* refractory to the parasite and thereby interrupt transmission.

4.3.5 Opportunities for intervention development and evaluation

Even with the gaps in current understanding that we have discussed, the knowledge base is sufficiently good to enable an assessment of certain development opportunities. The Committee has identified three priorities:

- *Develop a malaria vaccine*

  Advances in molecular biology and immunology have radically improved the prospects of researchers in recent years and there are now good grounds for optimism that vaccines will be available within 10 years. Calculations for the Committee demonstrate that a vaccine could be highly cost-effective, provided it can be delivered within the schedules of the Expanded Programme on Immunization. The Committee therefore considers this to be an excellent investment. Two sets of calculations (presented in Table 4.6 and Table 4.7) demonstrate how comparisons of the cost-effectiveness of different intervention options can aid decisions on where to invest, and on the characteristics that a future product should have.

  The first set of calculations is based on comparisons of the relative cost-effectiveness of a hypothetical vaccine and the main existing intervention, insecticide-impregnated bednets (Table 4.6). These give guidance on the kind of characteristics that a vaccine would need to compete with bednets. Bednets have been shown to reduce mortality from all causes by between 25% and 38% in large-scale field trials in The Gambia. If a hypothetical vaccine were to reduce mortality by 30%, it would be a highly cost-effective option, provided it were designed to be compatible with the existing EPI schedule. If it were not compatible with this schedule but required separate delivery, it would represent a less cost-effective option than bednets.

  The second set of calculations concerns the characteristics of the vaccine itself and the conditions that would alter its cost-effectiveness. These show that if a vaccine can be administered within the EPI schedule, its cost-effectiveness in a high-mortality area can still be excellent even if protection lasts only one year. They also show that the cost-effectiveness of such a vaccine rapidly falls in low-mortality areas (see Table 4.7).

  This type of analysis gives particularly useful guidance about the pragmatic kind of approach vaccine developers need to take: for example, the vaccine's effectiveness should be measured in children of the same age as the children to whom the EPI system delivers vaccines, rather than in children of a theoretically "optimal" age.

  It is estimated on the basis of ongoing work that a vaccine can now be developed for an investment of the order of US$ 50 million within about 10 years.

- *Develop new antimalarials*

  Future antimalarials will be needed to treat multidrug-resistant falciparum malaria and to replace chloroquine in areas of moderate chloroquine resistance. Work is under way to identify and validate new drug targets and to use them for testing compounds. Current efforts focus on the mechanisms of proteinase inhibition in the parasite's food vacuole, folate metabolism and phospholipid metabolism.

- *Evaluate a range of strategies to increase compliance with the aim of slowing the emergence of resistant strains*

Table 4.7 Cost-effectiveness of a potential malaria vaccine

Scenario	Cost (US$)	DALYs averted	Cost/DALY (US$)
High malaria mortality area[1]			
1. Best[2]			
a. Impact on 0–4 yr olds	7 768	21 123	0.37
b. Impact on 1–4 yr olds	7 768	11 801	0.66
2. Medium[3]			
a. Impact on 0–4 yr olds	229 127	21 123	10.85
b. Impact on 1–4 yr olds	229 127	11 801	19.42
3. Poor[4]			
a. Impact on 0–4 yr olds	497 094	21 123	23.53
b. Impact on 1–4 yr olds	497 094	11 801	42.12
Low malaria mortality area[1]			
4. Best[2]			
a. Impact on 0–4 yr olds	7 768	1 374	5.65
b. Impact on 1–4 yr olds	7 768	732	10.61
5. Medium[3]			
a. Impact on 0–4 yr olds	218 122	1 374	158.70
b. Impact on 1–4 yr olds	218 122	732	287.94
6. Poor[4]			
a. Impact on 0–4 yr olds	475 083	1 374	345.67
b. Impact on 1–4 yr olds	475 083	732	638.93

Notes:

1. Vaccine coverage 80%; high mortality areas vaccine reduces all-cause mortality by 30% in children covered; low mortality areas vaccine reduces malaria specific mortality, assumed to be 6.2/1000 deaths, by 30%; in options (a), vaccine assumed to be effective for 0–4 year olds; in options (b), vaccine assumed to be effective only in 1–4 year olds; no impact on transmission incorporated.
2. Vaccine delivered jointly with EPI; marginal cost of adding US$ 1 per dose; duration of protection 5 years.
3. First dose of vaccine delivered through EPI at marginal cost of US$ 5; duration of protection 1 year; 4 subsequent annual doses costing US$ 7.50 each.
4. Vaccine cannot be delivered through EPI; duration of protection 1 year; 5 annual courses required costing US$ 15 per fully immunized child.

Source: Supplementary paper 2

Research must continue to build on the existing work in this area. Studies in China have already shown, for example, that blister packs similar to those used for oral contraceptive pills can encourage compliance. Other approaches may need to be evaluated in different settings.

4.4 HIV/AIDS and other sexually transmitted diseases

In Chapter 3, we discussed the problems of poor reproductive health experienced by unacceptably large numbers of women in low-income countries. Our focus was on the difficulties of access to family planning and excess fertility, unsafe pregnancy and childbirth, and perinatal conditions. This section returns to the theme of reproductive health, but with the focus on STDs and the microbes that cause them. The two areas are inextricably linked: clearly, women can enjoy sexual health and safe motherhood only when they are free from infection and disease. The International Conference on Population and Development in Cairo in 1994 took a decision to include the prevention and treatment of sexually transmitted diseases, as well as the services to ensure safe motherhood, in the definition of reproductive health care. This Committee strongly endorses that expanded definition, and believes that the effective prevention and treatment of STDs in both women and men is of paramount importance.

4.4.1 The magnitude of the burden

HIV/AIDS. The HIV pandemic which began in the late 1970s has now affected every inhabited continent. By the end of the decade it is estimated that there will be some 26 million people living with HIV infection worldwide, the vast majority of them in sub-Saharan Africa and Asia.

Although the overall prevalence of HIV/AIDS is lower than for many other communicable diseases, its economic impact is greater because it incapacitates and kills young and middle-aged adults who are at their most productive, and to date it has also disproportionately affected skilled and managerial workers. In some capital cities in sub-Saharan Africa, 50% to 70% of hospital beds are occupied by AIDS patients, and TB cases (as well as cases from many other opportunistic infections) are also increasing sharply as a result of HIV in-

fection. The costs of caring for people with AIDS are also unprecedentedly high. Studies from a range of low-income and middle-income countries have indicated that the direct costs of medical care alone vary from between 60% of per capita GNP to several times per capita GNP. The average direct cost is about 150% of per capita GNP and indirect costs are probably about 10 times as high. In addition, family members of people with AIDS are affected; young children who lose their mothers to AIDS are more likely to die themselves and even older offspring are disadvantaged. In a study in Tanzania, teenagers' school attendance dropped by half if they had lost an adult female member of the household to AIDS.

In 1990, the burden of disease attributed to HIV/AIDS was almost 1% of the global total (Annex 1), and almost 3% of the burden in sub-Saharan Africa, where other STDs accounted for another 2% of the burden. In the same year in the age group worst-affected by HIV/AIDS, between ages 15 and 45, some 8% of all male deaths and 12% of all female deaths in the continent were attributed to HIV. Because of the delay between infection and the onset of disease, both disease burden and mortality are certain to increase in the medium term, and the costs of the pandemic will therefore remain unprecedentedly high for generations to come.

Projections of the course of the HIV pandemic have been generated for this Report which underscore its severity as a major threat to global health. They indicate that the total burden of disease attributable to HIV could more than treble worldwide by 2020. In sub-Saharan Africa, HIV is projected to account for 4.4% of burden by that time and in India, 4.6%; in Asia excluding India and China, HIV is expected to account for 3% of burden (Annex 1). Projections of AIDS deaths have also been generated; these appear in summary in Annex 1 and in greater detail in the companion volumes to this Report. In sub-Saharan Africa in 1990, deaths from HIV were estimated at 239 000. These are expected to rise rapidly to peak at more than 700 000 per annum in about 2005. In India, HIV deaths are expected to peak around the year 2010 with more than half a million deaths annually (Murray & Lopez 1996 and forthcoming).

The projections rely on a model developed for the Global Burden of Disease Study, using estimates supplied by the WHO Global Programme on AIDS. Any attempt to project the future burden of a communicable disease for which so little historical data are available is necessarily hazardous and must be viewed with caution. Earlier projections have assumed that, after an initial increase, the incidence of HIV infection will gradually decline to zero over a period of years, a scenario which we consider unlikely. The present projections are less optimistic and make the crude assumption that, for each region, the initial increase in incidence will be followed by a decline which will reach an equilibrium value equal to half the peak incidence. To estimate mortality from HIV, we have used the same assumptions as those of the WHO Global Programme on AIDS. The model is further explained in Annex 1.

Other sexually transmitted diseases. Sexually transmitted infections other than HIV—of which chlamydia, gonorrhoea and syphilis are the three most important causes of lost years of healthy life—together account for 1.4% of the global disease burden today and up to 15% of the burden in the urban populations of developing countries. Women—and children—bear a disproportionately heavy share of that burden and are more likely to suffer long-term effects than men. Chlamydial infection during pregnancy can result in infant pneumonia and blindness (trachoma), and untreated infection in women can lead to sterility. Congenital syphilis is still a significant problem in some regions. Eight out of 10 women with ectopic pregnancy have serological evidence of past chlamydial pelvic infection, and gonorrhoea is also a risk factor. Cancer of the cervix is the most common malignancy in women in developing countries and human papilloma virus is thought to be responsible for at least 70% to 80% of cases.

Drug resistance in gonorrhoea is an increasing problem. Penicillin-resistant strains of *Neisseria gonorrhoeae,* the causative organism, have been identified in up to 60% of samples tested in some developing countries. Recorded prevalences of *Chlamydia trachomatis* have risen in recent years. The rise has been attributed to increased rates of partner change and also to increased recognition of the disease.

There is an increasing body of evidence to suggest that HIV spreads more easily from person to person through sexual contact when one or both parties are also infected with other STDs. A large study in rural Tanzania has demonstrated that minimal treatment for STDs can cut transmission of HIV by around 40% (Grosskurth et al. 1995).

A number of demographic factors have been important in the spread of both HIV and other STDs: they include increased urbanization and the fact that high percentages of men in low-income countries must seek work hundreds of miles from their families, where they are more likely to take advantage of opportunities for commercial sex. Changing patterns of sexual behaviour and increased rates of partner change in some societies have also encouraged their spread. Those at greatest risk are young adults and adolescents.

Unsafe sexual activity accounts for a substantial proportion of total disease burden, according to analyses conducted for this Report. In the established market economies, fully 2% of the total burden in 1990 could be attributed to unsafe sex, while in India, other parts of Asia excluding China, and Latin America and the Caribbean, it is estimated to cause between 3.7% and 4.4% of the total burden. In sub-Saharan Africa, where population movement, poverty and inadequate health services have all favoured the rapid spread of STDs, as much as 6.5% of total disease burden in 1990 may be attributed to unsafe sex, with women suffering a disproportionately heavy share of this total. In China and the Middle Eastern crescent, unsafe sex is thought to be responsible for a relatively lower, but still significant, proportion of disease burden (Annex 2).

4.4.2 Current investment

The resources devoted to HIV research since the early 1980s are larger than for any other communicable disease. In the published literature for the period 1990–92, estimates for this Report suggest that spending on HIV/AIDS was around US$ 1 billion per year (Annex 5). This estimate fails to capture the rapid increase in funding for AIDS around 1990, which is unlikely to be reflected in data on grants that would have been awarded well before the papers were published. Funding has since climbed further: the U.S. National Institutes of Health alone had a budget of US$ 1.3 billion for research on HIV/AIDS in 1994 and investments by the private sector are also substantial. It is likely that today, total R&D funding for AIDS, including the contributions of the private sector, may exceed US$ 2 billion. However, a large part of this investment has been devoted to the development and testing of therapeutics in the industrialized countries. Research on vaccines and other prevention methods represents a small fraction of the total. AIDS vaccines research receives less than US$ 160 million a year, and of this less than US$ 5 million is devoted to vaccines intended for use in low-income countries. Spending for R&D on other STDs was not assessed.

4.4.3 Assessment of research needs

To identify priorities for R&D to address the rapidly growing burden from HIV and the remaining burden of other STDs, we have once again organized our analysis in terms of three broad groups of reasons to explain the persistence of the burden: (a) inadequate knowledge, (b) inadequate tools, and (c) failure to use existing tools efficiently.

A large proportion of STD cases go undiagnosed, particularly in women and girls, because 50% to 80% of their infections are asymptomatic. In addition, those women who do have symptoms, such as a vaginal discharge, are often unaware of any abnormality, and may also be discouraged from seeking medical attention through fear of stigmatization. Thus, even though most STDs other than HIV are relatively easily and cheaply treated, the burden remains high due to a lack of tools for diagnosis and failure to make services accessible to all who could benefit from them. Simple, affordable diagnostics for STDs are not generally available and without them, asymptomatic women will not receive treatment.

While diagnostics for HIV are reasonably good, interventions for treatment and prevention are inadequate. Existing antivirals against HIV are of limited efficacy and their cost puts them beyond the reach of most people in the low-income and middle-income regions, where 90% of infections occur. Recent advances with combinations of antivirals are encouraging, but combination therapies are even more costly than single drugs and even the established market economies are challenged by the prospect of financing their use. The emergence of resistance to antivirals has been observed to be rapid. There is no vaccine against HIV, and there are no practical female-controlled methods to prevent infection during sexual intercourse. The course of the research to date suggests that a lack of fundamental knowledge remains a serious obstacle to the development of most of these biomedical products.

In addition, a significant part of the burden from these diseases persists because of the health sector's failure to work adequately with other sectors to develop policies that tackle the root causes of vulnerability to STD infection. In the Committee's view, this can also be seen as a lack of effective tools, since policy instruments are themselves a form of tool. Those at greatest risk of infection are vulnerable or marginalized groups—often young, often female—whose poverty and/or lack of mutual control in partnerships puts them at heightened risk. Despite unprecedented volumes of published research into people's knowledge, attitudes, behaviour and practices relating to HIV and other STDs, the findings of these studies have rarely been used to design and implement policies that could increase vulnerable groups' control of their sexual health, such as changes to marital, divorce and property legislation. The health sector has only begun in the smallest degree to engage other sectors in helping to prevent the spread of infection and to reduce discrimination against those affected.

The Committee concludes that the reasons for the continued spread of HIV and its continuing high toll of disability and death must be attributed to a large extent to (a) a lack of knowledge of the disease itself and (b) a lack of tools (Table 4.8). The tools that may be required to address the burden of HIV include instruments of policy, as well as biomedical products. In the case of other STDs, lack of knowledge cannot be an explanation for the persistence of so great a burden; the Committee believes that some new tools (b), and some better use of existing tools (c), would together address much of that burden.

Table 4.8 Broad reasons for the persistence of HIV and other STDs

Condition:	Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools efficiently
HIV	+++	+++	
Other STDs		+++	+++

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

4.4.4 Priorities for strategic research

For HIV: As the above sections have argued, a greater understanding of HIV and its interaction with the human immune system is needed before a full range of effective products is likely to be developed. There are therefore strong arguments in favour of strategic research to:

- Continue virological studies of pathogenesis, but with greater focus on clinical isolates of the subtypes of HIV-1 found in high-prevalence regions, rather than continuing with laboratory isolates of subtype B, predominantly found in North America and Europe. This work should include continued effort to correlate genotype with phenotypic characteristics such as transmissibility, cell tropism and antigenicity with a view to vaccine design.
- Continue immunological studies to identify correlates of protection against HIV.

For all sexually transmitted diseases, including HIV: There is an equally important requirement for:

- Strategic health policy research aimed at identifying and quantifying the potential impact of different sectors (e.g. education, employers) on reducing vulnerability to infection.

In the shorter term, meanwhile, the knowledge base is adequate to enable some priorities for development and evaluation to be identified, although reliable cost-effectiveness assessments have not yet been made.

4.4.5 Key opportunities for intervention development and evaluation

In the Committee's view, three development activities are of particular priority:

- *Develop a safe, effective HIV vaccine that is suitable for low-income countries*

  Despite the comparatively large overall investment in HIV research to date, work on a vaccine has received disproportionately little funding (see Box 4.2). Yet the potential payoff from a successful vaccine may be greater than for any other intervention: vaccines provide relatively durable protection at relatively low cost. Detailed calculations of cost-effectiveness have not been performed for this Report although estimates by others indicate that vaccines would be an attractive investment. Critically, however, vaccines must be suitable for the epidemiological, virological and economic demands of high-prevalence regions.

- *Develop affordable and simple diagnostics for STDs*

  There is a clear need for cheap, effective and simple tools to improve the detection and diagnosis of STD infections, particularly for female use. Some activities are already under way (see Box 4.3). These diagnostics should be developed for incorporation into packages of health services, such as the Mother-Baby package and a family planning package discussed in Chapter 3.

- *Develop a vaginal microbicide*

  In common with other bodies, including UNAIDS, the Committee considers female-controlled methods of preventing infection with HIV and other STDs as a high priority and an International Working Group on Vaginal Microbicides is facilitating collaboration between different players. A number of microbicidal agents, including sulfated polysaccharides and existing spermicidal products, are under consideration. Because microbicides may also be spermicidal they would have the added advantage of protecting against unplanned pregnancy as well as against STDs. However, there may also be a need for microbicides that are not spermicidal, in order to allow women to conceive while still protecting themselves from infection.

  An important element of R&D to identify effective microbicides will be studies with potential users to determine acceptability and mechanisms for distribution. The required time and resources to develop and evaluate such a product are expected to be relatively modest.

  Some best buys on microbial threats are suggested in Box 4.4

4.5 Maintaining control of microbial threats: global surveillance

As we have argued, R&D efforts against microbial threats should be focused on organisms whose current and projected future burden is high and whose characteristics make their control complex for the reasons described above. Hence the focus on four diseases or disease clusters in this chapter. That said, the dynamic relationship between humans and microbes calls, by definition, for continued surveillance and readiness to respond to other unexpected microbial threats. While the emphasis should be on the four we have discussed, some additional effort should also be devoted to identifying and monitoring a limited number of other life-threatening organisms where (a) epidemiologic and microbiologic data identify a trend towards reduced control with the existing interventions, and (b) the *at-risk* population is considered to be large. These may include organisms that threaten hospital inpatient populations, and possi-

Box 4.2 AIDS vaccines: needs, opportunities and a new initiative

Despite worldwide efforts worth an estimated US$ 1.5 billion a year to prevent the spread of HIV, the virus is expected to infect more than 10 000 people each day between 1996 and 2000. Already, the direct costs of health care for people with HIV/AIDS exceed US$ 5 billion annually and are rising. Indirect costs are substantially higher. It has been estimated by WHO that even an immediate 10-to-15-fold increase in the available resources for prevention could reduce the number of new infections by at most half by the end of the decade. There is thus a growing realization that the current range of prevention activities will not be able to halt the epidemic, and that other biomedical interventions are urgently needed.

The development of safe and effective preventive vaccines against HIV would dramatically improve the prospects for controlling the epidemic. However, vaccines are a relatively neglected aspect of AIDS research. In 1993, less than US$ 160 million was invested in R&D on vaccines against HIV worldwide by the public and private sectors together—a small fraction of the total estimated R&D investment for AIDS—and of this only US$ 5 million was devoted specifically to vaccines research for low-income countries.

A vaccine for HIV will be useful only if it is made accessible to those at greatest risk of infection, mainly the populations of low-income and middle-income countries. However, the national research agencies and pharmaceuticals companies of the industrialized countries have so far dominated R&D for HIV vaccines, and their efforts have focused almost exclusively on products that would cater for the populations of those countries. For example, product development has been restricted to the subtype of HIV-1 found in North America and Europe, and to sequential study of the approaches that are considered safest, such as subunit vaccines. Approaches that carry greater perceived risk, such as the use of live attenuated virus, have not been commercially pursued. Some scientists and health policy-makers believe that if vaccines appropriate for global use are to be developed within the foreseeable future, a broader approach will be needed, based on multiple testing of empirical approaches.

The incentives for industry to invest in HIV vaccine research are limited by a number of factors:

- The science: although there have been rapid advances, there is no guarantee that a vaccine will be possible; risks are therefore high and the time line for development is long;
- The market: the epidemic of HIV/AIDS is slowing in the established market economies and accelerating in the low-income regions, particularly among marginalized or impoverished groups who cannot pay for expensive vaccines;
- Public policy: current policy on vaccine pricing, liability and bulk procurement are not considered favourable to industry, and it is not clear that HIV vaccines will receive any special considerations.

In order to overcome this market failure, a new global initiative has been formed. The International AIDS Vaccine Initiative is designed to accelerate the development of preventive vaccines. It was established following a series of meetings in 1994 and 1995 attended by scientists, public health officials, policy-makers, industry representatives and others. Its sole mandate is the development of a vaccine appropriate for where it is needed most. The initiative was incorporated in January 1996.

A small interim secretariat, housed temporarily at the Rockefeller Foundation in New York, is now working with a range of partners to broaden its support base and explore the options for encouraging investment by reducing the uncertainties and risks associated with vaccine development. Two options will be pursued:

- The development of a goal-oriented, targeted research effort that complements existing efforts and ensures that the needs of low-income countries are addressed. R&D will not be conducted directly by the initiative, but rather contracted out to those organizations worldwide that are best able to perform the tasks. Efforts will focus on HIV-1 subtypes that are prevalent in those regions where the epidemic is growing most rapidly. The initial seven-year R&D agenda has been costed at between US$ 500 million and US$ 600 million.
- Creating a more enabling environment for vaccine development through options such as: using international loan mechanisms to guarantee a market for a product with specified characteristics; reducing the potential costs of liability exposure (for example, by establishing a vaccine injury compensation programme or a specific vaccine insurance scheme); improving the legal and regulatory environment (for example, by harmonizing international regulatory procedures); and developing funding mechanisms that are sensitive to the needs and motives of industry, including the need for intellectual property rights.

bly agents of biological warfare. The strengthening of networks of surveillance laboratories with adequate staff capacity is an essential step towards this; the recent advances in information and communications technologies will enhance these efforts.

It is not for this Committee to attempt to create a de-

Box 4.3 New diagnostics for STDs needed: specifying the nature of a product

Sexually transmitted diseases are a major source of disease burden worldwide (Annex 1). Programmes to control and treat these diseases can be highly effective, but a large number of cases of infection go undiagnosed. Diagnosis is especially difficult in women, for whom most infections are without symptoms. The current diagnostic methods are often expensive and require trained staff, facilities such as refrigerators and sophisticated laboratory equipment. And in some cases, the results of tests are not available for one or two days. For all these reasons, the existing diagnostics can be unsuitable for use in low-income regions, whether rural or urban.

Effective diagnostics that meet global needs should be:

- accurate—appropriately sensitive and specific, taking into account the potential morbidity and cost associated with undetected infection and the cost of treatment;
- inexpensive—costing the provider less than US$ 1 per patient;
- simple—requiring minimal training, being simple to prepare and involving either straightforward equipment or no equipment;
- rapid—the results being available before the patient leaves the clinic;
- convenient—specimens being simple to collect and the test being acceptable within the local culture;
- stable—reagents having a long shelf-life and requiring no refrigeration;
- functional—being packaged simply and at low cost.

To hasten the development of appropriate new diagnostics, or the adaptation of existing ones, for use in settings with few resources, an international initiative has been formed. Initially independent and built up of STD experts from governmental and nongovernmental agencies, the STD Diagnostic Initiative has recently been moved to WHO. The initiative is striving to engage industry and the public sector in the search for better, more appropriate diagnostics and interacts with researchers, manufacturers, STD programme managers, clinicians, laboratory workers and representatives of international agencies. It has commissioned and shared the results of surveys of market requirements in low-income countries, has assisted with clinical testing of diagnostics, and has provided small grants and clinical specimens for research.

To further stimulate this process and attract the widest possible scientific participation, the Rockefeller Foundation in 1994 introduced its first Science for Development Prize: the STD Diagnostics Challenge. This prize, together with an award of US$ 1 million in cash, will be awarded to the first entrant who submits a rapid, reliable and inexpensive test or tests for chlamydia and gonorrhoea that is capable of detecting these infections while they are asymptomatic, and which meets a predetermined set of technical criteria governing its accuracy, costs and suitability for use in low-income countries.

The need for simple and cost-effective new diagnostics has wide acceptance. In 1995, the National Institute of Allergy and Infectious Disease (NIAID) of the U.S. National Institutes of Health released a call for new proposals to develop and evaluate simple and rapid tests for chlamydia and gonorrhoea. In September 1995, NIAID made four awards worth a total of US$ 2 million per annum over five years: two for chlamydia diagnostics, one for a gonorrhoea diagnostic, and one to an independent laboratory for evaluation of test performance.

finitive list of microbes that constitute such additional threats: others are more appropriately placed to do so within the existing mechanisms for infectious disease surveillance. The Committee's illustrative examples presented in Table 4.9 are simply suggestive. Resource allocation within this group should be guided by the relative size of the current burden and the potential future burden depending on the nature of the at-risk population, the current knowledge base, the promise of the R&D effort in terms of likely costs and time frames, and the existing investment (see Table 4.9).

4.6 Chapter summary and recommendations

Four communicable diseases or disease clusters have been identified as major threats to global health in coming decades: tuberculosis, pneumococcal disease, malaria, and sexually transmitted diseases including HIV/AIDS. The magnitude of the burden from these diseases today is high and their causative organisms pose strong technical challenges, such as the emergence and spread of drug resistance, that may affect future control. As a result, R&D efforts must be primarily devoted to the biomedical development of tools such as vaccines, new cost-effective drugs and diagnostics (see Table 4.10), with continued strategic research where the knowledge base is still inadequate for product development. In addition, some policy development is clearly needed to address the social factors that contribute to the spread of these infections.

Key opportunities for intervention development include improved forms of directly observed treatment, short-course, for tuberculosis and new prophylactic interventions to prevent the disease; pneumococcal vac-

Box 4.4 Best buys for R&D on the major microbial threats

For strategic research

- Sequence genomes of major pathogens
- Investigate factors influencing 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

cines suitable for young children in low-income countries; malaria vaccines; HIV vaccines, vaginal microbicides, and simple diagnostics and treatment algorithms for STDs.

The current levels of investment in R&D in TB, malaria and pneumonia are very low in relation to their share of global disease burden. HIV has received a far larger allocation of resources than the other communicable diseases discussed, but within that allocation, most funds have been spent in the established market economies. A much smaller amount has been devoted to R&D relevant to the HIV/AIDS burden in low-income countries, and R&D on STDs receives scant attention.

Recommendations

1. 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.

2. 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 antimicrobi-

Table 4.9 Additional microbial threats: illustrative examples

Microbe	Factors contributing to unstable control situation	Current trends
Shigella dysenteriae	Strains of *S. dysenteriae* Type 1 that are resistant to one or more drugs spread rapidly during 1980s.	Increasing resistance to affordable antimicrobials, especially in sub-Saharan Africa.
Trypanosoma parasites	Inadequate choice of drugs; significant toxicity problems with existing drugs.	Rapid resurgence in central Africa due to health system collapse.
Leishmania parasites	Enhanced pathogenicity in individuals co-infected with HIV.	Insidious spread in areas where antimalarial vector control efforts have ceased.
Enterococcus	Emergence of vancomycin-resistant strains.	An estimated 15% of enterococcal infections in intensive care units in the United States are vancomycin resistant.
Staphylococcus aureus	Emergence of multidrug-resistant strains in hospital environments, constituting a serious threat to elderly and other immuno-compromised populations.	Continued spread in hospitals and other care settings.

Table 4.10 Summary of priority interventions for the major microbial threats

Disease	Rank order among 96 causes of disease burden	Broad research direction needed towards 2020 to avert current and projected burden	Desired intervention(s) with high expected cost-effectiveness
Tuberculosis	7	++ New tools +++ Improve efficiency of existing interventions	New prophylactic interventions Improved formulation of short-course therapy for TB
Pneumococcus	1 (all ARI)	++ New tools +++ Improve efficiency of existing interventions	Trials of conjugate vaccines
Sexually transmitted diseases including HIV	Each now below 25, but HIV rising to 10 by 2020	+++ New tools + Improve efficiency of existing interventions for STDs other than HIV	HIV vaccine; vaginal microbicides; diagnostics
Malaria	11	+++ New tools + Improve efficiency of existing interventions	Vaccine, new first-line antimalarials

Note: The estimated rating ranges from little importance ('+') to extremely important ('++++').

al resistance, approaches to monitoring resistant strains, and approaches to slowing their emergence.

3. 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.

4. A Health Product Development Facility or Alliance (as discussed in Chapter 7) 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.