

Biotechnology and Sustainability

THE FIGHT AGAINST
INFECTIOUS DISEASE



OECD



BIOTECHNOLOGY AND SUSTAINABILITY THE FIGHT AGAINST INFECTIOUS DISEASE



ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

BIOTECHNOLOGY AND SUSTAINABILITY THE FIGHT AGAINST INFECTIOUS DISEASE

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Foreword

As we begin to analyse the economic impact of the outbreak of SARS, it seems improbable that any country could ignore or underestimate how infectious diseases can hamper sustainable economic growth. Yet, the number of deaths from infectious diseases continues to climb across the world, and the economic and social impacts, particularly of HIV/AIDS, continue to grow inexorably too.

It is abundantly clear that our global community must do more to deal with the human, social and economic costs of infectious disease. Official development assistance, co-operative research and development programmes, and strategies to overcome market failures all can play a role in turning back the tide of infectious disease. But what we need most is a real international partnership, with OECD countries shouldering much of the responsibility for delivery of the most vital of the pillars of sustainability – good health for all.

This pamphlet draws on the OECD Workshop on Infectious Diseases held in Lisbon in October 2002 and hosted by the government of Portugal, the Gulbenkian Foundation and their partners. It discusses some of the tools available to fight infectious disease. It reports some successes as well as many challenges: to make public-private partnerships work to deliver needed medicines and vaccines; to harness the phenomenal advances in the life sciences and technology in order to prevent and treat disease; and to find new ways to bring the benefits of intellectual property rights to a broader base of beneficiaries. These have all become familiar themes in international debate. But the OECD member countries have a particular responsibility in addressing these problems since together they account for a high proportion of global research and development capacity and market power.

If we want to reach – and not simply talk about – the targets set out in the UN Millennium Development Goals and reaffirmed at the World Summit on Sustainable Development in Johannesburg last year, then OECD countries will have to be the engine that drives sustainable global growth and good health. I therefore warmly welcome the publication of this pamphlet and hope it contributes to maintaining the momentum built at last year's Lisbon Workshop on Infectious Diseases and to delivering on the promise that biotechnology offers in the fight against infectious disease.



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**OECD Secretary-General
Donald J. Johnston**



A handwritten signature in black ink, which appears to read "Donald J. Johnston". The signature is written in a cursive, flowing style.

Preface

This pamphlet draws on a number of case studies to take stock of some of the lessons learned in the use of science and technology in the fight against infectious diseases.

Over 17 million people die each year from infectious diseases, many of which are classified as emerging or neglected. This collection of case studies shows that advances in the life sciences – biotechnology, genomics and informatics – can, if properly harnessed, contribute a great deal towards meeting this most challenging of humankind’s battles with nature.

The case studies featured were drawn from material presented at an OECD conference, “Biotechnology for Infectious Diseases: Addressing the Global Needs” held in Lisbon, Portugal, in October 2002. The workshop brought together experts from both the public and private sectors from over 30 countries in Europe, America, Africa, Australasia and Asia to consider the establishment of coherent international policies that might provide the right kind of environment for R&D on infectious diseases. Any errors or omissions in the short case studies presented in this pamphlet are the sole responsibility of the OECD.

The conference was hosted by the Portuguese government and the *Fundação Calouste Gulbenkian*, with additional financial support provided by the *Fundação Luso-Americana para o Desenvolvimento*, *Instituto de Cooperação Científica e Tecnológica Internacional*, *Ciência Viva*, *Fundação Portugal África*, the European Commission and the governments of Japan, Canada and the United Kingdom.

The OECD is immensely grateful to all of these bodies for their support for the Lisbon Conference as well as to Dr. Alexandre Quintanilha and his colleagues at the *Instituto de Biologia Molecular e Celular, Universidade do Porto*, who oversaw the organisation and delivery of proceedings; Dr. David Harper, CBE, Chief Scientist at the UK Department of Health, who chaired the conference; Dr. Philip Minor of the National Institute of Biological Standards, United Kingdom, who acted as conference rapporteur; and, last but not least, the many experts who took part. The rapporteur’s report of the conference can be found at www.oecd.org/biotechnology.



Biotechnology Unit
OECD Directorate for
Science, Technology and Industry
Paris, April 2003

Introduction

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*There can be no doubt
about the impact of
infectious diseases.*

No one in the modern world can be in any doubt about the impact of the growing number of infectious diseases we increasingly hear about in the media and encounter in our daily lives.

Unfortunately, the popular assumption that new forms of diseases seem to be cropping up more often than in our grandparents' time is largely true. Recent trends in how we live our lives, with increased travel, migration and concentration in urban areas, often side by side with animals, have accelerated the spread of new forms of infectious disease.

*Micro-organisms'
propensity to adapt is
causing resistance to
our front-line defences.*

Micro-organisms have a natural propensity to change and adapt. As a result of this natural process, together with changes in society, new diseases are emerging at an unprecedented rate, with a dramatic resurgence in some epidemic-prone diseases. Variants of micro-organisms that are resistant to the anti-microbials that form the front line of society's defences are developing.

*The result is a rapidly
evolving situation, as
the recent SARS
outbreak clearly shows.*

The result is a rapidly and sometimes dramatically changing global situation. At the time of writing, for example, there is growing international concern about the potential effects of a new form of pneumonia – severe acute respiratory syndrome, SARS – most likely caused by a newly emergent corona virus. Like many other infectious diseases, SARS has tragic human effects and threatens growth, economic development and prosperity. Several Asian countries are already seeing consumers spending less in SARS-affected areas as well as a downturn in travel and tourism. There is a growing perception of threat to investment given the increasingly mobile nature of capital.

The threat of infectious diseases

*HIV/AIDS was virtually
unknown 20 years ago,
but today infects more
than 40 million people
worldwide.*

The emergence of SARS is by no means an isolated event. Since the 1970s, at least 30 new infectious diseases have emerged for which no effective treatment exists. One of the most destructive diseases the modern world currently faces was virtually unknown 20 years ago, but today the HIV/AIDS epidemic has infected more than 40 million people worldwide, killed 3 million in 2001 and continues to spread around the globe.

Three global “priority” infectious diseases account for over 5 million deaths a year.

HIV/AIDS, together with the other global “priority” diseases, tuberculosis (TB) and malaria, account for over 300 million illnesses and more than 5 million deaths each year. These diseases are immensely destructive in economic and social as well as in human terms. Yet these “big three” still account for less than a third of the estimated annual total of 17 million deaths caused by infectious diseases.

Many more deaths are associated with so-called “neglected” or “emerging” diseases.

Even if diarrhoeal diseases – largely associated with lack of clean water in many countries – are added to the “big three”, some 7 million deaths associated with infectious disease a year are not accounted for. Many of these deaths – and many times that number of severe non-fatal illnesses – are associated with so-called “neglected” or “emerging” diseases.

Private and public investments to deal with these diseases have been insufficient.

Many if not most of the diseases associated with high mortality or morbidity suffered by those living in tropical areas fall into the category of “neglected” diseases. Private and public investment in developing ways to treat such diseases is generally small and insufficient. In the field of pharmaceutical treatment, for example, of the 1 223 new chemical entities (NCEs) that were subsequently commercialised between 1975 and 1997, only 13 (around 1%) were designed specifically to treat tropical diseases (and of these, two were improvements of existing treatments).

Developed countries are not immune.

It is perhaps therefore not that surprising that 95% of the 17 million deaths a year are in developing countries. However, the developed countries – predominantly OECD member countries – are not immune from the impact of these neglected and emerging diseases.

The West Nile virus has infected more than 1 700 people in the United States.

Since 1999, for example, West Nile virus, commonly found in Africa and the Middle East, has infected more than 1 700 people in the United States and caused more than 80 deaths. With immigration and personal and business travel, diseases spread faster than ever before. The traditional assumed borders to movement of diseases no longer offer the security that parts of the world have come to rely upon.

Diseases that appeared close to eradication are staging a comeback...

Diseases that once were thought easy to control or near to being eradicated at least in wealthier countries are reappearing, as mentioned in Case Study 1. In the early 1990s, the United States spent nearly USD 1 billion dealing with what were ultimately only 350 cases of multi-drug-resistant tuberculosis in New York. The resistant strain of the TB bacillus which originated in Russia and Asia exerted a serious financial drain on the world’s largest economy.

...and others might return through deliberate acts.

Diseases that were considered eradicated, either throughout the world, such as smallpox, or in large regions, such as plague, may also be a threat. In these cases, however, the potential agent of delivery would not be an innocent traveller or immigrant, but a terrorist deliberately acting to wreak havoc and bring death.

Infectious disease and sustainability

Given its impact...

These 17 million premature deaths and innumerable serious illnesses obviously affect economic growth, development and prosperity, as well as security and sustainability. This is brought starkly home by the case study on the impact of HIV/AIDS on the South African education system.

...the growing tide of infectious diseases will need to be turned back.

If the global community is serious about achieving sustainable development and growth in the world economy, the rise in infectious diseases will need to be halted and not only in the currently developed economies.

The urgency of this issue...

The international community has come to recognise the urgency of this issue, and a strong international consensus has been developing on the need to address inefficiencies in global health research for infectious diseases, the barriers to effective R&D and market failure.

...is recognised by the international community.

In 2000 the G8 community at Okinawa stated the need for "sustained action and coherent international co-operation to fully mobilise new and existing medical, technical and financial resources in the fight against infectious diseases" and proposed an initiative to tackle major infectious diseases worldwide. This commitment was reiterated in 2002 at the G8 summit in Kananaskis (Canada) and at the Johannesburg (South Africa) World Summit on Sustainable Development.

There is no doubt that it is in the world's collective interest to find solutions to the emergence or re-emergence of new or previously unrecognised pathogens and the diverse threats to public health from such diseases.

Recent international activity includes a number of public-private partnerships.

A number of public-private partnerships have been established, also at the international level, such as the Medicines for Malaria Venture, the Global Alliance for TB Drug Development and the Global Alliance on Vaccines and Immunisation. These are complemented by partnerships such as Stop TB and Roll Back Malaria which aim to control these diseases which receive reinforcement from the Global Fund on AIDS, TB and Malaria.

A number of potential products for treating emerging and neglected diseases are ready for late-stage development but lack funding to bring them through late phase clinical trials. Therefore, in 2002 the European Commission established a European Clinical Trials Platform to support "a common programme of research activities concerning clinical trials of both preventive and therapeutic interventions for HIV/AIDS, malaria and TB". The platform aims to facilitate and accelerate clinical trials, act as a broker between the EC and other international partners and make European trial sites attractive to industry.

However, initiatives on emerging and neglected diseases are far fewer.

While many of these recent high-publicity ventures focus on the “big three” and several are making notable progress, there are far fewer initiatives on the emerging or neglected diseases that account for such large-scale human suffering.

More of OECD countries’ science and resources...

OECD countries could do a great deal in this area. Together, they account for over 95% of basic scientific research, command 85% of the world’s economic resources and act as home to only 18% of the world’s population.

...could be used to address these diseases.

Bringing their science and technology to bear on the problems of emerging and neglected diseases would not only serve humanity, it would help to drive economic growth, development and prosperity in both developing and developed countries. Together they could meet the challenges of infectious disease, whether emerging such as SARS, neglected such as West Nile virus or deliberately introduced by terrorist acts.

A new “health pact” between governments and development agencies is needed.

Money alone will not solve the problems. The key message in the December 2001 report of the Commission for Macroeconomics and Health was that the resources and know-how exist to save millions of lives. However, the Commission considers that a new “health pact” between governments and development agencies is needed, with both parties making significant increases in their resources for health. This means increased funding but also more focused attention on mobilisation, management and delivery of resources and greater coherence in international policy making and action.

OECD’s Lisbon Workshop on “Biotechnology for Infectious Diseases: Addressing the Global Needs”

A key challenge for the international community is to work together to fight infectious disease...

A key challenge for the international community is to help the many efforts being made worldwide to become mutually reinforcing. We need to identify areas where action is lacking or insufficiently known. We need to better understand the factors that motivate R&D decisions, how to focus a research agenda to meet global health needs and what policy mechanisms might successfully act as incentives to bring R&D capacity to bear.

...and biotechnology, genomics and informatics offer many useful tools.

Biotechnology, genomics and informatics offer a growing range of approaches to help prevent, monitor, detect, diagnose and treat infectious diseases. Appropriate policies are however necessary to ensure that the right tools reach the right people at the right time.

At the conference hosted by the Portuguese government ...

The OECD conference, hosted by the government of Portugal, brought together experts from over 30 member and non-member countries under the auspices of OECD’s Working Party on Biotechnology to review case studies and take stock of lessons learned as a basis for establishing coherent international policies that may provide the right kind of environment for R&D on infectious diseases.

...policy issues, R&D and tools for combating were the focus of discussion.

Advances in biotechnology, genomics and informatics and their potential for providing effective tools to combat infectious diseases were at the heart of the debate. Interestingly, the decoding of the genomes of the main malaria parasite (*plasmodium falciparum*) and the mosquito (*anopheles gambiae*) that spreads it was announced during the week of the conference.

This pamphlet brings out some of the key themes of the conference.

This pamphlet presents some of the main themes addressed at the conference and points to some successes and to some challenges facing the international community for deploying biotechnology and appropriate R&D to meet the growing threat from infectious disease. It is not intended to be a detailed report of the conference.

Readers interested in finding out more about the Lisbon workshop are directed to the OECD Web site, where they will find the programme of the meeting, the rapporteur's report and abstracts of many of the presentations, including those from which the case studies in this pamphlet are drawn.

Portugal's hosting of the conference may be symbolic.

In the 19th and early 20th centuries, Portugal, like most of southern Europe, suffered major malaria epidemics, with over 100 000 cases a year. Eradication was finally and successfully achieved in 1958. After that date, the country saw a surge of economic growth associated with increased foreign investment and tourism.

The battle it has waged against infectious diseases and must again wage today is a challenge and a burden to be shared with all the global scientific community.

Portugal is now experiencing new waves of infectious diseases owing in part to significant numbers of immigrants. It is thus profoundly affected by the issue of dealing with infectious diseases: how to maintain economic development, growth and prosperity both at home and overseas and how to harness the scientific and technological capacity of a country enjoying the benefits of that growth for the benefit of all. For a country with a proud history of discovery, the fight against infectious diseases will be challenge and a burden to be shared with all in the global scientific community.

The Human and Economic Challenges

It is often difficult to understand the full impact of infectious diseases both on people...

The impact of infectious diseases on people, societies and countries is often talked about, but the statistics used often seem abstract or difficult to understand. Their treatment by the media may sometimes lead to the assumption that affected societies will somehow adapt or recover.

...and on society.

Unfortunately, this is not necessarily case, especially when outbreaks are in countries with relatively poor communications and stretched public resources. Infectious diseases are by their very nature self-sustaining and their most devastating impacts progressively affect the sustainability of the communities they attack.

This case study illustrates the self-sustaining nature of infectious diseases...

The case study describing the systemic impact of the AIDS pandemic on the education system in South Africa amply illustrates the self-sustaining nature of infectious disease and uses statistics that are understandable to all.

...and their destructive economic effects.

It was chosen first to give a context for the nature and size of the problems caused by infectious diseases and second to illustrate the nature and destructive scale of the economic challenges caused by such diseases, even in relatively developed transitional economies.

Case Study 1. The Systemic Impacts of the AIDS Pandemic

Three million people died of AIDS in 2001.

Worldwide, 40 million people are believed to have AIDS. Three million died of the disease in 2001. In Sub-Saharan Africa the disease is present on such an appalling scale that its effect goes well beyond the lives of its victims. The structure and functioning of the societies concerned are being systematically eroded. Statistics on the effect of AIDS on education are relatively accessible and reveal the extent of the social erosion. If a cure or vaccine became immediately available, the effects would persist for decades because of the severe degradation of the social fabric.

The peak ages of HIV infection are 20 to 40.

The most direct demographic consequence of AIDS is an increase in mortality in the age groups that typically have the lowest mortality rates. Since AIDS is primarily spread sexually, the peak ages of HIV infection are 20 to 40, and the peak ages of AIDS death are five to ten years later. AIDS has been identified as the major cause of deaths of adults aged 15-44 in Abidjan and of adults aged 15-59 in Tanzania.

AIDS creates orphans.

One of the worst consequences of AIDS is that it creates AIDS orphans as children's parents die from the disease.

In South Africa, 2 million children are expected to be orphaned by the end of the decade, and teachers are leaving the profession faster and faster.

There are 10 million schoolchildren in South Africa. Two million are expected to be orphaned by the end of the decade. A quarter of these orphans will be in the province of KwaZulu-Natal, where 36% of the population is infected with HIV and will die of AIDS. Enrolment in these schools dropped by 12% in 1999 and 24% in 2000. Teachers are leaving the profession faster and faster; the exodus is driven by the increase in demand for educated workers in other parts of the economy because of the effects of the disease. It is predicted that 60 000 extra teachers will be needed by 2008. Today the total teacher workforce is 75 000.

But educators also suffer from AIDS.

Educators themselves also suffer from AIDS, with a peak mortality between ages 35 and 39 for both men and women. The disease is thus a significant destabilising force in much of the region. It is removing many of the most productive members of society and devastating the social and economic infrastructures.

Investment in education, careers and economic advancement practically become non-issues.

The rate of infection is such that monthly monitoring is necessary. Today in Sub-Saharan Africa a 15-year-old girl has a 52% chance of reaching age 60. By 2010 she will have about a 30% chance. With this kind of outlook for African youth, investment in education, careers and economic advancement becomes almost irrelevant. In South Africa, there is currently a 2.6% annual decline in enrolment and rising pupil absenteeism.

The education system has strong effects on other social systems.

The education system does not exist in isolation, and other effects are likely to occur:

- There will be growing numbers of dependent orphans, school drop-outs and other vulnerable children in the community and in migration patterns.
- Household and community “wealth” will decline owing to loss of bread-winners and subverted expenditure.
- With the decline in the number of experienced teachers in communities, fewer will be available to guide and influence community life.
- The growing incidence of illness and mortality will change the social patterns of community life and work.
- The flow of skilled labour will decrease and the flow of unskilled and dependent labour will increase.
- Child labour on the land and in the home may increase.

Policy makers need to understand the broader impacts of the HIV/AIDS epidemic and how it can increase poverty in many countries.

Policy makers have assumed HIV/AIDS to be almost exclusively a public health issue and have often failed to recognise it for the development, economic and systemic management challenge it is. They need to understand the broader impacts of the HIV/AIDS epidemic, how it can undermine entire social structures in a profound and enduring way, increasing and deepen the poverty level in many countries.

A multi-sectoral approach, greater policy coherence and sustainable solutions are needed.

In 2001, G8 members agreed that an effective response to HIV/AIDS and other infectious diseases will require society-wide action. Two years later, the challenge increases. To respond effectively it will be necessary to move from a sectoral to a multi-sectoral approach and to seek greater policy coherence and sustainable solutions in the fight against infectious diseases.

Surveillance

Most infectious disease outbreaks can be successfully responded to with effective surveillance.

Almost all infectious disease outbreaks can be responded to more successfully if they are detected early. Early detection largely relies on effective surveillance. Of course, surveillance and detection are closely linked. The current SARS outbreak serves to demonstrate this point. At first, the disease is identified by the symptoms observed—hence the name, severe acute respiratory syndrome. Detection of disease and surveillance of its occurrence and spread are based initially on symptomatic reporting. Once the disease agent is identified, other, more exact methods can be used to monitor occurrence and outbreak, so that, at least in principle, faster ameliorative action can be taken.

Current methods of surveillance have strengths and weaknesses.

The two systems of surveillance — symptomatic and pre-symptomatic, which are based on monitoring the presence of an infective agent — have strengths and weaknesses. Each is only as good as the reporting and response system in which they are located. This has been one of the lessons learned — this time in China — from the current SARS outbreak.

Effective surveillance depends on time and accuracy, and advances in biotechnology and informatics can help with both.

Effective surveillance is time-dependent, but it is also dependent on accuracy. Advances in biotechnology and informatics can help with both, for example, by offering micro-arrays that detect multiple pathogens and almost real-time alerting over IT networks. Bringing the best in high-technology sciences together (in this example, genomics, bioinformatics and information technology) — so-called converging science — offers much for the future. However, even such systems depend as much on their context and response infrastructure as the more traditional surveillance systems.

This case study looks at the application of converging sciences to resistant TB strains.

The case study chosen here — surveillance for antimicrobial-resistant strains of tuberculosis — is an example of the use of the converging sciences of genetic fingerprinting, nanotechnology and automated digital analysis to follow and predict patterns of spread of these difficult-to-treat TB strains. Besides showing the potential of biotechnology and other sciences for accurate surveillance, it amply demonstrates the challenges — not least the need to catalogue extant strains of TB in different parts of the world to get the most out of the technology. Surveillance systems that do not differentiate effectively between different strains of a pathogen have economic consequences. The techniques described here were largely developed as a consequence of outbreaks of antimicrobial-resistant TB that were not initially recognised as such. In one such case in the early 1990s the United States spent nearly USD 1 billion dealing with what became just 350 cases of multi-drug-resistant tuberculosis in New York alone.

Case Study 2. Converging Sciences for Improved Surveillance

Tuberculosis kills 2.5 million people a year but was thought to be a disease of the past in developed regions.

Although tuberculosis kills around 2.5 million people a year worldwide, in most developed regions the disease was thought until recently to be a thing of the past. The use of antibiotics and better living conditions meant for many years that cases were few and far between. However, it has recently become a resurgent disease, particularly in Eastern Europe. Its decline in Western Europe and the United States is now threatened by a number of factors:

1. More and more strains are drug-resistant, owing in part to the need to take antibiotics for very long periods to eliminate the disease completely. Many patients do not finish the full course of treatment. Because the causal micro-organisms are not eliminated, drug-resistant or tolerant strains are selected for and multiply in patients.
2. HIV/AIDS impairs patients' immunity and makes them more vulnerable to TB. TB and HIV/AIDS rise in parallel.
3. There is increased migration from endemic areas. As a result the disease and resistant strains are imported into areas where they were not previously a problem.

The incidence of TB in Eastern European countries doubled in ten years between 1990 and 2001.

The incidence of TB in Eastern European countries doubled between 1990 and 2001. Many of the isolates were resistant to one or many antibiotic drugs. Russia is among the 22 countries that account for most of the world's TB, with an estimated incidence of 132 cases per 100 000 population in 2000. In the global ranking of countries by number of TB cases, Russia ranks tenth. Moreover, the Russian prison system, where there are 3 200 cases per 100 000 individuals, 35-40% of it drug-resistant, is a dangerous reservoir of tuberculosis.

There is a need for accurate information and easy ways to identify resistant strains.

Drug resistance makes control difficult and presents an obvious hazard to world health. The disease is harder to treat, and patients remain infected and therefore infectious for others over longer periods if physicians are not aware of the drug resistance. The threat is obvious, and accurate information and easy ways to identify resistant strains should they arise are needed.

Conventional methods for diagnosis have certain limitations.

Conventional methods for diagnosing tuberculosis rely largely upon stain and culture procedures dating back to 1882 when Robert Koch identified the organism. The test is inexpensive and can yield results within a day, but it has a number of limitations. It is not specific for *Mycobacterium tuberculosis* (the causal agent of TB) and so can indicate false positives. The sensitivity of the smear also may be limited by factors such as the concentration of bacilli in the specimen (a degree of skill is required for this to result in an easy-to-read assessment). The positive identification of drug-resistant tuberculosis depends on its growth in culture which may take from four to eight weeks.

Modern molecular biological methods, known as “genetic fingerprinting”...

In contrast, modern molecular biological methods of strain identification can be simple, accurate and easy to apply. Since the mid-1980s several amplification technologies have been developed which hold promise for rapid detection of tuberculosis. Among these, polymerase chain reaction (PCR) is a very powerful tool and its application has become popularly known as “genetic fingerprinting”.

...bring significant benefits, such as...

Significant benefits can be gained by using these molecular-based diagnostics to monitor the spread of drug resistance. For example, the genetic “fingerprint” of strains that are known to be drug-resistant can be easily and unambiguously established by examining the nucleic acid of the organism by PCR, supplemented by other procedures. When this fingerprint is found in an unknown strain it is certain to be drug-resistant. These methods have been applied in Eastern European hot spots for resistant strains including Latvia (22% of all isolates are strains resistant to two or more drugs) and Estonia (12% of all isolates are strains resistant to two or more drugs).

...rapid field detection and a move to a virtual surveillance network of infectious agents.

Unfortunately the data are not comprehensive. Only about a quarter of the European region is covered because of shortcomings in obtaining isolates. There are political and economic as well as technical reasons for these shortcomings, which technological solutions may nevertheless overcome. Bringing together genetic fingerprinting methods with nanotechnology and automated digital analysis offers the possibility of rapid field detection and a move to development of a virtual surveillance network of infectious agents without the need for resource-intensive molecular biology laboratories or surveillance data collation centres at many sites.

Converging science offers new approaches, but needs to be set in the context of a coherent overall strategy.

Converging science offers new approaches but needs to be part of a coherent overall strategy, even if specific tasks within the strategy may change as new technologies are deployed. A particular problem for applying technology to identify TB strains by genetic fingerprinting in a broader area than that in which it was developed is simply the propensity of micro-organisms to evolve and adapt.

A more comprehensive catalogue of drug-resistant strains circulating in the world is needed...

As a result, strains circulating in other regions may be different from those in Europe and therefore not identified as drug-resistant by their fingerprint. For example 13% of isolates from India were found to be multiple-drug-resistant strains that were similar in terms of their genetic fingerprint to those circulating in Europe. However when all of the isolates were tested in culture about 20% were resistant. A more comprehensive catalogue of the world’s drug-resistant strains is needed.

...and global surveillance must be maintained.

In this case, global surveillance and a global collection of isolates must be maintained. These organisms pose a major threat to public health worldwide, particularly because of increasing movements of individuals and populations. The threat cannot be overcome by concentrating solely on developed countries.

Technology needs infrastructure and international communication and co-operation.

There are obvious lessons to be learned from this case study. Technology can do much to improve surveillance, but whatever the approach used, infrastructure and appropriate international communication and co-operation are necessary.

Detection and Diagnosis

Diagnosis has been revolutionised through the use of “point-of-care” diagnostics.

Effective diagnosis falls into a category similar to effective detection or effective surveillance. The challenges are to recognise infective agents quickly and accurately.

The growing use of so-called “point-of-care” diagnostics has radically changed the science of diagnosis. These diagnostic tests are used by physicians or other health professionals where they actually care for patients. They allow for rapid diagnosis without the need to collect samples, maintain them in an uncorrupted form, send them to a remote laboratory for analysis and wait for the results. They are faster and in many cases eliminate false negatives or positives.

The key challenges are to make such diagnostics widely applicable and available.

The key challenges are to make point-of-care diagnostics available for a wide range of infectious diseases, including neglected and emerging ones, supply them at a low cost, and ensure that personnel are adequately trained in how to use them.

Case Study 3. Biotechnology for Point-of-care Diagnostics

Biomedical diagnostics play a crucial role in the effective diagnosis and treatment of patients.

Biomedical diagnostics, like laboratory tests, play a crucial role in the effective diagnosis and treatment of patients in healthcare systems throughout the world. For correct and timely treatment, laboratory tests complement conventional physical examination to confirm diagnoses by doctors and nurses.

Diagnosis based on symptoms...

Diagnostic tests have recently gained in importance because of the shortcomings of an approach based primarily on symptoms or clinical signs of disease. The increase in atypical infections, such as TB in conjunction with HIV and the occurrence of asymptomatic infections, make diagnostic testing vital.

...can be unreliable, undermining their relevance for treatment.

To improve effective treatment, governments of many developing countries have adopted a national essential drugs policy, which involves lists of essential drugs and standard treatment guidelines for each country's health problems. However, the diagnosis on which the treatment recommended in the guidelines is based is often unreliable owing to a lack of appropriate and effective laboratory tests. As a result, the relevance of national essential drugs policies and standard treatment guidelines is undermined.

Useful laboratory tests are often unavailable.

There are many reasons for inadequate availability of relevant laboratory test results. These include lack of diagnostic assays, selection of inappropriate laboratory diagnostics by health authorities, limited maintenance of diagnostic equipment, incorrect use of diagnostic equipment and tests by health workers, limited possibilities for quality control and assurance, patient expectations and out-of-pocket fees that make laboratory tests unaffordable for some segments of the population.

In the absence of appropriate and effective laboratory diagnostics, individual patients' health will worsen and communities will suffer. New tools are needed to improve the effectiveness of laboratory diagnosis but it is also necessary to develop affordable, simple and robust point-of-care diagnostic tests that can be performed outside the laboratory.

Developments in automation and near-patient care offer real opportunities for low-income countries.

It is expensive to develop simple but robust assays. However cost-containment pressures in industrialised countries have recently steered the market towards automation and near-patient care. Since the point-of-care diagnostics used in industrialised countries have the technological basis of the simple tests needed in low-income countries, there is now a real opportunity to benefit from these developments.

Point-of-care diagnostic and test devices are used close to the patient...

Point-of-care diagnostic and test devices perform clinical laboratory analyses close to patients, whether inside or outside a hospital, but at a distance from the clinical laboratory. Tests currently available include those for glucose, pregnancy, infectious disease (respiratory, sexually transmitted), critical care analytes (blood gases, electrolytes, metabolites, etc.), prothrombin time and cardiac markers.

...and at least 70 are available today.

There are at least 70 analytes for which a miniaturised version of a traditional laboratory-based test is currently available. Over 100 companies sell these tests around the world. In 1999, point-of-care devices (excluding those for diabetes and pregnancy testing at home) generated approximately USD 1.5 billion in sales worldwide.

Biotechnology, together with advances in a range of technologies, offers new solutions to meet today's health-care delivery needs.

Many of the point-of care technologies used today were designed 10-20 years ago and provide qualitative test results that are read visually and recorded by hand. This approach no longer meets the needs of today's healthcare delivery models. Biotechnology, together with advances in digital technologies, optical and near infrared techniques as well as minimally invasive devices to collect blood, breath, saliva, interstitial fluid and sweat samples offer new solutions.

In the field of infectious diseases, molecular diagnostic methods replace conventional methods that lacked sensitivity, specificity or were simply too slow. These new molecular techniques have already significantly affected the diagnosis and management of infectious diseases. In many cases, molecular diagnostic tests provide relevant results almost immediately. This allows clinicians to decide and start the correct course of treatment more promptly, as standard infectious disease tests are generally much slower.

Future point-of-care methods may have capabilities that older methods did not ...

While such tests are not yet available, the new point-of-care methods have capabilities for detecting and identifying bacteria, viruses, parasites and fungi that older methods do not. They provide ways to screen for a broad range of agents in a single test. For instance, the 16S rRNA gene sequences of bacteria can be used to detect all eubacteria and to identify bacteria at the genus and species levels. The development of multiple assays such as multiplex PCR means that several bacterial species can be detected and identified in a single assay. Molecular methods are especially useful for bacteria that are hard to culture, such as *Neisseria*, *Legionella*,

...and allow for tests that would be impossible with conventional techniques.

New methods on the horizon...

...also offer a real opportunity to meet the needs of those afflicted with neglected or resurgent diseases.

Borrelia and Mycobacterium species.

It is also now possible to perform tests that would be impossible with conventional techniques. For instance, virulence genes in infectious agents can be directly identified, so that pathogenic bacteria can be distinguished from accompanying colonizer bacteria. Such new assays also facilitate better methods of clinical research.

Methods based on micro-arrays and biosensors are on the horizon. In the medical sector, biosensors have largely been based on antibody technology, with an antigen triggering a transducer or linking to an enzyme amplification system. Biosensors based on gene recognition hold out much promise, particularly if coupled with micro-array technologies which make it possible to process together several different probes targeting many different pathogens.

While these technologies may be developed initially to meet the demands of evolving health care systems in OECD countries, the opportunity to spin out the technology at relatively low cost to meet the needs of those afflicted with neglected or re-emergent diseases should not be missed.

Prevention

Evaluations of preventive medicines tend to underestimate the benefits.

Two case studies of vaccine delivery...

... address so-called “reverse vaccinology”...

...and local needs in vaccine design and production.

The venerable adage that “an ounce of prevention is worth a pound of cure” is as true for cost effectiveness as for human suffering.

Cost-effectiveness assessments of preventive medicines, particularly vaccination programmes, have perhaps tended to underestimate cost effectiveness given that the savings gained by avoiding the opportunity costs associated with lost skills and days of employment (see Case Study 1) may not be included in the analyses.

The case studies presented here illustrate two facets of vaccine delivery: high-technology, genome-based, molecular approaches to vaccine design using “reverse vaccinology” and adapting technology to local needs.

The first describes a wholly new approach to vaccine design that has only become possible with the advent of genetic sequencing and whole organism genomics. Conventional methods of developing vaccines took years and were often unsuccessful, while vaccine design based on computer analysis of the entire genetic sequence of microbial pathogens – so-called “reverse vaccinology” – yields much faster and more effective results.

The second case study addresses the fact that a vaccine for a particular disease may be vital in one country but marginal in another. Technology – and vaccine design and production – need to be targeted to local needs, even in a global marketplace.

Case Study 4. Genomics Offers Solutions: Reverse Vaccinology

Vaccines are among the most cost-effective methods for promoting human and animal health.

Vaccines are among the most cost-effective methods for promoting human and animal health. They have been in clinical use for at least 200 years. In the past, they were derived by purely empirical methods; for example the pathogen was grown under abnormal conditions in unusual host animals or cell types until variants could be isolated, tested for virulence and used as vaccines if suitable. Alternatively, or until a variant could be isolated, the pathogen was killed or attenuated and tested as a vaccine.

Developments in molecular biology and genomics over the past decade have raised the possibility of replacing this successful but essentially random and time-consuming method.

Reverse vaccinology offers a “fast track” approach to finding vaccine candidates...

The complete genomic sequence of a human pathogen represents in fact a new field to be exploited for designing novel vaccines and antimicrobial drugs. Reverse vaccinology, a new method based on genomic information and computer predictions offers a “fast-track” approach to finding vaccine candidates for diseases that previously had frustrated researchers.

...and has been applied successfully to create a vaccine against meningococcus, which causes meningitis...

The technique has been successfully used to generate a vaccine against a deadly bacterium known as meningococcus that has escaped scientists for decades. It is one of the most common causes of meningitis, a severe disease of the brain. It normally lives harmlessly in the throat but if it infects the brain, the disease must be recognised at once and treated very aggressively with antibiotics or a previously healthy person will be dead within a few hours or be left severely brain damaged.

Meningococcus is one of several bacteria that can cause meningitis, and it can also cause septicaemia. In this case the bacteria infect the entire body. Again if the disease is not treated rapidly the victim will die, and it is often necessary to amputate limbs to save lives. Teenagers, young adults and the very young are particularly at risk.

Serotype A is the cause of most major epidemics in developing countries.

There are four known serotypes or groups of meningococcus at present, termed A, B, C, W and Y. Meningococcal serotypes A, B and C are responsible for the vast majority of morbidity and mortality. Serotype A is the cause of most major epidemics in developing countries. Explosive group A outbreaks typically occur in countries of the so-called meningitis belt which extends across Africa from Senegal to Ethiopia. A number of epidemics have occurred outside the African continent since 1970 in India, Nepal, Mongolia, Brazil, Chile, Cuba and Vietnam. In other areas of the world, group A infections are less common, and groups B and C cause most meningococcal disease.

While a vaccine is available for group C, there is no vaccine yet for group A.

A group C vaccine has been available internationally since 1999. It was developed in the United Kingdom and has proved safe and highly efficient in controlling group C meningococcal disease in that country. No vaccines are yet available for group A and B strains.

The group A strain that is the cause of most major epidemics in developing countries is much less a health threat in developed countries and the UK vaccine programme gave development of a vaccine against group A lower priority than a vaccine against group C. For similar reasons, no other vaccine programme in any other developed country has successfully developed a group A vaccine.

A consortium was established to develop group A vaccines.

In 2002, however, a private-public consortium involving a major vaccine manufacturer, non-governmental organisations (NGOs) and international organisations was established to speed up the development of group A vaccines.

Group B poses particular problems...

Group B meningococcus poses a different problem from groups A and C as some of the molecules that present target antigens on the organism are very like those found in human tissue. The immune response produced by vaccination with such antigens would be likely to attack the organs of the person vaccinated and produce serious side effects. Other components of the bacterium must therefore be used. Efforts over 40 years led to 15-20 possibilities, none of which proved effective enough.

...and reverse vaccinology was used to identify candidate proteins that have since been used to develop a vaccine.

Reverse vaccinology was therefore tried. The entire sequence of the genome of the organism was determined and the proteins likely to be surface components (and thus target antigens to stimulate the body's immune system) were identified through computer predictions on the basis of their structure or by analogy with other known proteins, and 600 candidate proteins were selected. Of these, 350 were expressed by standard molecular biological methods and 29 were found to be promising in animal trials. Five of these candidates were included in a vaccine that is currently undergoing clinical trials.

This process took only 18 months compared to the 40 years of the ultimately unsuccessful standard approach.

This sounds like, and is, an enormous programme of work, yet the whole process took only 18 months (recall the 40 unsuccessful years of the standard approach). The process illustrated by the work on meningococcus type B is one of the most exciting and promising approaches to modern vaccine development. The same approach is now being applied to several micro-organisms and is likely to lead to the development of many novel vaccines.

This case study illustrates not only the power of genomics allied with information technology in reverse vaccinology but also some notable aspects of the economics of vaccine development.

Vaccines are not an attractive area for the private sector.

Although vaccines represent the most cost-effective medical interventions known, the balance of risk and rewards is generally less attractive to the private sector than for the development of therapeutic medicines, simply because R&D and production costs tend to be higher and potential financial returns lower. Overall, the global vaccine market forms only around 2% of the USD 240 billion world pharmaceutical market.

Their development and manufacturing are often challenging and risky.

Vaccine manufacturing is often more challenging than manufacturing of therapeutic medicines and strict batch control is necessary. Often strict requirements for storage and transport add to the difficulties and, together with relatively low rates of return, may make development of vaccines, particularly for markets in poor countries, a risky investment for the private sector.

The structure of market incentives and disincentives would seem to need reassessment.

The structure of market incentives and disincentives for vaccine development, especially for emerging and neglected diseases that predominantly affect poorer countries, may need reassessment if breakthroughs are to be made. Governments may need to take on a greater share of the R&D risk, either through public-private partnerships or through market mechanisms.

Case Study 5. Adapting Technology to Local Needs: Vaccine Development and Production

National needs differ...

A vaccine against a particular disease may be vital in one country but marginal in another. Highly cost-effective vaccines against diseases in developed countries may be of limited significance in developing countries. Conversely, a major killer in a developing country may be unimportant elsewhere.

...as rotavirus indicates.

Rotavirus offers an example of such differing national needs. Rotavirus is the most common cause of severe diarrhoea among children. Oral rehydration therapy (ORT) remains the basic treatment for rotaviral symptoms, but there is still no effective preventive measure, no cure and even ORT is often not used in developing countries. Rotavirus affects 130 million children under the age of 5 every year and results in over 600 000 deaths, the majority in developing countries.

A rotavirus vaccine was originally developed in the United States but was withdrawn from the market.

A rotavirus vaccine based on a live attenuated virus was licensed in the United States in 1998. It was originally developed in the United States National Institute of Allergy and Infectious Disease and was the first effective vaccine to prevent rotavirus gastroenteritis approved for use in the United States. It reduced hospital admissions and it was hoped that it would shortly reach developing countries, where the need is so pressing. However, by July 1999, soon after the vaccine was introduced, 15 vaccinated infants had developed an uncommon but potentially life-threatening form of intestinal obstruction called intussusception. The vaccine was therefore withdrawn from the market and the company abandoned work on it.

Intussusception is a form of intestinal obstruction that can require surgery.

Intussusception, diagnosed most often in infancy and childhood, strikes about 2 000 infants (one in every 1 900) in the United States in the first year of life. Incidence begins to rise at about 2-3 months of life, peaks at 4-9 months, and gradually declines at around 18 months. The condition often resolves itself, but the blockage can require surgery. In the United States, intussusception is rarely fatal.

The US Centers for Disease Control and Prevention (CDC) conducted a series of studies to examine evidence for a temporal association between the rotavirus vaccine and intussusception. From epidemiology data, CDC experts projected there would be one extra case of intussusception for each 2 500-5 000 infants receiving the vaccine. More recently, after further analysis of the data, the CDC revised the risk magnitude downward by approximately half.

The vaccine had demonstrated high levels of efficacy.

In clinical trials carried out in the United States and Europe involving 10 000 subjects, the vaccine demonstrated 48-83% efficacy for any severity of rotavirus gastroenteritis; 70-100% efficacy for severe rotavirus gastroenteritis; and up to 100% efficacy for hospitalisation due to rotavirus gastroenteritis.

The next candidate vaccine may well have to undergo more rigorous testing.

The withdrawal of this vaccine means that the next candidate vaccine may well have to undergo more rigorous testing, involving larger and more expensive clinical trials. This may become a dauntingly high barrier to entry to the development of another vaccine.

In India, rotavirus infection in the young is commonly fatal...

In India, rotavirus infection in the young is commonly fatal. About 20 000 children and infants die annually from it, 1 000 times more than in any OECD country. A vaccine is badly needed. The withdrawn rotavirus vaccine was never tested in India. Considering the country's high fatality rates, it is likely that a risk-benefit assessment (carried out for all medicines) of the vaccine in India would have yielded different conclusions. Indeed, given the genetic variability in the human population, it is possible that the side effects suspected in the United States may not have occurred in an Indian population.

...and India and other countries are developing the vaccine in their own facilities.

The solution has been for India and other highly affected developing countries to develop a vaccine in their own facilities at their own expense. Novel vaccines from other manufacturers, including Indian producers, are presently in clinical trials.

The balance between the risks and benefits of licensing medicines may vary between different countries.

This case study shows that there is a balance to be struck between risks and benefits in the licensing of medicines and that the balance may vary among countries. Taking account of this variability in risk-benefit assessments when authorising medicines is a major challenge for licensing authorities. This case study also shows that while there is an increasing trend towards harmonising medicine approval procedures in different countries, responses in different human populations may show subtle variations. Recognising and exploiting these natural genetic variations is the focus of the new science of pharmacogenetics – which promises much by way of more effective treatments.

This case study finally shows that capacity to produce vaccines is not restricted to “developed” countries. India has a well-developed generic drug industry and is currently developing vaccines against leprosy, rabies and Japanese encephalitis. The Indian vaccine market is growing at around 8-10% a year and the country relies on domestic production of diphtheria, tetanus and pertussis vaccines. In 2001, in Thailand, local vaccine manufacture accounted for USD 7.6 million out of a USD 27.6 million domestic market.

Developing country manufacturing is increasing.

Vaccines produced in these countries supply more than their domestic markets. Indeed, a number of the pharmaceutical multinationals active in the vaccines market use manufacturing facilities in such countries and increasingly rely on them.

Vaccine production requires manufacturing capability and know-how.

However, vaccine production requires not only manufacturing capability but also know-how to produce a consistently safe and effective biological product. This know-how is critical to vaccine manufacture and – above all – to vaccine development. The extent to which developing countries can positively affect new product development will depend partly on their ability to develop R&D capacity and to access new technologies.

Lessons from public-private partnerships will be important.

There are a number of public-private partnerships between multinationals, NGOs and developing country manufacturers and more are under consideration. Lessons learned from these early attempts will be of great significance in shaping a vision for the future of the vaccine industry and in meeting global health needs.

Manufacturers will have to be able to pursue a business model different from that commonly followed today.

This being said, if vaccines are to be developed for neglected diseases that occur predominantly in poorer countries, manufacturers will have to be able to pursue a business model different from the one commonly followed today. R&D risks need to be offset to some extent, and this is as much a challenge for entities operating in developed as in developing countries (although there may be marginal cost benefits to the latter).

Treatment

Most R&D is directed at treatment...

Surveillance, detection, diagnosis and prevention are all essential in combating infectious diseases, but most R&D effort and public and private investment are directed at treatment.

...but effective treatments for neglected and/or emerging diseases are few and far between.

However, effective treatments for neglected and emerging diseases are relatively few and far between. As noted by Alexandre Quintanilha in the introduction, of the 1 223 new chemical entities commercialised between 1975 and 1997, only 13 were intended specifically to treat tropical diseases.

A number of high-profile ventures involving public and private sectors, NGOs and philanthropists (perhaps most notably Bill and Melinda Gates) have been established to address the challenges of malaria, TB and AIDS. Much less progress has been made in addressing the neglected diseases.

However, there is some cause for optimism.

There is some cause for optimism. The case study on genome sequencing as a strategy to find treatments for Chagas disease is a collaboration between developing and developed country scientists to address a neglected disease affecting 18 million people a year.

Case Study 6. Biotechnology for Chagas Disease

Chagas disease is a "neglected" disease that affects 18 million people.

Chagas disease, caused by the parasite *Trypanosoma cruzi* (*T. Cruzi*), is recognised by the World Health Organization (WHO) as a "neglected" disease, one with significant impact on the world's most vulnerable populations but which receives little funding or public attention. It affects 18 million people a year in North and South America, with Brazil accounting for about a third of the cases.

It is generally spread by insects.

Both humans and many domestic and wild animals can carry the parasite, but it is most often spread by insects infected with *T. cruzi* that often live in thatched roofs and walls of houses.

Acute effects appear soon after infection...

Chagas disease has both short- and long-term effects. The acute effects appear soon after infection, generally in children. Symptoms can include fever, swelling at the site of the insect bite and of the lymph glands, and enlargement of the liver and spleen. Long-term effects can occur up to 20 years after infection.

...and can kill.

In 25-30% of cases, Chagas disease is a slow and insidious killer, attacking the heart or gastrointestinal tract over decades. During the chronic phase of the disease, the parasite causes irreversible damage to internal organs such as the heart, oesophagus and colon. Patients with late-stage effects become progressively more ill and die, usually from heart failure.

No available drug has been shown consistently to cure patients in the chronic phase. The availability of such a drug would dramatically change the management of Chagas disease in the clinic and in the community.

The drugs currently available for treatment leave much to be desired. They are often ineffective for curing long-standing chronic infections, are difficult to administer and lead to severe side effects in adults. The development of a safe, efficacious, easily administered and affordable drug would be a major advance in public health.

*Research on *T. cruzi* is difficult...*

Research on *T. cruzi* is not easy. The parasite exhibits considerable biological and genetic variability, thus giving rise to different clinical forms of Chagas disease, as well as to different degrees of virulence, pathogenicity and susceptibility to drugs.

...and scientists are collaborating to fulfil a number of scientific objectives.

Scientists from developing and developed countries are now collaborating to sequence the genomes of *T. cruzi* and the related *Leishmania major* and *T. brucei*. The genome sequencing projects' main objectives are to:

1. Increase dramatically knowledge about the (molecular) biology of these parasites, which are, from an evolutionary standpoint, very ancient and present a number of unique features and molecular processes.
2. Identify, as fast as possible, new genes with key cellular functions, which could be eligible as targets for new drugs.
3. Identify new antigens which could be useful in diagnostics or for vaccine development.
4. Build expertise and collaborative North-South and South-South networks for genome research in the fields of mapping, large-scale sequencing, bioinformatics, research on protein structure-function relationships, etc.
5. Contribute to the overall knowledge of genome structure and comparative biology/evolution.

The current strategy is to employ a protease inhibitor.

The current lead strategy for developing a treatment is to employ a protease inhibitor specific to the Chagas disease parasite. The inhibition of proteases that cause disease has been the focus of biotechnology research since the mid-1990s and has led to important drug development opportunities for osteoporosis, rheumatoid arthritis, asthma, atherosclerosis and cancer.

A partnership was recently formed to carry out clinical trials.

A partnership between a major biopharmaceutical company and a non-profit organisation was recently formed to carry out clinical trials on a new drug candidate based on a cysteine protease inhibitor. The biopharmaceutical company has given the non-profit organisation an exclusive licence free of any royalty fees or cash payments to develop the compound for parasitic infections in humans. The overall goal is to sponsor all development activities, including production of the therapeutic substance, safety studies and Phase I clinical trials.

If successful, the compound could represent the first new treatment for Chagas disease in decades.

Initial safety studies are currently under way to evaluate the compound in humans. If clinical trials are successful, it could represent the first new treatment for Chagas disease in decades and a proof-of-concept breakthrough for inhibiting cysteine proteases in other parasitic organisms. This compound is specific to the trypanosomal cysteine protease cruzain and is lethal to the parasite that causes the Chagas infection, but it does not harm patients since humans do not produce the protease.

Genomics offers new strategies...

Genomics offers new strategies for dealing with infectious diseases, including the neglected ones. The protease inhibitor route may prove successful and could open the door to other candidate treatments for parasitic diseases.

...but the paucity of case studies underlines the challenges that lie ahead.

However, the paucity of case studies to choose from in presenting these advances underlines the challenges that lie ahead if a real impression is to be made on the human misery and economic instability that neglected infectious diseases continue to cause.

Delivering the R&D Agenda

The following sections address structural issues.

The previous sections have dealt with the different strategies for dealing with infectious diseases (surveillance, prevention, treatment). The next three sections address the structural issues to be addressed if the new approaches contained in these strategies are to be made available.

This first section deals with delivering a global R&D agenda that can deliver on strategies for dealing with infectious diseases. As for other disease challenges already described, a successful strategy involves both public and private sector actors.

The second section addresses possible incentives for developing such products. The third considers how partnerships might be established to deliver products.

The case studies illustrate what biotechnology is doing and can do...

As for each of the previous sections, case studies are chosen to illustrate some key considerations, and the focus is on what biotechnology is doing and can do. The treatment of each topic is necessarily short – comprehensive consideration of any of these topics would take at least a book.

...and some aspects of a common R&D and supply agenda.

The case study presented in this section describes how lessons learned from difficulties experienced in developing one vaccine were applied to ensure success in development and deployment of a subsequent vaccine. Improved technology played a role, but the key success factors in the latter case were based on successful relationship building and advance agreement of common goals.

Case Study 7. Preventing Vaccine Shortages: What Is Needed?

Unprecedented and unanticipated disruptions in the supply of vaccines have recently occurred.

Unprecedented and unanticipated disruptions in the supply of a number of essential vaccines have recently occurred in a number of OECD countries. These were at times significant, with extended shortages of vaccines for preventable childhood infectious diseases, including diphtheria, tetanus toxoids and the acellular pertussis vaccine; MMR, the measles, mumps, rubella vaccine combination; varicella; and the pneumococcal conjugate vaccine. Adult tetanus and diphtheria toxoids were also reported in short supply.

Why did this problem occur? Does it reflect a systemic problem in development, manufacturing or the regulatory environment? Why is there an apparent fragility of supply, and what can be done about it?

The introduction of a new vaccine presents logistical problems...

Introduction of a new vaccine presents logistical problems, which include the supply of product from the manufacturer, delivery to the purchaser, delivery from there to point of use and administration. The amount required and effective distribution and delivery to the target group are governed by the size and geographical distribution of the target population. As collaboration is essential, partnerships among industry, the public health community, the private provider and government are needed.

...and vaccine manufacturing faces special challenges.

Currently, only four companies supply 90% of all vaccines worldwide. Two decades ago, a dozen companies made vaccines, but most have left the market or been driven out by a variety of pressures. Vaccines require the use of biological organisms, viruses and bacteria and their manufacture faces special challenges.

It is a time-consuming and often unpredictable endeavour. If vaccines are difficult and time-consuming to produce, the regulatory approval process for new and existing vaccines is complex and protracted, with timetables that are difficult to forecast. Regulators must approve every lot (batch) of vaccine for release. Given that production schedules can run 12 months or longer, abrupt changes in policy that affect demand or move a company to leave the field can result, and have resulted, in supply interruptions. For example, it takes from 27 to 32 weeks to produce a purified bulk lot of tetanus vaccine. This is followed by eight to ten weeks of bulk lot testing and another four to six weeks of filling, packaging and final approvals. All in all, it takes about eleven months to produce a single lot of tetanus vaccine. This is a typical vaccine production timeline.

Abrupt changes have resulted in supply interruptions...

With production time lines so long and manufacturers so few, the withdrawal of one manufacturer can have a significant impact.

Following recent advances in understanding the molecular and cellular bases of immunisation and the advent of techniques like reverse vaccinology, the present time should be the “golden age” of vaccine development. There is scant enthusiasm however for vaccine development in much of the pharmaceutical industry owing to low return on investments, high R&D risks and the regulatory environment.

...and shortages can occur because of poor information flows.

Shortages can also occur because of poor information flows. Effective targeting of vaccines depends critically on information to evaluate the benefits of different courses of actions.

The introduction of one vaccine was difficult...

In the United Kingdom, for example, the introduction of vaccines against *Haemophilus influenzae* B was difficult. Vaccine supply was not secure although the campaign was planned two years in advance. One year before the start of the campaign the predicted requirements for the vaccine were known in detail.

...and demand rapidly outstripped supply. The programme was successful despite these problems.

Nonetheless only one manufacturer was ready on time. There was disagreement between the manufacturer and purchasers of the vaccine about the number of doses. Doctors administering the vaccine were allowed to order as much as they thought necessary from the Health Department. This resulted in over-ordering and hoarding of vaccine. Demand rapidly outstripped supply and shortages resulted. The programme was successful despite these problems, and *Haemophilus influenzae* B vaccine is now used

These lessons had been learned when the meningococcal C vaccine was launched in 1994.

routinely and effectively in the United Kingdom. The launch would have been smoother if it had been possible to set firm requirements on the basis of clear information.

These lessons had been learned when the meningococcal C vaccine was launched in 1994. The problems encountered in the early stages of the *Haemophilus influenza* B vaccine campaign were avoided by involving the agencies purchasing and delivering vaccines extremely closely in the development process. The purchaser was the UK Department of Health which had a very clear idea of what was needed. The development programme was based on a partnership between the manufacturer and government agencies such as the Centre for Disease Surveillance and Control (CDSC), the Centre for Applied Microbiological Research and the National Institute for Biological Standards and Control. As a result, all parties were aware of the various needs with respect to supply, quality and target group.

The campaign was successful and some features were used elsewhere.

The campaign described in the case study was extremely successful in its impact on meningitis caused by type C in the target groups. Some features of the campaign, such as the centralised supply of vaccine, were in fact pioneered in developing countries.

The challenges for effective partnerships in poorer countries are likely to be greater.

Although the case study describes a success story, it of course concerns a market that can bear relatively high R&D costs and subsequent prices (although the United Kingdom negotiates a bulk rate for vaccines supplied through its National Health Service). The challenges for effective partnerships for diseases predominantly in poorer countries are likely to be greater.

Vaccination programmes depend on accurate information.

To be effective, vaccination programmes depend on accurate information. The WHO has established a system of monitoring delivery of vaccines to ensure that they are kept at optimal temperatures from manufacture to point of use. This ensures the quality of the vaccine administered. Detailed information on target groups and on cost-effectiveness to justify fully the course of action taken may be more difficult to obtain. Nonetheless, OECD countries cannot be complacent. There is a strong economic case for giving priority to preventive interventions and for encouraging the vaccine industry.

It is important to improve information flows, remove disincentives and create new incentives.

To avoid a return of epidemics of preventable infectious diseases and to prepare against unexpected infectious outbreaks it is important to understand and remove existing industry disincentives, improve information flows and create new incentives for vaccine development.

Creating Incentives

A number of factors act as disincentives to R&D for vaccines and treatments for infectious diseases.

The view that infectious diseases are a threat to economic growth and security is now broadly recognised by policy makers, economists and business people. Yet R&D for new drugs and vaccines, and the distribution of existing ones, clearly are not taking place at the level required to fight infectious disease. Lack of interest in developing drugs for tropical infectious diseases is not of course a new phenomenon in the pharmaceutical industry.

A number of factors act as disincentives to R&D for vaccines and treatments for infectious diseases. Costs and risks are greater for infectious diseases that affect predominantly the developing countries than they are for diseases of the developed world. Fixed costs for R&D are high in these disease areas because development and clinical trials often present unusual challenges. Variable costs are also high owing to a number of factors: the complexity of multi-country regulatory approval procedures, resources required for production scale-up and distribution; the potentially differentiated packaging and formulation needs of tropical countries; the expense of multicultural, multilingual marketing and medical information programmes. There are high risks not only of clinical failure in development, but of market failure owing to low return on investment.

However, nothing on the horizon will replace pharmaceutical and biotechnology companies for R&D on infectious diseases.

However, pharmaceutical and biotechnology companies are not likely to be replaced soon as the source of R&D on infectious diseases, particularly neglected diseases. R&D on medicines for neglected diseases bears small returns compared to that for other potential markets. For example, in 2000, worldwide sales for six drugs approved in the United States for malaria and TB had combined total sales of only USD 75 million. In comparison, the average annual return on commercial sales of one drug in today's mainstream market is about USD 265 million.

There is a need for new incentives.

The lack of investment in neglected diseases calls for new incentives for drug development.

Various approaches have been suggested.

What can public policy do? A number of approaches have been suggested. One is for rich countries to sign a pledge to buy enough vaccines for developing countries at a guaranteed minimum purchase price, thereby galvanising research in this area. The challenge is to be able to raise sufficient capital on a sustainable and predictable basis. As aid policies are often motivated by externalities such as advocacy, commercial or political pressures and business cycles, this may be difficult. An additional problem is that product development takes on average 10-12 years. A purchase fund might have to be committed for this length of time, if not longer, and this has obvious drawbacks.

The case study presents a model for incentives.

The case study presents a model for incentives largely based on the orphan drug legislation in many OECD countries (for example, Australia, the European Union, Japan, the United States).

Case Study 8. Orphan Drug Models

Orphan drug legislation combines incentives that lower both the cost and risks of drug development.

A combination of aid policies and incentives may be necessary to achieve long-term success. For example, the drug industry has recognised the potential of the mix of incentives in US and European orphan drug laws. The term “orphan drug” reflects the fact that no company would be interested in R&D to treat rare diseases affecting small numbers of patients, as it could not achieve a reasonable return on investment. Orphan drug legislation combines incentives that lower the cost and risks of drug development, thus appealing to both small and large companies. The economic rationale for orphan drug legislation is to provide a mechanism to make the rare disease market more attractive to drug developers. The US Orphan Drug Act includes five economic and regulatory incentives to accomplish this goal:

- Technical and administrative assistance.
- Grants to cover clinical trial expenses.
- User fees, *i.e.* registration fees paid for review of a marketing application.
- Tax credits to be subtracted from the company’s taxes.
- Market exclusivity (granted within the territorial market of the legislation concerned).

These incentives affect the various segments of the industry in different ways.

These incentives affect various segments of the industry in different ways. Tax credits appeal to all segments of the industry but especially to larger companies, which carry most orphan products through to approval.

Grants and protocol assistance are especially useful to smaller companies. These incentives encourage smaller, less experienced pharmaceutical manufacturers to seek regulatory approval of orphan products.

Market exclusivity provisions are helpful to the biotechnology industry.

The market exclusivity provision is very attractive to sponsors of products that are not patentable (*e.g.* shelf chemicals, natural substances and chemicals already described in the scientific or medical literature) or for which the patents have already expired.

This provision is also helpful to the biotechnology industry. One reason is that biotechnology R&D is fuelled by venture capitalists, who typically require some assurance of intellectual property protection once the product resulting from their investment reaches the marketplace.

Despite orphan drug legislation, relatively few products have been targeted to neglected diseases.

Technically, most if not all neglected infectious diseases could be considered orphan diseases because of their very low prevalence in developed countries. However, despite the large numbers of products that have emerged since the orphan drug legislation, relatively few have been targeted to neglected diseases.

There may be a number of reasons for this.

There may be a number of reasons why the incentives in orphan drug legislation are insufficient to encourage development of products targeted at neglected diseases. The cost structure for an orphan drug may be inconsistent with that of other pharmaceutical products (*i.e.* it may be too expensive to develop compared to competing R&D opportunities). Alternatively, demand may be sensitive to price (*i.e.* it may be so expensive that too few can afford it or third-party payers cannot reimburse). A product targeted at developing countries is likely to be unprofitable unless it is also useful in developed countries, in which case differential pricing might be an option provided that sufficient checks and balances are in place.

Where a reasonable market does not exist, market exclusivity is of little value.

However, if there is not a reasonable market for an orphan product targeted at neglected diseases in developed countries, differential pricing is unlikely to be an option. In such cases, the much-valued market exclusivity aspect of orphan drug legislation – tied as it is to the territory in which the particular legislation operates – would be of little or no value.

Some suggest that an incentive system is needed that goes beyond the market for such drugs.

This has led some to suggest the need for an incentive system that goes beyond the market for such drugs. It would provide a period of market exclusivity, not on the orphan or neglected disease product itself, for which even a guaranteed market may not be a sufficient incentive, but on another product, which the sponsor of the orphan drug feels would represent a sufficient incentive if its period of market exclusivity were extended. This variation of market exclusivity is known as “transferable” or “roaming exclusivity”.

It could take a variety of forms.

Such a period of market protection could take the form of a patent extension, enforceable in multiple countries through existing international treaties, or a period of market exclusivity provided by the regulatory agency of the country granting the orphan approval, enforceable only in that country or in countries with mutual recognition agreements. A possible precedent was provided in the United States to justify the addition of a paediatric studies provision to the FDA Modernization Act of 1997. Drug sponsors are awarded a six-month extension of market exclusivity for all products they own which have the same active ingredient as the product for which the paediatric study was conducted.

Various approaches may be valuable components of a solution.

The approaches described in the case study may all be valuable elements of a solution to the challenge of obtaining new drugs and vaccines for the fight against infectious diseases. Further opportunities are arising from research on bioterrorism. No public health response to bioterrorism is likely to prove effective if it does not address the overall problems of microbial resistance and the challenges of drug discovery and development for naturally occurring infectious diseases, particularly new and resurgent ones.

There is a need to take stock of what has worked or may work.

There is however, a need to take stock of what has worked or may work in future. The relative fragmentation of the many proposals for new incentives may in the long term be counterproductive. The feasibility of these proposals for achieving policy coherence and effectively and efficiently encouraging private-sector R&D on infectious diseases needs to be examined.

Partnership

Pharmaceutical innovation is lengthy and costly...

Pharmaceutical innovation can be described as a linear pattern of events which is initiated by basic scientific research, followed by applied and more product-oriented research activities, clinical development and testing, commercial manufacturing and finally marketing and diffusion. Today this process can take an average of 12 years and cost USD 500-800 million. More than 75% of this cost is attributed to development phase failures.

...and measures to ease the financial burden are called for.

Over the past decade governments have adopted measures designed to ease the financial and regulatory burden on the pharmaceutical and biotechnology sectors, to take account of the risks inherent in the early stages of product development in the industry, and to respond to public health concerns that innovative products be made available to patients as quickly as possible. Many of the intended effects of these policies and proposals relate to reducing risk, making the process more predictable and moving effective and safe products to market faster.

The public sector has also entered into partnerships with the private sector.

However, these policies are not sufficient to overcome the risks involved in drug discovery and development in areas that are not commercially viable. The public sector has to step in to take a greater share of the R&D risk, e.g. by entering into public-private partnerships (PPPs).

Partners commit to a common goal through the joint provision of resources and expertise.

With such partnerships, the public and private sectors commit to a common goal through the joint provision of resources and expertise and agree to share the risks and rewards. PPPs may take place at different stages of the discovery process, including the product's commercialisation and distribution.

Partnerships are now being set up on a global scale and are supported by unprecedented political will.

PPPs are not a new concept. The novelty is in the scale and pervasiveness of such engagements, as partnerships are now being set up on a global scale and are supported by unprecedented political will. One of the key characteristics of these partnerships is that the partners may come from multilateral or bilateral agencies, NGOs, international organisations and the private sector. Many are supply-driven and are based, for example, on donations from the pharmaceutical industry for reasons which range from a shift to greater corporate social responsibility or image building to market penetration. Other partnerships are demand-driven, and are largely initiated by the public sector to overcome market failure, for reasons which range from public health concerns to political commitment and human solidarity.

Case Study 9. Sharing the Risks of Drug Development through Public-Private Partnerships

PPPs bring health-care products and services to developing countries.

A number of today's public-private partnerships bring health-care products and services to developing countries. For example, the International Trachoma Initiative, a partnership between a philanthropic foundation and a global pharmaceutical industry, was formed to combat trachoma, a disease that blinds millions in developing countries. The initiative includes the donation of a drug, Zithromax, used for the treatment of trachoma, community-based public health initiatives and educational tools.

PPPs have successfully brought new products to the market.

Other PPPs are proving successful in bringing new products to the market. For example, Lapdap is a combination of two classical antimalarial drugs, chlorproguanil (Lapudrine) and dapson. It is being developed in the United Kingdom through collaboration between a company and a university. It is intended for use in Africa in areas where other therapies have failed because of drug resistance. Lapdap had its origins in Kenya in the 1980s. The goal was to develop a "new" safe and effective alternative to chloroquine and sulphadoxine/pyrimethamine (S/P) to treat malaria in Africa.

Preliminary clinical trials carried out in Africa were followed by a drug development programme.

Preliminary clinical trials were carried out in Africa to demonstrate proof of principle. The studies were intended to show efficacy and to detect resistant variants but were not performed to standards of good clinical practice (GCP). They have been since followed by a formal three-year drug development programme made possible through a private-public partnership, for which the UK government, industry and the WHO each paid a third of the costs. The efficacy was shown to be 96% in clinical trials involving 2 500 persons in accordance with GCP standards. The data were submitted in 2002 to the United Kingdom and African regulatory authorities. A programme of monitoring will follow the granting of a licence to establish effectiveness in field usage and an adverse event profile. The Lapdap development project was only possible as a public-private collaboration.

PPPs face further challenges.

The last few years have witnessed a growing number of PPPs, which offer extraordinary opportunities. However, PPPs face challenges for going forward.

Cross-sectoral partnerships present organisational complexities.

Cross-sectoral partnerships involve considerable organisational complexities. It will be important to identify benchmarks of successful management, including indicators to measure progress against goals to ensure that goodwill and resources do not dissipate.

Conclusions

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The challenges and problems posed by infectious diseases are extremely urgent.

The challenges and problems posed by infectious diseases are extremely urgent. We should not forget that the biggest natural disaster of the last century was not fire or flood, earthquake or drought, but the influenza epidemic of 1918-1919 that killed 25 million people. We must not lull ourselves into a false sense of security that such an event could not happen again. We must hope that the efforts to contain the spread of the SARS virus will be successful, but it cannot be thought that the global response to HIV/AIDS so far has been anything short of catastrophic.

The very concept of sustainable global economic growth is at stake.

Infectious diseases pose a great threat to the economic survival of the poorest countries and to growth and development in many more. Statistics and data on the effect of AIDS, malaria and TB indicate that the social structures and functioning of societies increasingly affected by these diseases are being systematically eroded. The very concept of sustainable global economic growth is at stake.

The case studies show that biotechnology needs to be seen as part of the solution, but advances in the science alone are far from enough.

The case studies described in this pamphlet show that biotechnology and related genomic sciences have great potential to help deliver on successful strategies to fight disease, whether through surveillance, detection and diagnosis, prevention or treatment. They also point to a number of very significant barriers to the delivery of effective products for neglected and emerging diseases. It is clear that biotechnology needs to be seen as part of the solution, as it can make a real and valuable contribution to a more effective R&D effort, but scientific advances alone are not enough, even when they are delivered.

A number of mechanisms to improve the current situation and overcome the main problems were proposed by speakers at the Lisbon Conference.

A number of mechanisms to improve the current situation and overcome the failure of the market model to deliver useful products to fight neglected diseases in particular were proposed by speakers at the Lisbon Conference and are reported here. Some suggest that we use additional push/pull incentives, for example, by creating a purchase fund and “an international commission to govern the Research Agenda”, or by modifying the current orphan drug frameworks to create incentives for the biotechnology sector. Others point to the recent success of a number of public-private partnerships in bringing new products to the market and in making them available to the countries that need them most.

<p><i>So far, we have very little information on the effectiveness of the proposed incentive mechanisms.</i></p>	<p>Most of these proposals are not new, and some are already in place. They deal variously with efforts to reduce the cost of R&D, improve returns on investment and reduce the risk of investment or a combination of the three.</p>
<p><i>Different intervention models might work better for different market segments.</i></p>	<p>However, no one mechanism is likely to be enough, on its own, to achieve the kind of progress that is so clearly necessary. So far there is little information on how well any of the proposed incentive mechanisms actually delivers on goals and even less on how various efforts may interact.</p>
<p><i>Metrics need to be in place,...</i></p>	<p>Thinking through first principles suggests that different intervention models might work better for different sectors of any market. The “infectious diseases” sector is no different. What might work best for markets focused on launching biotechnology products – where financial risk is of central concern – might not be appropriate for long-term efforts to eradicate specific controllable diseases. Minimising risks may help encourage investment, but only if the right risks are minimised.</p>
<p><i>... mechanisms have to be examined,...</i></p>	<p>These considerations suggest the following conclusions:</p> <p>First, metrics are needed to judge the success or otherwise of a plethora of initiatives. Good practice suggests that these will already be present for many of the programmes under way, but they may need to be integrated into a co-ordinated whole in order to track the full impacts of the initiatives in place.</p>
<p><i>... “gaps” or “overlaps” identified...</i></p>	<p>Second, a clearer analysis could be made of which mechanisms and potential interventions best fit which sectors of the infectious disease “market”.</p>
<p><i>...and corporate governance structures and philosophies challenged.</i></p>	<p>Third, the initiatives in place could be better mapped and “gaps” or “overlaps” identified.</p>
<p><i>OECD countries may have a special responsibility to help halt the spread of infectious diseases.</i></p>	<p>And fourth, the clear imperative to fight infectious disease challenges both public-sector and private-sector life-science entities to consider the future of their corporate governance structures and philosophies.</p>
<p><i>The OECD can have an important role to play.</i></p>	<p>It is the responsibility of all to deal with these challenges. OECD countries perhaps have a special responsibility to help to halt the spread of infectious diseases. The OECD area’s 30 member countries command roughly 85% of the world’s economic resources, account for 95% of official development assistance (ODA) worldwide and are responsible for over 95% of basic scientific research. OECD countries cannot afford to ignore the problems of infectious disease, and not just for moral reasons. Costs to OECD health systems will inevitably come under pressure as infectious diseases and drug-resistance spread.</p>
	<p>The OECD can play an important role. It has done and continues to do analytical work designed to improve economic performance, reduce risk and encourage adoption of sustainable practices. It also has a significant body of work on the responsible application of existing and new technologies (notably biotechnology), on the functioning of markets and on issues of corporate governance. It has substantial analytical capabilities together with institutional</p>

strengths in cross-disciplinary work. The OECD could add value to many of the challenges set out in this pamphlet given the political will, careful targeting of its role and collaboration with other major players.

OECD involvement can only be a small part of a much larger whole.

Just as biotechnology may be part of the answer but is by no means anything like all of it, OECD involvement in these issues can only be a small part of a much larger whole that includes the immensely valuable work of the World Health Organization and many other international and national actors, governmental, non-governmental or business based.

Complementarity and partnership are essential and...

Complementarity and partnership are thus essential. Our collective challenge today is to navigate the many proposals and activities to achieve policy coherence and prevent the dilution of resources and efforts.

...OECD countries must work together to reverse the rising tide of infectious diseases.

The evidence points to a stark but simple alternative for all countries. Find sustainable solutions now to help solve current infectious disease crises or pay the costs of international humanitarian disasters, collapsing economies and political instability. In short, OECD member countries must work together to reverse the rising tide of infectious diseases if our planet is to have the sustainable future we all desire so much.

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The list of conference speakers and participants can be found at www.oecd.org/biotechnology