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FIGHTING DISEASES OF DEVELOPING COUNTRIES

Better drugs and vaccines are needed to fight HIV/AIDS, tuberculosis (TB), malaria and other tropical diseases. Pharmaceutical research has typically focussed on developing drugs, vaccines and other interventions[1] for diseases prevalent in developed countries, where people can afford to buy treatments; it has tended to overlook those disorders that predominantly affect developing countries. This briefing outlines the extent of the problem, describes a number of recent initiatives to stimulate research and development (R&D) into diseases of the developing world and examines the UK policy issues associated with funding such research.

Global burden of disease

According to the World Health Organization (WHO), the main causes of illness and death in developed countries are cancer and diseases of the respiratory, cardiovascular and nervous systems. In the developing world, communicable diseases are the main problem; principal causes of death are respiratory infections, HIV/AIDS, infections at birth, diarrhoeal disease and tropical diseases such as malaria (Table 1). Failure to use existing treatments effectively, inadequate or non-existent interventions, and insufficient knowledge of disease all contribute to the burden of disease.

Tackling diseases of the developing world involves many factors, including the development of effective medicines, health systems, infrastructure and education. This note restricts itself to the policy issues associated with the development of effective interventions. It is estimated that only 10% of the world's medical research is devoted to conditions that account for 90% of the global disease burden. This is known as the 10/90 gap. There is thus an urgent need to develop better drugs and vaccines for diseases that are largely confined to developing countries. Many drugs for diseases prevalent in the developing world, including malaria, 'neglected diseases' (Box 1), TB and HIV/AIDS, are toxic, antiquated, and/or have serious side effects; many organisms that cause these diseases are becoming resistant to treatment. For instance, the treatment of leishmaniasis relies on drugs developed in the 1940s, which can cause kidney failure; the parasite that causes malaria rapidly adapts itself to new drugs. Although effective treatments have been developed for some diseases, for example HIV/AIDS, ensuring access to them in resource poor countries is an issue, because of problems of cost and availability (Postnotes 210, 160).

Table 1. Main causes of death in 2002[2]

In developed countries	(000s)	In high mortality developing countries[b]	(000s)
All causes	13,430	All causes	27,116
Heart attacks	3,076	Lower respiratory tract infections	2,806
Stroke	1,784	HIV/AIDS	2,553
Lung, tracheal, bronchial cancer	610	Heart attacks	2,529
Lower respiratory tract infections	450	Infections at birth	1,784
COPD[a]	423	Diarrhoeal disease	1,535
Colon, rectal cancer	350	Stroke	1,455
Diabetes	245	Malaria	1,246
Self inflicted injuries	234	TB	961
Hypertensive heart disease	234	COPD	764
Stomach cancer	227	Measles	546

Notes: [a]COPD is chronic obstructive pulmonary disease. [b]Data from low mortality developing countries not shown. Mortality classified according to WHO strata.

Developing new medicines

The drug development process

The basic medical research that underpins drug development may be funded by government, industry or

medical charities. In contrast, the drug development process is time consuming and expensive (Box 2). It is primarily funded by the pharmaceutical industry.

Box 1. Neglected diseases

Neglected diseases are so called because they have been largely overlooked in terms of research into developing new drugs. They include:

- African trypanosomiasis (sleeping sickness), which can be fatal if untreated. Some 48,000 cases were reported to the WHO in 1999, although it is estimated that ~300,000 people in Africa carry the infection.
- Leishmaniasis, which is usually fatal if untreated. It is endemic in 88 developing countries around the world. Most of the 500,000 new cases reported each year are from the Indian sub-continent.
- Chagas disease, which affects people in Central and South America. Around 18 million people live with the infection, and it kills ~50,000 people each year.
- Diseases such as filariasis, dengue and schistosomiasis.

Box 2. Developing drugs and vaccines

Drug development builds on basic research and consists of:

- Discovery research - the process where new active substances are synthesised and tested. Thousands of substances may be screened at this stage.
- Animal studies. Short-and long-term studies are undertaken to investigate therapeutic and toxic effects.
- Phase 1 clinical trials. Substances performing well in animal studies are given to 50-100 healthy volunteers to see if they are well tolerated.
- Phase 2 clinical trials. Drugs that perform well in phase 1 trials will then be given to a few hundred patients to assess safety and efficacy.
- Phase 3 clinical trials. Double blind, randomised, controlled trials involving several thousand patients to test the performance of the drug against a control.
- Regulatory review. Companies wishing to market their products as medicines must first seek a licence from a regulatory body. Such bodies seek to ensure a drug meets safety, efficacy and quality standards.
- Once a drug has been marketed, companies undertake ongoing (phase 4) trials to obtain further information about a drug's side-effects and effectiveness.

Estimates of the cost of drug development differ. The Association of British Pharmaceutical Industry (ABPI), however, suggests that it takes 10-12 years and ~$640 million to develop each new drug. This is a reflection of the high attrition rate (most new drug candidates never reach the market) and the high cost of clinical trials. The process for developing preventive interventions, such as vaccines, is slightly different, as trials need to recruit healthy volunteers. Associated costs are likely to be higher. An important aspect for all clinical trials are the ethical considerations given to the communities in which testing is being carried out.

In order to recoup R&D costs, a pharmaceutical company will seek to gain market exclusivity by patenting new compounds. A patent lasts for 20 years, but companies seek them at an early stage in the development process, thus reducing the effective patent life. Many countries (including the EU and US) have laws that provide a partial restoration of patent times lost during clinical testing and regulatory review. On average, the effective patent life of a new drug is around 12 years.

Current research targets

So which diseases does the development process outlined above target? A survey of new drugs registered between 1975 and 1999 with US and EU regulatory bodies shows that[3]:

- The majority target diseases such as cancer (8%), diseases of the central nervous system (15.1%), cardiovascular disease (12.8%) and non-infectious respiratory conditions (6.4%) that are prevalent in developed countries. A survey by the ABPI in 2001 shows that these diseases also form the main focus of drug companies' current research programmes[4].
- Only a small proportion of new drugs specifically target diseases that are largely confined to developing countries. For instance, 0.3% of all new drugs were targeted at malaria; of 1,393 chemical entities taken to market between 1975 and 1999, only 16 were for neglected diseases, malaria and TB.

Overall, research shows that there is a 13-fold greater chance of a drug being brought to market for central nervous system disease than for those diseases that account for a third of the worldwide disease burden[3].

Public private partnerships (PPPs)

Drugs are seldom entirely developed and manufactured in developing countries; China's development of the anti-malarial artemisinin is a rare example. However, a number of partnerships between governments, aid agencies, the private sector and affected communities have been set up to tackle diseases such as HIV/AIDS, malaria and TB. Such PPPs, of which more than 80 exist, often include developing countries as partners[5].

Many PPPs are aimed primarily at improving access to existing interventions and building capacity to deliver healthcare. For instance, the Global Fund to Fight AIDS TB and malaria supports 300 programmes in 130 countries. The Fund needs $2.3 billion to meet its commitments in 2005; this will rise to $3.4 billion in 2006[6]. Few PPPs are related to product development. Some with a focus on developing new vaccines and treatments are described in Box 3. PPPs have already made significant progress in developing better drugs and vaccines for a range of conditions. However, many require additional funding, especially for large scale Phase 3 clinical trials. A key issue for the G8 meeting in July 2005 will be how to secure such funding.

Policy issues

UK policy proposals

Recent years have seen the publication of a number of key government policy documents on diseases that affect developing countries. The Performance and Innovation Unit (PIU) produced a report for government on *Tackling the diseases of poverty*[7]; the Department for International Development (DFID) has published strategies on research[8] and HIV/AIDS[9]. In general, the main thrust of UK policy is a commitment to the internationally agreed Millennium Development Goals (MDGs) to be achieved by 2015[10]. The Goals include reducing child mortality,

improving maternal health and combating HIV/AIDS, malaria and other diseases. Currently, however, most MDGs are seriously off track.

Box 3. Some Public Private Partnerships

Global Alliance for Vaccines and Immunization (GAVI)
GAVI was launched in 2000 to improve access to established and underused vaccines and to accelerate the development of new ones. To date, GAVI has raised a total of $2.3 billion; of this, $1.5 billion was donated by the Bill and Melinda Gates Foundation. GAVI partners include governments (the UK has pledged $63 million), WHO, UNICEF, World Bank, foundations, vaccine manufacturers and research institutes. So far, $532 million has been spent in 70 developing countries, most of which has been targeted at supplying vaccines. Current research is focussing on bringing vaccines for pneumonia and viral diarrhoea to market.

Medicines for Malaria Venture (MMV)
Launched in 1999, MMV funds research to discover, develop and deliver affordable new anti-malarial drugs. It has raised $107 million in total; 60% of this was donated by the Bill and Melinda Gates Foundation. DFID donated ~$10 million and the Wellcome Trust ~$3 million. In collaboration with around 40 public and private research laboratories around the world, MMV is managing 21 different anti-malarial projects. MMV estimate that it will take an additional $300 million by 2010 to take five promising products through clinical trials.

Global Alliance for TB Drug Development (TB Alliance)
The TB Alliance was created to accelerate and ensure the development of new, faster-acting and affordable TB drugs. In its first five years of operation, the Alliance has been pledged ~$40 million, mostly from the Bill and Melinda Gates and Rockefeller Foundations. It has three main strands of research: developing derivatives of existing TB drugs; researching antibiotics that have not been used against TB before; and exploring entirely new drugs. One of the main priorities is to shorten treatment times and simplify regimens. It currently has ten drug development agreements. For each drug in development, an additional $60-70 million is required to proceed through Phase 3 trials.

Drugs for Neglected Diseases Initiative (DNDi)
DNDi aims to develop affordable new drugs to treat neglected diseases, by translating basic research about parasites into the development of new treatments. The charity Medecins Sans Frontieres teamed up with five research institutions[11] to launch DNDi in 2003. Each partner provides financial support or research expertise on a not-for-profit basis. DNDi works closely with the Special Programme for Research and Training in Tropical Diseases (TDR)[12]. It currently has 18 projects at various stages of development to deliver better interventions for leishmaniasis, Chagas disease, sleeping sickness and malaria. DNDi estimates that it will require ~$315 million over 10-12 years to develop 6-8 drugs for neglected diseases.

Since 2001, the UK has donated $178.2 million to the Global Fund to Fight AIDS, TB and malaria and has pledged a further $92.6 million for 2005; it has also donated $36 million to the International AIDS Vaccine Initiative. As discussed in more detail below, the PIU report identified a number of complementary policy options to encourage research and accelerate action against the diseases affecting developing countries.

International Finance Facility (IFF)
HM Treasury and DFID proposed setting up an IFF in January 2003, to raise an additional $50 billion per year to support the achievement of the MDGs. Under the proposal, donors would raise additional funds from international capital markets by issuing bonds backed by long-term, legally binding, donor commitments. This would allow an immediate doubling of the funds available and sustain funding in a predictable manner up to the MDG 2015 deadline. The aim of the IFF is to increase the available resources for development work through existing mechanisms and partnerships rather than to fund R&D. A separate proposal, the IFF for Immunisation (IFFIm) is specifically designed to meet GAVI's funding needs (Box 3).

The UK is using its 2005 presidency of the G8 to promote the IFF. Members of the G8 agree that more resources are needed for development, but differ on notions of scale and mechanisms. The EU members are likely to support the central thrust of the IFF. For instance, President Chirac supports the IFF, but called for taxes on international capital flows and airline travel to help fund repayments. However, the US has made it clear that it will not participate in the IFF and does not support the idea of further taxes to fund development aid.

Advance purchase commitments (APCs)
Recent years have seen considerable debate as to what is the most effective means of encouraging further research into new drugs and vaccines. APCs have been a focus of much recent debate for encouraging vaccine research. The idea is that governments give legally binding commitments to purchase vaccines for particular diseases in advance of them being developed to provide an incentive to private companies to invest in vaccine R&D. APCs represent an additional mechanism to existing investments and incentives for R&D.

It has been suggested that APCs are likely to work best when applied later in the development process, when the risks of failure are lower. For instance, vaccines for pneumonia and viral diarrhoea might benefit from APCs. Although the prospect of a malaria vaccine is further off, recent research suggests that a vaccine developed by GlaxoSmithKline, the Mozambique Ministry of Health and the Malaria Vaccine Initiative might be effective in protecting against malaria. In trials, the vaccine reduced the overall risk of malarial infection by 30% and by 58% for severe malaria[13]. The development of such a vaccine might also benefit from an APC agreement.

No decisions have been made on which vaccines should be prioritised for APCs. In November 2004, the Chancellor of the Exchequer announced that the UK would be willing to work with other international organisations to enter into APCs for malaria. A recent World Bank consultation explored the potential of APCs for several vaccines. The G8 meeting in July may discuss proposals for a Global HIV Vaccine Enterprise. However, research into developing an effective HIV vaccine is still

at a relatively early stage, and investment in this area is seen as being very high risk. It is thus not clear whether an APC is the most effective mechanism for stimulating research into HIV vaccines[14].

R&D tax credits

Another strand of UK policy for encouraging research into new vaccines and drugs is via R&D tax credits. Since April 2003, UK companies have been able to claim additional tax credits on all money invested in R&D on vaccines and drugs for malaria, TB and HIV/AIDS. These tax credits are additional to the tax relief already allowed for R&D investment. Companies can also claim additional tax relief against donations toward independent research into these diseases by charities, universities and scientific research organizations.

Stimulating R&D

Encouraging industry involvement

A number of other incentives have been proposed to encourage big pharmaceutical companies to invest in research for diseases of the developing world. For instance, patent extensions, fast track evaluations or guaranteed periods of market exclusivity can all be used to increase revenue flows for companies, although these approaches are controversial. Such approaches have been used to encourage research to develop orphan drugs (to treat diseases that affect small numbers of people and for which there is thus no viable market).

Analysis by the Pharmaceutical R&D Policy Group at the London School of Economics shows an upturn in the number of drugs for diseases of the developing world in the pipeline, including drugs for malaria, TB, neglected diseases and diarrhoea. It also demonstrates that industry is actively involved in this process. Researchers have identified 63 new drugs at various stages of development since 2000, including 19 new products in clinical trials. These projects are being developed by one of two main models:

- PPPs working with small companies or academic institutions. The companies are reimbursed by the PPP in return for their R&D contributions.
- Large pharmaceutical companies motivated by non-commercial interests, such as public relations, ethical or strategic considerations, working alone or in PPPs.

The researchers point out that the main driver behind this growth in R&D has been the establishment of PPPs. They suggest that the biggest challenge facing policy makers is not to find new ways to get industry involved, but to find the additional funds that are urgently needed by PPPs to keep these projects on track.

Public sector research in the UK

The House of Commons Science and Technology Select Committee recently highlighted the erosion of the UK's development sciences research base[15]. Whilst underlining the importance of North-South partnerships in R&D, the Committee recommended the establishment of a cross-cutting UK Development Sciences Research Board, which would award grants for development sciences R&D to UK institutions, with an initial budget of £100 million per annum. The Government has responded by setting up an advisory group, with representatives from DFID, research councils and the Office of Science and Technology, to assess the nature, objectives and form of such an advisory Board. The working group would also determine the funding required by such a Board, alongside current science and aid budgets. Its conclusions will be considered as part of the 2006 spending review.

Overview

- Prior to 2000, very few resources were devoted to developing new drugs and vaccines to tackle diseases primarily affecting developing countries.
- In the last five years, much progress has been made by companies and PPPs set up to address this issue. Such initiatives mean that there are currently 63 new drugs in various stages of development.
- The main focus of these initiatives has been on malaria, HIV/AIDS, TB and the most neglected diseases: sleeping sickness, leishmaniasis and Chagas disease.
- Many stakeholders see an urgent need to set up new funding mechanisms to secure future funding for the PPP driven projects currently underway. They see the UK's chairmanship of the G8 as being an ideal opportunity to advance policy in this area.
- It is likely that the key to effective policy in this field will be to use multiple approaches that can foster a variety of partnerships and align the incentives of different stakeholders. Continued investment in drugs and vaccines already available is also important.

Endnotes

1 Such as pesticide treated mosquito nets
2 World Health Report, WHO, 2004
3 Trouiller P et al, *The Lancet*, 359, 2189, 2002
4 *A to Z medicines research in Britain*, ABPI, London, 2002
5 www.ippph.org
6 www.theglobalfund.org/en/
7 www.number-10.gov.uk/su/health/08/content01.htm
8 www.infrastructureconnect.info/pdf/news/altstrat-vs6_1.pdf
9 www.dfid.gov.uk/pubs/files/hivaidstakingaction.pdf
10 www.un.org/millenniumgoals/
11 The Oswaldo Cruz Foundation (Brazil), Indian Council for Medical Research, Kenya Medical Research Institute, Ministry of Health Malaysia and the Pasteur Institute (France)
12 TDR is funded by the WHO, the World Bank and the United Nations Development Programme
13 Alonso PL et al, *The Lancet*, 364, 9443, 2004
14 www.economics.ox.ac.uk/members/andrew.farlow/CIPIH10December2004.pdf
15 The Use of Science in International Development Policy, 13th report, House of Commons Science and Technology Committee

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