OECD CONFERENCE ON BIOTECHNOLOGY FOR INFECTIOUS DISEASES: ADDRESSING THE GLOBAL NEEDS

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RAPPORTEURS' REPORT

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Rapporteurs' Report

Introduction and context

1. Infectious disease is a global concern. Ninety five percent of the annual 17 million deaths from infectious diseases are in developing countries where malaria, HIV and TB account for about half the total. Forty million people are infected with HIV world-wide and the globalisation of trade and travel means that infections can no longer be regarded as local problems. The wider effects of infectious diseases extend beyond the risks of disseminating infection from the affected country and pose a threat to global economic development and security in a general sense. There is international interest in addressing the issues; there have been meetings of WTO and the global summit in Johannesburg and others in which global development and the infectious disease burden have been considered. The difficulties in developing vaccines for neglected diseases are based in part on technological problems, as for HIV, but also on political will and economic circumstances. Increased funding is needed and the question of sustainability recurred. OECD has a formal memorandum of understanding with WHO which establishes a complementarity of aims and approaches. In this context the objectives of the meeting were:

i. To review the risks of infectious diseases including the economic impacts to identify the most important global challenges.

ii. To identify relevant trends in science and technology, the contribution which may be expected from biotechnology, bioinformatics and their application and to establish if there is a specific research agenda and what policies are needed to upgrade preparedness.

iii. To review case studies and options for best practice to improve access and use.

iv. To consider policy and strategy options to encourage relevant research and development.

Understanding the challenges, developing the solutions

2. The first session concerned the scientific and technological aspects of infectious diseases and possible areas of activity.

3. Tuberculosis is a resurgent disease in European countries. Many new cases in Western Europe are found in non-native groups, illustrating the global nature of diseases, but incidence is also rising in eastern European countries, and is spectacularly high in the prison populations of Russia and the newly independent states. Moreover, the isolates are increasingly found to be resistant to antibiotics. Information on the strains and their properties is not comprehensive; for example data from standardised WHO controlled susceptibility surveys available only from 24% of the European region of WHO. It is likely that the strains occurring in the USA and Europe are only a small proportion of those occurring world-wide; there is evidence for different strains in India where there is a large programme on the disease. Molecular biological techniques have a major role to play in surveillance.

4. Emergent diseases and agents may be classified in a number of ways, including the identification of an entirely new disease and agent, as for HIV, identification of an infectious aetiology for an old disease, such as Helicobacter in gastric ulcer, identification of a disease agent for a known infectious disease such as fifth disease, presentations of old diseases in new groups, such as botulism in drug abusers, the occurrence of carriage or disease in particular groups, notably the immuno suppressed, and the resurgence of disease due to failures of interventions, such as diphtheria in Russia or pertussis in the UK in the 1970s. An intervention in one area may have implications in another; for instance the replacement of barrier contraception by oral, non barrier methods may decrease the frequency of unwanted pregnancy but have an adverse effect on the incidence of sexually transmitted diseases.

5. Antibiotic resistance poses a particular threat to medical interventions and can arise in a variety of ways, such that the resistance is specific for a particular group of drugs, or more wide spread. Selection can be rapid, complete and largely irreversible on a population basis.

6. Vaccine development can benefit from genomic approaches. Where the sequence of a pathogen is known it may be possible to identify candidate proteins which may have promise as immunogens, which can be evaluated further. This could be applied to TB and malaria, for example, and is already well advanced for the group B meningococci. However, the main obstacle to development is financial incentive. A satisfactory vaccine against group A meningococcus is almost certainly potentially available, based on the same strategy as that used to develop the group C vaccine in the United Kingdom. However, development was stopped because the countries where this group is a problem were in Africa, where commercial returns are very poor. This is a general problem in vaccine development. Moreover, returns on vaccines are poor in general compared to those on pharmaceutical drugs. Vaccine shortages occur in the USA as a result of this and the increasing stringency of GMP requirements. The solution is not readily discernible.

7. Novel approaches to vaccines are being explored, and include DNA vaccines in which the nucleic acid encoding the antigen is injected and expressed in the recipient. This appears to work on a laboratory scale in a number of instances including leishmaniasis in dogs and is in human clinical trial for some antigens. Portions of pathogens can be expressed in bacterial systems and used to confer protection at least in animal models. Likewise novel vectors such as those in which portions of pathogens are expressed in other viruses such as vaccinia, or where the relevant parts of a virus such as West Nile or Japanese Encephalitis virus are expressed in the background of the closely related yellow fever virus vaccine are also at an advanced stage of trial. This could provide a rapid response to specific needs when required.

8. The needs of developing countries such as Thailand and to a different degree Senegal are specific in many respects, as the diseases they suffer are often specific to them. For example, dengue virus and Japanese Encephalitis virus are largely, but not exclusively, diseases affecting developing countries, whereas parasitic diseases such as malaria and trypanosomiaisis are not major concerns for developed countries. These neglected diseases are difficult to deal with when most of the biotechnological expertise lies with developed countries. The need for self-reliance and national production was underlined in a number of cases, firstly from the point of view of cost to less wealthy countries, and secondly to ensure that country specific disease needs can be met. The products have to be appropriate to the infrastructure to ensure effectiveness. Old methods for dealing with pathogens such as trypanosomiasis may still be among the most effective, but novel biological procedures such as molecular approaches to diagnostic pathogen characterisation and resultant surveillance may make a major contribution, if they can be made cost-effective.

9. Infectious diseases are not simply or even primarily a health problem. The impact of HIV/AIDS on education in South Africa is corrosive and catastrophic. It is likely that the effect on other elements of the social fabric is equally devastating, but the information is, at this stage, not as readily available. It is likely that other infectious diseases, of which malaria is only one example, also have a devastating effect but are not recorded because they have a lower profile, or because they have been endemic for a long time. The impact of infectious diseases on development in particular countries may be extreme; the impact on global economic development and security follows from this.

10. The risk benefit analysis of clinical trials and product development is specific to the country concerned and the disease burden, and ideally this would affect regulatory approaches. Technology may play a part in dealing with infectious diseases but politics and social context are also very important. Obstacles to vaccine development for developing countries include regulatory and ethical issues, reduced profitability (as in developed countries), as well as the difficulty and slowness of the process. It was agreed that vaccines are needed although the profitability is a problem, and the application of biotechnology is not always needed. The level of political will plays a large part in their development.

Controlling communicable diseases.

11. Despite the difficulties, there is an enormous amount of activity in the area of developing country infectious disease. It includes major programmes on HIV/AIDS where education and behavioural social actions can have a profound effect, specific and appropriate actions on TB including diagnosis and treatment, and work on malaria to educate and take preventative measures such as the use of insecticide impregnated bed nets. In all cases, the most important factor for success is the commitment of governments. Partnerships are also effective, for example in the eradication of river blindness which has released millions of hectare for cultivation and removed the threat from millions of people, in the development of new malarial treatments and the use of leprosy treatments, work on the development of new methods for the practical treatment of sleeping sickness and filariaisis. The most significant infectious diseases in developing countries are not currently preventable by vaccination. While great obstacles can be seen, they can be partly over come.

Managing changing patterns of disease

12. Biological resource centres have been set up in several countries and OECD has established a task force to harmonise and co-ordinate efforts, including the establishment of quality systems and uniform practices with respect to access and distribution. The centres are intended as a resource for the scientific and industrial communities. Surveillance plays a major role in the identification of consistent changes in patterns of disease and uniform systems of proven validity are a major asset; again co-ordination within a region is an advantage as is preventing duplication of surveillance systems, for example by having systems dedicated to a single disease. Mathematical modelling of epidemic spread with appropriate biological inputs is valuable in generating preparedness for epidemics, such as those that may result from the appearance of a pandemic influenza strain or a deliberate release. The value of such exercises is at least in determining what parameters are likely to be most significant in dealing with an epidemic, for example speed of response or in the case of animal epidemics the use of vaccination or slaughter policies.

13. Vaccine shortages occur in global and national programmes and arise for a variety of reasons including the difficulties of production and prediction of needs and social effects such as over-ordering by users. Methods for dealing with the issue depend on clear and accurate information on real needs and can be extremely effective. Production of vaccines in the global context is evolving; developing country manufacture is improving particularly in the large-scale usage vaccines, as multinational companies concentrate increasingly on high value products for developed markets.

14. Clinical trials in developing countries can be carried out under a public private partnership. Trials of an anti-malarial have been carried out successfully in one such arrangement and the product is to be submitted for licensure shortly. Trials assess efficacy under optimum conditions of use and follow up; effectiveness in real usage requires post licensure investigations and is likely to be a major issue.

15. Big pharmaceutical companies may wish to carry out clinical trials in developing countries for a variety of reasons including the nature of the product. There are potential major advantages for both the company and the country, but also significant pitfalls, including difficulties of a practical and public relations nature. The benefits for the country may include increased expertise and possibly health delivery and increased exposure to the global scientific community.

16. Surveillance and activities in infectious diseases need to be funded in a sustainable manner and to be reliable indicators of the situation pertaining. Systems are in place, which may act to promote these desirable ends, including some funding from sources such as the European Union.

Building a global R&D strategy: options and partnerships

17. The development of products intended specifically for low income countries or for very small markets is highly problematic. It is possible to devise methods which will encourage developments by promoting research and pre-licensing activities, for example by funding or tax credits ("push") or by enhancing profits post licensure by providing secure markets, or providing better exclusivity for the product. The effectiveness of such procedures is not established. There is a need to examine the range of possible policy options to identify effective and efficient strategies. On the other hand, schemes are in place in the USA to encourage companies to carry out high-risk research; an example of a successful outcome is the development of DNA microarray technologies. In this case, while the research itself was high risk, the market was highly profitable.

18. Partnerships between public and private sectors can take many forms depending on the nature of the sectors involved and the point of intervention. Partnerships are most effective with larger companies where the development decision is marginal; this could include both TB and malaria. In other contexts, the intervention may take place at an early stage of development or closer to the point of delivery. Partnerships may involve governments, agencies, philanthropists and industry. In general, however, they are under funded. There is a need to examine public/private partnerships more closely to determine whether and how they can overcome market failure and align R&D with needs in the area of biotechnology and infectious diseases. Public private issues have played a large part in the supply of water in various parts of the world, with varying effects. They are not confined to the highest income countries; India for example has developing activities of this type. Best practice involves clear demarcation of responsibilities and expertise focus and accurate monitoring of progress.

19. Thus the management of biological resources from the cells through existing vaccines to the development of new vaccines is a complex activity. There is a great deal of effort in the area; in some aspects, there is a degree of confusion concerning the value and outcomes. However, public private partnerships are a potentially useful addition to the development of products where the market is doubtful or restricted.

Building a global R&D strategy: proposed strategies to address the needs of developing countries

20. There is a great imbalance between R&D expenditure and the burden of disease. A framework might assist in setting priorities for R&D investments. However, as yet, there is no agreement amongst funders on the scope and design of such a framework.

21. Better health for the world's poor is not just a goal in its own right but would have a major effect on economic development and poverty reduction. The know-how to save millions of lives exists.. The CMH/WHO report recommends increased funding from governments towards health for the poor, directed at developing countries and an increase in funding for the development of new diagnostics, drugs and vaccines. The report also calls for more attention to resource mobilisation and the coherence of international policies including trade agreements. The conference recognised the need for international agencies to take stock of what each is doing and identify gaps. There is also a call to identify best practice in PPPs, examine capacity building and technology transfer. There is a further need to monitor and measure health inputs and health gains.

22. The Orphan Drug Act has helped in bringing small use products to market and could be modified to act as a stronger incentive for the development of treatments of diseases of developing countries as well as rare diseases in developed countries.

General discussion

23. The transfer of technology to developing countries is a key element so that countries can develop their own R&D infrastructure and capabilities to meet their own needs. Vulnerable populations exist within OECD countries and encompass more than just the obvious categories such as prisoners. The regulatory framework needs to be considered with respect to how it affects the application of biotechnology, specifically in developing countries. In the coming months the framework operating in the EU will be reviewed, providing a window of opportunity. This would include consideration of the orphan drug legislation. There was a need to analyse partnerships with some care; for example who sets the agenda, which issues could not be addressed through public private partnerships and the exact role of developing countries in such partnerships. A better analysis of the cost of R&D and the nature of incentives should be undertaken, and a consideration that there may be alternative methods for achieving the same effects. Biotechnology has a role in the process of development of products, but other steps may be rate limiting. Finally, the point that the process depended on political will at the level of both peoples and governments was reiterated.

Summary

24. There is a great deal of activity in the general area of infectious diseases in developing countries, although it is not commensurate with the scale of the problem. Biotechnology can play a part in improving health in these areas and is already doing so to some extent. The practical issues of developing appropriate products for markets with relatively low economic value are formidable; partnerships of various kinds can play a part. The developing countries themselves must be closely involved in the planning and execution of the development of appropriate and sustainable processes to aid development of needed treatments. Measures of the extent to which the system is able to deliver goals must be developed.