



Ensuring Innovation for Neglected Diseases

Research and Development (R&D) Conference

8th June 2005, London

On 8th June 2005, Médecins Sans Frontières (MSF) organised a conference in London to identify strategies to increase research and development (R&D) for neglected diseases, discuss recent initiatives in the field and examine ways to ensure patients' needs are central to defining the R&D agenda. The conference brought together around 200 people from over 20 countries. Participants came from a large diversity of groups, including academia, public-private-partnerships, governmental and non-governmental organisations, pharmaceutical industry and media. A CD-Rom containing all the presentations given and a full list of participants is available from mai.do@paris.msf.org on request.

Context

The concept and problem of neglected diseases are today recognised and are on the agenda of various international fora. Dr Bernard Pécoul, of the Drugs for Neglected Disease Initiative (DNDi), exemplified the lack of research and development (R&D) for neglected diseases – Sleeping Sickness and Visceral Leishmaniasis are both fatal if untreated, and existing drugs are old, toxic, and expensive; there are no effective drugs to treat chronic Chagas, which can be fatal; there are no drugs in existence for the treatment of Buruli Ulcer; and the specific research needs for HIV/AIDS in developing countries remain neglected.

The creation of not-for-profit initiatives such as the DNDi, and of public-private partnerships (PPP) such as those working on the development of tuberculosis drugs and diagnostics, malaria and HIV vaccines, and microbicides, is a promising development for the acceleration of the development and implementation of health tools for the poor. These positive developments however do not significantly change the existing 10/90 gap in health research spending.

Many questions remain: are PPPs a sufficient response or is there a need for a more dramatic change for R&D of neglected diseases? How is the research agenda determined, and how can it best reflect the needs of patients? Who is responsible for R&D for neglected diseases, when market forces are insufficient to generate a response? How can existing mechanisms be changed to facilitate R&D into neglected diseases? Is the PPP model the most appropriate, and is it sustainable?

Patients' needs

Several concrete field experience-based examples were presented to illustrate how patients' needs should drive the R&D agenda.

Dr Shyam Sundar, Chairman of Benaras Hindu University's Medical Department in India, highlighted the necessity to respond to patients' needs through innovation in leishmaniasis treatment. Treatments currently in widest use are highly toxic and responsible for significant patient mortality rates, have become increasingly ineffectual through the development of resistance (antimonials), or impose a high burden on health structures through the necessity to hospitalise patients (e.g. amphotericin). Leishmaniasis also provides an extremely telling illustration of the lack of innovation for neglected diseases: no newer drugs were developed specifically for the treatment of leishmaniasis, but rather were discovered during trials to have properties against leishmaniasis. Miltefosine is now available as first oral treatment but as it is toxic during pregnancy its use in women of child bearing

age is problematic. Also, efficacy in East African patients still needs to be demonstrated. The antileishmanial activity of paramomycin was first demonstrated in the 1960's and has been shown to be effective in phase II studies; phase III studies still need to be concluded. There are problems of access with newer treatments – most are out of reach of patients as they are too expensive, e.g. Miltefosine US\$145 per treatment course, liposomal amphotericin B (Ambisome®) approx. US\$3,000 per treatment course as differential pricing is not available in South Asia.

Discussions centred on the cost of Ambisome® - Dr Hogerzeil stressed that price did not constitute a blocking issue for the inclusion of a product on the Essential Medicines List (EML); if on the basis of medical effectiveness Ambisome® could be included on the list, he suggested this would lead to greater production and possible differential pricing agreements. Daniel Berman of MSF's Campaign for Access to Essential Medicines commented that there had been a collective failure by NGOs and other health organisations in terms of access to Ambisome®. Whilst Gilead had considered offering a differential price for the South Asian market, no-one has offered to negotiate an agreement and take responsibility for distribution of the drug. Dr Hamied of Cipla noted that there was a lack of transparency regarding the costing of liposomes which also acts as a barrier.

Dr Felipe Garcia de la Vega, from MSF's Campaign for Access to Essential Medicines, talked of the specific R&D needs in paediatric HIV/AIDS, based on his experience with MSF in Mozambique. Owing to the amounts of research HIV/AIDS attracts in industrialised countries, the disease is often not considered as "neglected" – yet the needs of patients in developing countries, and specifically children, remain unmet. Because of the difficulties in diagnosing children in field settings, over half of infants born HIV-positive will die before their 2nd birthday; nevertheless it remains difficult to even diagnose HIV in this age group due to lack of a simple and cheap nucleic acid test. There are no adapted paediatric antiretroviral (ARV) formulations for treating patients in resource-poor contexts.

Putting patients' needs at the centre of the R&D agenda

Chlamydia diagnostics provide an example of how tools can be developed that meet the needs and are appropriate to resource poor settings. Dr Helen Lee's unit at Cambridge University aims to develop such appropriate diagnostics for resource-poor settings. The absence of a simple and reliable test for chlamydia has long been an obstacle for STI diagnosis in resource poor settings. Dr Lee developed a rapid test that is low-tech and eliminated the need for refrigeration, complex pipette handling, or centrifugation and is thus well adapted to resource poor settings.

But how to ensure that patients' needs and not markets define R&D priorities? Dr Hans Hogerzeil, Director of Medicines Policy and Standards, WHO, presented the results of a WHO study commissioned by the Dutch government for the European Commission. The objective of the study was to identify a methodology for defining the R&D agenda from a public policy perspective and to outline the main R&D needs for Europe and the world.

The study introduced the notion of a pharmaceutical gap for certain diseases. A pharmaceutical gap can occur when there is no treatment or diagnostic tool in existence, when available treatments will soon become ineffective through the emergence of resistance, or when existing treatments are unsuitable for or ill-adapted to patients' needs. An R&D agenda can therefore be set on the basis of any pharmaceutical gaps that have been identified, by analysing current and future projections of the burden of a disease. Dr Hogerzeil spoke about the problem of increasing antimicrobial resistance. There is a burning need for completely new antibiotics – for developed and developing countries alike – but there is a pharmaceutical gap because pharmaceutical companies do not want to invest in R&D as physicians would have to restrict and reserve new antibiotics for special cases which would keep sales relatively low. This illustrated how market driven priority setting for R&D is not only detrimental for the needs of developing countries but also for Europe and the industrialised world.

What are the public and private responsibilities in addressing the R&D needs for neglected diseases?

Sir John Sulston, 2002 Nobel laureate in medicine and physiology, provided an overview of the contributions that can be made by the private and public sectors to R&D, and the limitations inherent

to each approach. Publicly financed R&D can arguably be more efficient, for several reasons: the research can focus on social not market needs, the burden of marketing costs is removed, and the research benefits from an open sharing of knowledge. Indeed public R&D was the key factor in the development of early vaccines for example, and the human genome project demonstrated that efficient genomic sequencing could be done on the largest scale in public labs. Among charitable contributions to R&D the Gates Foundation is the most relevant today. However all the private sources together are neither sufficient nor stable enough to meet the needs. Talk of financial incentives is often inappropriate: the key is in harnessing the natural idealism of scientists. Money is needed for research requirements and decent salaries, not for fortunes.

Dr Michel Pletschette, of DG Research and Technological Development, spoke of the European Commission's current focus on the "major diseases" (HIV/AIDS, malaria and tuberculosis). The Commission's investment in tropical diseases has so far been focused on prevention. With the EU's 7th Research Framework Program (FP7) currently under discussion, member countries should be mobilised so that neglected diseases will be included and receive appropriate funding. Improvements in the EDCTP (European & Developing Countries Clinical Trials Partnership) will be necessary too. Several incentives for private industry have been studied (tax breaks, advance purchase, transferable IP, etc.) and decisions will need to be taken. Jana Armstrong of DNDi urged that the procedures for the selection of projects be modified for FP7, in light of the difficulties to disburse all the funds available for EDCTP under FP6.

Other discussions centred on the public sector's most obvious contributions: to provide leadership in defining priorities, to provide funding and an environment that stimulates R&D. Current budget deficits in a number of OECD countries suggests that increased financing will be a hard won battle. Other possible fields of public sector input concern capacity building in developing countries. Public sector-led capacity building could also help remove some regulatory barriers to R&D in neglected diseases. Drugs for neglected diseases face extra hurdles as the US Food & Drug Administration (FDA) and the European Agency for the Evaluation of Medical products (EMA) base their approvals on home society perceived risk-benefits ratio. Developing country drug regulatory authorities (DRA) may not have the capacity to assess new chemical entities. Dr Hamied, Chairman of Cipla, stressed the urgent need to build capacity in areas such as toxicology, pharmacology, and the completion of clinical trials.

Dr Paul Herrling, Head of Corporate Research at Novartis, provided an illustration of a possible private sector response through his presentation on the "Novartis experiment": the creation of the Novartis Institute for Tropical Diseases (NITD) in Singapore with co-funding from the Singapore government. The initiative capitalises on the local expertise and motivation of researchers to develop new treatment and prevention tools for dengue and TB. The advantage of the NITD is that it can freely access compound libraries and expertise throughout the global Novartis family.

Questions concerned NITD's affirmed intention to make future treatments available to developing countries without profit. Dr Herrling explained that although the NITD's focus remains centred on tropical diseases, Novartis has retained a viable commercial long-term perspective. The target diseases' similarities with other pathologies such as, for dengue, Hepatitis C or the West Nile Virus, may stimulate R&D also for these diseases. The commercial returns in industrialised countries could therefore provide sustainable returns for the NITD in the longer term. Dr Hentschel of the Medicines for Malaria Venture commented that such an initiative was possible thanks to the strength of intellectual property protection in Singapore, whereas others contested that strong IP protection was not a sufficient nor necessary incentive for investment into neglected diseases.

Public-private partnerships

Dr Helen Lee highlighted the potential unlocked by PPPs. Small companies and academic centres are freer to invest in R&D for neglected diseases, but have limited human and other resources. Larger companies possess these resources, but have little incentive to invest due to their dependence on market constraints. By creating a structure that blurs traditional boundaries, you can harness respective strengths of the public sector (access to public funding, access to researchers, access to

university expertise) and the private sector (expertise in Good Manufacturing Practices, in patents, in clinical trials, and business experience). A panel of representatives from different PPPs involved in R&D for tropical or neglected diseases shared their perspective on the benefits and challenges faced by the PPP model. The representatives included Dr Maria Freire, of the Global TB Alliance for Drug Development, Dr Giorgio Roscigno, of the Foundation for Innovative New Diagnostics (FIND), Dr Chris Hentschel, of the Medicines for Malaria Venture (MMV), Dr Frans van der Boom of the International AIDS Vaccine Initiative (IAVI), and Tessa Matholie of the International Partnership for Microbicides (IPM).

A key question of the debate was if PPPs are already the answer for R&D of neglected diseases. For Dr Hentschel, PPPs have undoubtedly revolutionised the R&D pipeline for neglected diseases. Echoing Dr Garcia de la Vega's call for field-adapted paediatric antiretroviral formulations, he argued that fastest solution would be to create a PPP to address the issue.

Dr Mary Moran of the London School of Economics presented her research on the 61 neglected diseases drug projects in the pipeline at the end of 2004. PPPs are responsible for over 80% of these drug development projects, and therefore seem ideally placed to respond. PPPs suit industry needs, be they small and medium enterprises who can exploit the niche sector of PPP sub-contracting, or multinational corporations who benefit for strategic commercial reasons or corporate social responsibility motivations. PPPs are also an efficient means to allocate public money to viable projects.

Ellen 't Hoen of MSF acknowledged the work by PPPs but questioned whether we would find having one drug development initiative – as is the case for TB drugs - for cancer or cardiovascular disease a sufficient response to the need. She argued that more fundamental changes and greater action had to take place. Dr Pletschette of the European Commission expressed his doubts concerning PPPs' potential contribution.

The Bill & Melinda Gates Foundation's overarching role in funding PPPs (up to 60% of MMV's funding for example) raised questions about the future of the partnerships should the Foundation's support come to an end: how current efforts can be sustained? Dr Freire spoke of the formidable financial difficulties the TB Alliance would face if nothing was forthcoming next year. Some suggested that PPPs were in a good position to attract government money now that R&D for neglected diseases was more visible on the international agenda, provided the model proved successful in developing, and delivering products. Dr Lee also spoke of the "oxygen depletion effect" of Gates Foundation financing: when a PPP is funded it monopolises the scientific approach to a disease, and other approaches have difficulties in attracting funding.

PPPs' relationships with private industry were also a source of questions. How can PPPs gain access to private industry's compound libraries? Does this have to be done at the expense of guaranteeing wide access? The question of who retains control of the intellectual property was raised. Dr van der Boom insisted that the IAVI had the authority to approach another manufacturer if a contracted company was unable to provide products of reasonable quality and price, in a reasonable timeframe. Dr Maria Freire from the TB Alliance said that she does not experience problems in accessing compound libraries as long as screening specifications are sufficiently well defined. PPPs in general agreed that funding and regulatory barriers are the main bottlenecks at the moment.

The discussions around PPPs also centred on the definition of the R&D agenda for neglected diseases. How can PPPs address the lack of research into basic science, which is particularly needed for tuberculosis drugs and diagnostics development? How does the Gates Foundation's unique role in financing the majority of PPPs influence R&D priority setting and project selection? Dr Hentschel noted that the Foundation occasionally could have a "macro effect" on project selection, but "not a micro effect" on staffing choices or project management. Nicolas de la Torre from MSF asked why PPPs had decided not to sign the DNDi appeal (see below); Chris Hentschel responded that they felt that the situation analysis by DNDi was too negative. Shortly after the conference, some PPPs and major pharmaceutical companies addressed a separate letter to G8 leaders asking for greater investment into R&D for neglected diseases through increased funding of PPPs.

How to finance R&D in neglected diseases?

How much does R&D cost? Mr Andrew Farlow, of the University of Oxford, proposed that rather than relying on existing studies whose methodologies may be disputed, the easiest way to arrive at a figure would be to divide total global pharmaceutical spending by output of new chemical entities (NCE). Mr Farlow argued that the best way to make R&D more cost efficient is to link as much as possible the reward to the product developer to the true costs of development, as well as to the product's therapeutic value. It is therefore not cost effective to give large incentives to industry.

Graham Dukes, of the University of Oslo, provided an overview of the failures of the current system, ranging from the weakness of public governance to wasteful private marketing, and excessive investment in me-too drugs. Mr Farlow suggested that private industry suffers from the high cost of capital, high risks, and a high risk of crowding out, which may explain why there is little private investment in R&D in neglected diseases. Do we therefore need fundamental changes to the system, as it clearly isn't working in its current form?

Stewart Tyson of DfID presented the proposal for the creation of an International Financing Facility (IFF). The idea is to frontload R&D spending: OECD countries would issue bonds to raise money on capital markets, and pay back over the long-term through future aid budgets. Dr Moran proposed the IFF cash fund could be used to subsidise industry incentives and input to PPPs.

Although the IFF would mobilise new funds, concerns were raised during the discussions that the facility did not solve the fundamental imbalance in R&D in neglected diseases today: the need to create conditions that will enable researchers and scientists to respond to developing countries' needs. The current system, entrenched through intellectual property law and coercive bilateral or multilateral free trade agreements, finances the cost of R&D through higher medicine prices, via patents. But how appropriate is this system, when it is applied to countries where there is no market, such as Africa? When seven out of every ten new drugs developed in the US present no incremental therapeutic value? When significant public investment in drug development does not guarantee low drug prices or wide access once they are marketed?

Mr Love, Director of the Consumer Project for Technology, presented an alternative model for identifying, and addressing, R&D needs proposes a new paradigm which separates the cost of R&D from revenues achieved through sales and marketing. By creating, through an international R&D treaty, a market for R&D, similar to the Kyoto Protocol's creation of a market for carbon emission reductions. States would be obliged to dedicate a certain percentage of their GDP to R&D - they would retain the ability to finance this in the way they chose. Credits would be earned for financing R&D in accordance with disease priority, and could be traded amongst states.

During discussions around the treaty, concerns were raised about this project's feasibility given the current political climate and the US administration's reluctance to endorse the Kyoto Protocol. Mr Love suggested that it is possible to get a momentum going as US citizens are also victims of the failures of the current system in terms of access to medicines. He described the project as "inherently winnable" within seven years. Ms. Sakiko Fukuda Parr of Harvard University commented that the project was similar to the international campaign to ban landmines or the creation of the international criminal court, in that it's success will depend on mobilising civil society rather than only on governmental will.

Questions also focussed on how R&D funding would be distributed in the proposed system. Mr Love presented a possible option, which involves financing innovation through the creation of a government prize fund, in which products offering increased therapeutic benefit would attract greater financial recompense than me-too products.

R&D Appeal to governments

The Conference coincided with the launch of an appeal spearheaded by DNDi and supported by MSF. Dr Karim Laouabdia, Director of the MSF Campaign for Access to Essential Medicines in his closing remarks reminded participants that government action and political leadership is essential: in defining

the R&D priority agenda, in providing sustained funding and identifying new funding mechanisms for R&D into neglected diseases, and in reducing barriers in drug development for neglected diseases such as access to patent protected molecules, technology transfer and barriers in regulatory approval. The Appeal is part of a year-long drive, until the World Health Assembly in 2006. More information about the Appeal can be found at www.researchappeal.com

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