FINANCING MEDICAL INNOVATION THROUGH ALTERNATIVE MECHANISMS

How to boost R&D for a low-cost, point-of-care rapid diagnostic test and better drugs for tuberculosis

11 April 2008
Conference Summary

Context

On 11 April 2008, Médecins Sans Frontières (MSF) convened a one-day consultation of tuberculosis (TB) public health experts, scientists, diagnostics and drug developers, health economists and intellectual property specialists aiming to feed into the World Health Organization Intergovernmental Working Group on Public Health Innovation and Intellectual Property (WHO IGWG).

The IGWG is tasked with finding new ways to finance essential health R&D. WHO was asked to stimulate the development of proposals that focus on separating the link between paying for the cost of R&D and the price of the end product.[1]

The IGWG negotiations offer unprecedented opportunities. For the first time, governments and the public health community are taking on the task of addressing the consequences of relying on patents to finance health R&D – consequences which include the lack of health needs-driven R&D and barriers to the developing countries' access to new diagnostics, drugs and vaccines.

The meeting objective was to contribute to developing proposals that can be taken up in the context of the IGWG. To translate the talk into action, in sum, by grounding the IGWG process in the reality of tuberculosis R&D needs.

[1] World Health Assembly Resolution WHA 60.30 requested the WHO Director-General "to encourage the development of proposals for health-needs driven research and development (R&D) for discussion at the Intergovernmental Working Group that includes a range of incentive mechanisms including also addressing the linkage between the cost of research and development and the price of medicines, vaccines, diagnostic kits and other health-care products and a method for tailoring the optimal mix of incentives to a particular condition or product, with the objective of addressing diseases that disproportionately affect developing countries." www.who.int/gb/ebwha/pdf_files/WHA60/A60_R30-en.pdf

Tuberculosis R&D: what are the needs, what are the gaps?

The global situation as regards TB control is dismal – with around 1.6 million deaths per year, nine million new infections, almost half a million of which are multi-drug resistant (MDR) strains, TB is a global health emergency.

Médecins Sans Frontières field teams' experience with TB bears witness to the needs to develop new tools: they struggle to diagnose patients because of inadequate and outdated tools for rapid diagnosis, and struggle to treat them because of inadequate and outdated drugs. The fuelling of the TB epidemic by HIV and the increasing spread of multi-drug resistance has further increased the urgency for these tools to be developed.

The lack of a sensitive low-cost, point-of-care rapid diagnostic test for detection of active tuberculosis, suitable for use in resource-poor settings, and of simpler techniques for rapid detection of drug resistance are key barriers to TB control in the world's high burden countries. Also, there are no simple tools to detect TB in children.

Although TB can be cured, current treatment is complex and long-lasting, involving a combination of antibiotic drugs which were developed over 35 years ago. The chemotherapy regimen is particularly long and toxic for MDR-TB treatment (which can last up to two years), making adherence difficult. Moreover, current TB drugs negatively interact with antiretrovirals (ARVs), making co-treatment of TB/HIV co-infected patients very complex.

Scientific opportunities do exist, but they are not translated into the products and tools that are so desperately needed. The IGWG, as an intergovernmental process mandated with pursuing and setting up new and alternative financing mechanisms to boost drug and diagnostic development, therefore has the potential to change this dire picture.

Discussions and Presentations

An agenda and full list of participants is available in the annexes.

Tuberculosis diagnostic R&D – what needs to happen?

R&D for better TB diagnostics has increased in the past years with the arrival of new actors. However, current R&D efforts are still woefully insufficient to deliver the radically better and simpler tests that are needed.

A presentation by Ruth McNerney of the London School of Hygiene and Tropical Medicine noted the important gaps in our knowledge of many aspects of TB such as host-organism interactions, mechanisms of persistence, and surrogate markers of disease. These gaps must urgently be addressed through increased funding and coordinated research.

Developing simple, point-of-care tests soon requires innovative strategies, both financial and scientific. These might include dramatic simplification of current diagnostic methods such as culture and nucleic acid amplification, or detection of TB specific antigens, antibodies or biomarkers that could be use for the development of diagnostics test as simple as a dipstick. Identification of biomarkers that allow sensitive and specific detection of active TB disease is a major scientific challenge.

Javid Syed of the Treatment Action Group noted that tuberculosis R&D financing – estimated at an annual US$429 million in 2006, of which barely 7% are allocated to diagnostics R&D - is currently falling far short. Funding would need a five-fold increase to reach the estimated needs, including basic science and operational research, at US$2 billion.[2]

Participants referred to ongoing discussions such as those held in an expert meeting convened by Treatment Action Group (TAG) and the AIDS and Rights Alliance for Southern Africa (ARASA) in Cambridge in early April 2008, suggest specific opportunities to address the gaps in current diagnostic R&D:

- In the short-term, identified antigens or other biomarkers exist that could be systematically explored to see if they can lead to a first generation of point-of-care tests in the coming three to five years. The most fruitful way forward is to work with a combination of different antigens that would optimise the sensibility and sensitivity of any test. However that would require actors who now work separately to join together to share the current status of their individual research, sum up these results and perform further tests together. Protecting knowledge through patent monopoly stands in the way of this kind of innovative collaboration. One possible solution to this is the creation of patent pools where such knowledge could be openly shared.[3]
- In the medium-term, biomarker research needs to focus on molecules distinguishing active disease. The magnitude of the task is such that research consortia and other innovative models of how research is carried out will be needed. Mechanisms and funding will be necessary to ensure that new biomarkers will be further validated and taken forward to test development.

[2] Tuberculosis R&D – A Critical Analysis of Funding Trends, Treatment Action Group (TAG), November 2007; www.treatmentactiongroup.org

[3] Since this meeting, patent pools have been included as part of the World Health Organization's May 2008 Global Strategy on Public Health, Innovation, Intellectual Property. http://www.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf

- In the long-term, basic research efforts need to be increased to understand important gaps in knowledge about the biology of the disease that prevents test development.

Tuberculosis drug R&D – what needs to happen?

Martina Casenghi of MSF noted how although the situation has significantly improved in the last 10 years, the TB drug pipeline is still relatively weak. About 40 compounds are currently in the pipeline but if we consider attrition rates - on average only one compound out of 20 makes it through the development stages, and the fact that TB drugs have to be used in combinations, it is clear that the number of compounds is not sufficient to provide a new treatment regimen.

The weaknesses of TB drug R&D is particularly striking when compared to the HIV drug pipeline: about 100 and 30 compounds respectively are in preclinical and clinical development for HIV, against only 40 compounds in the entire TB drug pipeline.

If the potential of the public and not-for-profit sectors to help develop diagnostics and drugs is to be realised, they will need increased access to private sector pharmaceutical services and expertise. Jerome Premmereur of the TB Alliance said that mechanisms will also need to be established to ensure access to compound libraries and to build appropriate libraries with potential to exhibit anti-TB properties, particularly novel and natural products. There will also need to be more coordination between TB drug and diagnostics research, since some of the same development and assessment tools are important to both groups.

Worldwide, only US$20 million is spent annually for clinical trials for TB drugs compared to around US$300 million for HIV drugs in the US alone.[4] Therefore there is a need for funding bodies to support the creation of a TB clinical trial platform and the massive expansion of clinical trial capacity, particularly in developing countries. Paul Herrling of Novartis noted that the fluctuating funding available for trial sites is particularly problematic and needs to be addressed.

There is an immediate priority to shorten the time of clinical drug development. Criteria for compassionate use must be established by WHO and regulatory authorities for important candidate drugs.

Mario Raviglione of WHO said that strong political leadership is required to improve collaboration among scientists, drug and diagnostic developers, care providers, and affected individuals, in both developed and developing countries, and develop a global priority research agenda for TB as there are currently many different research agendas.

A dramatic funding increase is needed to support drug research and development activities. Javid Syed of TAG noted how this is above all a matter of political prioritisation: with respectively US$187 and US$183 million, US National Institutes of Health (NIH) funding both for smallpox and for anthrax exceed that for TB research.[5]

[4] TAG op.cit.
[5] Kaufmann and Parida, Nature Med, 2007 Mar;13(3):299-303

Alternative financing mechanisms – possible solutions to stimulate R&D

Advanced Market Commitments (AMC)
presented by Tania Cernuschi of GAVI Alliance

The AMC is an innovative financing model that aims to create incentives for innovation by subsidising pharmaceutical companies for the development of new medical tools that they would otherwise find unattractive commercially. Donors commit to providing funds to subsidise the development of these tools and thereby reduce the risk for pharmaceutical companies of investing in products for poor country markets.

The subsidy is only paid out once certain conditions on product specification are fulfilled and the product is indeed purchased by the countries: where there is medical need as defined the donors.

The GAVI Alliance set up a disease expert group who were tasked to recommend the most suitable disease for a pilot AMC. In 2006 the decision was made to move forward with a pilot AMC to increase the supply and delivery of a vaccine against pneumococcal disease. The aim is to get life-saving vaccines to developing countries faster and at a sustainable price.

The idea is that companies are paid a guaranteed higher price during the initial AMC period (AMC price) and in return firms are then obliged to sell at lower long run price (tail price). The tail price allows countries to know for certain how much the final price of the vaccine will be after the AMC comes to an end. To industry, the assurance of future price is an incentive for more timely investment and for additional companies to be attracted into the new 'market' thus stimulating competition. It was acknowledged that little competition will exist for pneumococcal vaccines during the initial years.

Discussions focused on the potential role of an AMC centred around its role as a pull mechanism, additional to current mechanisms to stimulate R&D. Participants raised the question of the potential contribution of AMCs when the product whose development is to be stimulated is still a long way from completion. How can the different parameters of an AMC be designed, for example, when so much in terms of specifications, development costs, product price are still to a large degree unknown?

Participants remarked that the AMC looks more and more like a purchase fund for a product that already exists, rather than a mechanism that will kick-start new R&D efforts.

Nevertheless, AMCs were felt to be a potentially interesting mechanism for increasing access and accelerating delivery of developed products. The experience of the GAVI pilot project for the pneumococcal vaccine would be a useful first experience to assess once it is operational.

Neglected Diseases Fund
presented by Paul Herrling, Head of Corporate Research, Novartis.

This proposal would see the creation of a pool of funds along the lines of the Global Fund, GAVI and the IFF, funded by governments of both developed and developing world. A management committee nominated by funders would be established to evaluate and fund selected projects. In addition, the committee would monitor the progress of each project and

make further funding decisions for further phases of development. In essence, this proposal would mirror the structures the pharmaceutical industry employs in product development but without the commercial imperative.

Beneficiaries of the fund would be required to exclusively license their intellectual property rights (IPR) to the funding body for the neglected disease, but are allowed to exploit their IPR in more affluent markets - provided that royalties are paid to the fund. In case the new molecule has advantages in the treatment of a disease with greater commercial value, the inventor/company will be allowed to do so on the condition that compensation will be paid to the fund for data developed with financing meant for neglected diseases.

Questions were raised about ensuring the access at affordable prices to any products developed. Participants also noted concerns surrounding the governance of such a Fund: how to avoid conflicts of interest between those making the decisions, and those potentially benefiting from the funds monies?

FIND's operational model
presented by Giorgio Roscigno, CEO, Foundation for Innovative New Diagnostics
FIND is a Gates Foundation-funded initiative that is driving TB diagnostic development forward through public-private partnerships. At present there are ten products in the pipeline – those more advanced in the pipeline (four products) are targeted for use at reference laboratory level, three more at the microscopy centre/peripheral laboratories level and a further three targeted for use at the primary health care level/health post. These products are due to be launched over the next five years.

FIND conducts its operations in a start-up venture mode. Each project portfolio is managed as a separate business unit with product lines, well-defined targets and timing at each stage of the R&D process. Co-investment with partners lowers risk and reduces break-even time. Existing and new diagnostics are recruited into evaluation in high-quality clinical trials for registration purposes and for use in large-scale demonstration projects to provide information on cost, ease of use and public health impact.

The prospect of a point-of-care antigen diagnostic test is being brought forward through FIND bringing together an array of players at key points of development – from the academics who work on the discovery of biomarkers to a spin-off product development partnership that can generate the technology to identify unknown antibody targets serving as key reagents for point-of-care development and then finally to commercial partners who can conduct the extensive clinical trials required and come up with prototype products.

Prize fund proposal
presented by James Love, Director of Knowledge, Ecology International
Prize funds are established mechanisms to stimulate innovation by offering a lump sum or prize as a reward for innovation. Prizes have been – and continue to be used – in a wide variety of industries. The advantage of prize funds used in the area of public health is that they can stimulate R&D without relying on sales to fund drug or diagnostics development. They also allow governments to prioritise R&D and steer it towards areas of greatest medical need.

A proposed prize for a TB diagnostic test could be worth US$100 million. As with the AMC, the specifications of a product could be influenced by ensuring that only products conforming to set specifications would qualify for the prize. In the case of a TB diagnostic test, these specifications would relate to the final product cost, its effectiveness and sensitivity as a test, and its possible use and adaptation to resource-poor settings. Participants noted that this did not ensure that a product would be used. They also raised questions about how to define a prize has been won – what governance for the prize fund?

The presentation explained how the prize fund model could be tailored to suit different objectives, rather than a simple winner-takes-all approach. In order both to encourage incremental innovation and provide funds to researchers in the years before any product is developed and sizeable rewards can therefore be expected, a percentage of the fund could be reserved to reward participants who were deemed to have made a significant contribution to advancing the solution of the problem. Prizes also could be flexibly awarded in other ways to reward sharing or transfer of technology and know-how. For instance, rewarding scientists to be open about the results of their research in the area of the prize fund could be done in order to stimulate more information sharing.

Participants raised questions about whether a prize fund could prove enough of an incentive to get industry interested. Here, the amounts promised by the fund was thought to be crucial: if the money available was sizeable enough, representatives from industry felt they would participate in such a mechanism. Determining what size the fund needed to be therefore becomes a central question if new actors, whether from industry, research institutes, donors, and so on, are to be brought into the field.

Questions centred on the predictability of funding from a prize fund: how would scientists currently dependent on grant funding be able to rely on the rewards from a fund? It was felt that prizes, as with other mechanisms discussed, should not be seen as a replacement for grant funding and other mechanisms, but as complementary, in addition to other mechanisms. If the prize fund is large enough it may generate enough interest to provide grants to researchers.

Discussions also focused on the value of a prize fund in drawing attention to an issue by making the R&D needs more ‘high profile’, and in helping to increase the prestige associated with working on a disease or particular health problem. Even if the prize alone is not enough to stimulate development of, for instance, a TB diagnostic test, then its very existence can enhance interest in the development of such a test more widely in academia and industry.

Conclusions

The presentations and discussions of the gaps in tuberculosis R&D made it very clear that the sheer scope of the problems make it essential that more actors need to become involved. The base of institutions working on tuberculosis – be they public, private, academic, corporate, research, funder – needs to be broadened.

There is a need for priority setting in tuberculosis R&D, as many different research agendas co-exist, and the most urgent medical needs don’t necessarily attract the most investment or research effort (for example detection of active versus latent tuberculosis).

Access to knowledge was identified as a first particularly problematic area. Alternatives to intellectual property mechanisms, which encourage secrecy and lead to duplication of work, need to be devised in order to encourage greater collaboration among academics and research institutes. There is all too often no real cohesion between different groups, with many initiatives working in isolation – this must change to avoid duplication of effort and to help accelerate scientific progress notably in basic science and discovery of antigens and biomarkers.

Money is a second crucial issue. Academic researchers need larger and more sustainable long-term grant funding, to facilitate for example the sharing of antigens.

But new financial mechanisms are needed – both push and pull. There was broad agreement on the need for solutions to be adapted for different timescales – short-term, medium-term and long-term. A wide range of different mechanisms was therefore necessary as no one mechanism can answer all the problems.

Ambitious proposals for alternative financing mechanisms attracted considerable interest. In particular, the idea of prize fund to stimulate TB diagnostics stimulated the interest of participants.

Any financial mechanism must also ensure access to knowledge. As such, any pledge for further financing has to come with the relevant rules around both the access to the developed product, and to the intellectual property rights surrounding its development – it is necessary, for example, for mechanisms to include provisions that allow for automatic licenses or free technology transfer to generic producers from day 1.

Discussions furthering these new financial mechanisms must take place at a global level, as many raise difficult issues of governance, and independence from conflict of interests. The work of WHO, notably through the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property which is tasked to design new ways of prioritising and incentivising essential health R&D, is therefore crucial in this respect.

-ENDS-

Annex: 1 **Meeting Agenda - 11th April 2008**

How to boost R&D for a low-cost point-of-care rapid diagnostic test and better drugs for tuberculosis

Case studies to feed the WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG)

9.00 – 9.10 Welcome
Dr. Tido von Schoen-Angerer, *MSF Campaign for Access to Essential Medicines*

9.10 – 10.40
Panel 1
The gaps: needs and opportunities in TB diagnostic and drugs development
Moderator: Prof. Paul van Helden, *Stellenbosch University*

a. Progress and main challenges in the development of a point-of-care test for active TB
Dr. Ruth McNerney, *London School of Hygiene and Tropical Medicine*

b. Progress and main challenges in TB drug R&D
Dr. Martina Casenghi, *MSF Campaign for Access to Essential Medicines*

c. Tracking the shortfall in TB research funding
Mr. Javid Sayed, *Treatment Action Group (TAG)*

Discussion

10.40 – 11.00

a. How to mover forward on the TB research movement
Dr. Mario Raviglione, *World Health Organization, Stop TB Department*

b. The research and development goals of the Global Plan to Stop TB 2006-2015
Dr. Marcos Espinal, *Stop TB*

11.00 – 11.15 Coffee break

11.15 – 13.00
Panel 2
The models: Overview of proposals for new financing for R&D
Moderator: Ms Ellen 't Hoen, *MSF Campaign for Access to Essential Medicines*

This session will assess different models for R&D financing. Participants will be asked to assess the advantages and limitations of the mechanisms and try to answer the question:

which would be most suitable for the development of a low-cost TB diagnostic test and which for TB drugs?

a. Advanced Market Commitments
   Ms. Tania Cernuschi, *GAVI Alliance*

b. Funding Full Development of the Emerging Pipeline in TB
   Prof. Paul Herrling, *Novartis*

c. The role of prizes for low-cost POC rapid diagnostic test and better drugs for TB
   Mr. James Love, *Knowledge Ecology International*

d. How to boost R&D for a low-cost, POC raid diagnostic test and better drugs for TB
   Dr. Giorgio Roscigno, *FIND*

Discussion

14.00 –17.00 Roundtable: Applying the models to the gaps

Moderator: Prof. Susan Foster, *University of Boston*

- Is money really the limiting factor? Will these proposed mechanisms stimulate the kind of research that we need to develop a TB test? Would having a prize or similar mechanism stimulate R&D, or do we need to fill some other gaps first, such as basic science or lack of capacity?
  Discussant: Prof. Paul van Helden, *Stellenbosch University*

- How do we apply the mechanisms to stimulate TB research? Can we imagine innovative models that divide the process into separate stages? Can we have multiple prizes for different steps? Can we move towards a multi-partner model to address the expertise gaps?
  Discussant: Prof. Aidan Hollis, *University of Calgary*

- What mechanism would be attractive for the developers of TB diagnostics? What incentives would bring multiple development partners to the table?
  Discussant: Dr. Mark Perkins, *FIND*

- How can we address the IP issues during the development as well as the resulting?
  Discussant: Mr. Sisule Musungu, *Iqsensato (excused)*

17.00 – 18.00 Conclusions

Dr. Tido von Schoen-Angerer,
MSF Campaign for Access to Essential Medicines

Annex 2: **Participants list**

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