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Health Partnerships Review

Focusing collaborative efforts on research and innovation for the health of the poor

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Published by the Global Forum for Health Research, May 2008

ISBN 978-2-940401-05-5

Suggested citation:
Health Partnerships Review, Global Forum for Health Research, Geneva, 2008
Stephen Matlin, Andrés de Francisco, Lakshmi Sundaram, Hannah-Sarah Faich, Monika Gehner (eds.)

Keywords:
1. Public–private partnerships. 2. Product development partnerships. 3. Health. 4. Research.
5. Low- and middle-income countries. 6. Global Forum for Health Research.

Additional copies of Health Partnerships Review can be ordered (at no charge) via the website www.globalforumhealth.org or from

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Editing and design by Inís Communication – www.inis.ie

Printed in May 2008.

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Focusing collaborative efforts on research and innovation for the health of the poor

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Focusing collaborative efforts on research and innovation for the health of the poor

The poor die young. Data from every part of the world show that, whether comparing richer and poorer populations within or between countries, those that are least well off have shorter life expectancies and heavier burdens of disease than those that are relatively wealthy. While the highest attainable standard of health has been declared a human right, this health inequity reflects a collective neglect at national and global levels – neglect of diseases, of health systems and ultimately of people.

Three areas of failure can be highlighted that represent different dimensions of the problem – failures of science (where basic knowledge or tools are lacking), failures of the market (where economic incentives for the production of needed medicines are lacking), and public health failures (where systems and programmes to implement available interventions are lacking).

"The Global Forum for Health Research has helped broker and facilitate the founding of some of the public–private partnerships."

Collaborative mechanisms to address these failures and to reverse the neglect have emerged in the last few years. The establishment in the 1970s of the Special Programme for Research and Training in Tropical Diseases (TDR) as a joint programme sponsored by a group of intergovernmental agencies (current sponsors are UNICEF, UNDP, the World Bank and the World Health Organization (WHO)) was the first collective effort on a global scale to close the gap in one crucial area – the dearth of effective, affordable drugs for a range of tropical parasitic diseases affecting millions of people in low- and middle-income countries (LMICs). The Merck Mectizan Donation Programme initiated in the late 1980s, providing free ivermectin to WHO for the treatment of river blindness, created an innovative partnership between the private and public sectors. It underscored the need for attention to delivery if effective and affordable drugs for diseases of the poor are to be accessible to those in need of them.

Subsequently, public–private partnerships (PPPs) have gained growing popularity as mechanisms for increasing access to essential drugs. With the creation of product development partnerships (PDPs) like the International AIDS Vaccine Initiative and Medicines for Malaria Venture by the Rockefeller Foundation and the subsequent support given to PDPs by the Bill and Melinda Gates Foundation, an important change in the landscape has taken place in the last few years and a growing pipeline of candidates has been established in the search for vaccines and drugs for a range of diseases that are of major importance in LMICs.

Since its establishment a decade ago, the Global Forum for Health Research has paid close attention to this burgeoning field, including by helping to broker and facilitate the founding of some of the partnerships. For several years, the Global Forum's Initiative for Public–Private Partnerships for Health studied the growth of the PDPs, providing important insights into their characteristics and needs as they expanded into new territory.

The PDPs have now reached a critical point in their evolution. The successful generation of a strong pipeline of candidate drugs and vaccines for clinical trials presents a new challenge: a major increase in funding will be required if the investments already made in research and development – so far, mainly by the philanthropic foundations and to a limited but growing extent by the public sector in some high-income countries – are not to be wasted. The scale of investments now needed to ensure that the best candidates go forward into clinical trials greatly exceeds the levels of funding that have so far been provided for the PDPs. Importantly, it is a scale that exceeds the funding capacity of any one donor in the public or philanthropic sectors and demands collective effort.

But the challenges are not just financial. With the expanding pipeline of possible new drugs and vaccines comes the need to address the wider picture – both to ensure that the organizational capacities and human and technical resources are in place so that the pipeline functions from end to end. It is also important to create the environment of legislative, regulatory and service infrastructures that will ensure that the new products are effective, safe, affordable and accessible to those in need and that they are taken up and used.

For *Health Partnerships Review,* the Global Forum has commissioned a series of chapters examining the characteristics of PPPs that aim to improve the health of the world's poorest people. The writers cover crucial issues:

- development of a framework for assessing and comparing performance between PDPs;
- stimulation of basic biomedical research in both developing and developed countries;
- organization and resourcing of clinical trials in disease-endemic countries;
- approaches by individual PDPs for managing portfolios of products;
- intellectual property management;
- regulatory strategies for product registration;
- innovations in partnerships for health services delivery;
- social innovation to complement technological innovation.

Issues highlighted include the roles of different actors in partnerships involving public sector and philanthropic donors, the private sector, nongovernmental organizations, communities and researchers in developed and developing countries.

The picture of PPPs that emerges is multifaceted and complex. The PPP approach has evidently served to focus attention on some neglected areas and has galvanized action that is bringing

new resources and innovative solutions to address some health problems. But many challenges remain if their promise is to be fulfilled, including greater and more sustainable financing over the longer term and better mechanisms for coordination.

Challenges raised in *Health Partnerships Review* include:

- Research targeted on the diseases of LMICs is still woefully under-resourced.
- It is critical that the driving principles for promoting PPPs are rooted in the concept of equity of health.
- The complex ethical and human rights issues involved in clinical trials are best addressed through community mobilization and involvement.
- LMIC partners must be empowered to fully participate in North-South collaborative programmes to ensure their success and sustainability.
- Joint planning and prioritization of the research agenda by all stakeholders, including from LMICs, is essential.
- Conducting and coordinating multiple PDP protocols has resulted in sponsors and donors benefiting from best practices and operating procedures across trials.
- A common advocacy strategy among various initiatives and stakeholders in product-development maximizes impact on the target audience.
- A handful of innovative LMICs, who are adjusting and refining their national innovation systems, have emerged as major global contributors to the manufacture of essential drugs and vaccines.
- LMICs should strengthen their local health systems and ensure that these are closely linked to public and private sector organizations in their countries to cultivate innovation.
- Social innovations are needed within health systems to achieve maximum uptake of essential new drugs, vaccines and diagnostics.
- PDPs do not just result in transfer of technology, but also of the institutional and organizational capacity needed to successfully conduct clinical trials in vaccine development.
- The establishment of inventories of the intellectual property rights held and licensing status in key global health fields could assist PDPs in their interactions with academic institutions.
- An effective and efficient drug development pipeline will require the continued development of an international clinical trials system that engages local investigators, communities and ethical review committees.

"The scale of investments now needed to ensure that the best candidates go forward into clinical trials exceeds the funding capacity of any one donor in the public or philanthropic sectors and demands collective effort."

We hope that *Health Partnerships Review* will contribute to the debate about the future role of PPPs and provide pointers to key areas for urgent attention to sustain and increase the momentum to reach the goals towards which the PPPs are striving. The ethical imperative of reducing health inequities, of closing the gap between the health of the poorest and those who are better off, demands the utmost collective effort.

Stephen Matlin
Executive Director
Global Forum for Health Research

Canaliser les efforts collectifs sur la recherche et l'innovation, afin d'améliorer la santé des populations pauvres

La réduction des iniquités en matière de santé, lesquelles découlent de l'écart qui s'est creusé entre les populations les plus démunies et les populations riches sur le plan de la santé, est un impératif éthique auquel nous ne pourrons nous plier que si nous déployons des efforts collectifs colossaux.

De plus en plus de partenariats public-privé (PPP) sont établis en vue d'accroître l'accès à des médicaments essentiels. En outre, la création de PPP pour le développement de produits (PDP), tels que l'International AIDS Vaccine Initiative et la Medicines for Malaria Venture, et le concours financier accordé aux PDP par la Bill and Melinda Gates Foundation témoignent de la profonde mutation qui s'est opérée dans le domaine de la recherche en santé au cours des dernières années.

Cela dit, les PDP doivent désormais franchir une étape cruciale. En effet, la production de solides réserves de candidats médicaments et de candidats vaccins soulève un nouveau défi : il faut accroître considérablement le financement des partenariats, afin que les investissements ayant déjà été consentis en recherche et développement (R&D) soient fructueux. À l'heure actuelle, le volume d'investissements nécessaire pour que les meilleurs produits en développement fassent l'objet d'essais cliniques dépasse largement le niveau de financement des PDP, et, plus important encore, il excède les capacités de financement de n'importe quel bailleur de fonds du secteur public ou philanthropique. Un tel volume d'investissements suppose donc un effort collectif.

Néanmoins, les enjeux ne se situent pas uniquement sur le plan financier. Ainsi, la mise au point d'un nombre croissant de candidats médicaments et de candidats vaccins nécessite que l'on dispose des capacités organisationnelles et des ressources humaines et techniques qui permettront à ces produits de passer par toutes les phases du développement. Il importe également de mettre en place des infrastructures juridiques et réglementaires et des infrastructures de services pour veiller à ce que les nouveaux produits soient sûrs, efficaces, abordables et accessibles aux populations qui sont dans le besoin, d'une part, et qu'ils soient adoptés et utilisés par ces populations, d'autre part.

Le Forum mondial pour la recherche en santé (Global Forum for Health Research) a commandé une série d'articles sur les PPP pour *Health Partnerships Review* qui portent sur des sujets cruciaux:

- l'établissement d'un cadre de référence permettant d'évaluer les PDP;
- la promotion de la recherche fondamentale en biomédecine dans les pays développés et en développement ;
- l'organisation et le financement d'essais cliniques dans les pays où sévissent des maladies endémiques ;
- les stratégies établies par les différents PDP pour la gestion du pipeline ;
- la gestion de la propriété intellectuelle et les stratégies réglementaires relatives à l'homologation des produits ;
- les partenariats innovateurs consacrés à la prestation des services de soins de santé ;
- les innovations sociales qui se veulent un complément des innovations technologiques.

Nous espérons que *Health Partnerships Review* viendra alimenter le débat sur le rôle que sont appelés à jouer les PPPs et qu'il mettra en évidence les principaux aspects sur lesquels il faut se concentrer dans l'immédiat.

Stephen Matlin
Directeur général
Forum mondial pour la recherche en santé

Enfoque em esforços colaborativos em pesquisa e inovações em prol da saúde de populações pobres

A imperiosidade ética para reduzir as desigualdades em saúde, de diminuir as diferenças de saúde entre as populações pobres e as mais favorecidas, demanda um esforço coletivo supremo.

Parcerias público-privadas (PPPs) têm obtido popularidade cada vez maior como mecanismos para aumentar o acesso a fármacos essenciais. A criação de parcerias para desenvolvimento de produtos (PDPs), como a International AIDS Vaccine Initiative (Iniciativa Internacional para Vacinas contra a AIDS) e Medicines for Malaria Venture (Projeto para medicamentos antipalúdicos), e o apoio subsequente oferecido às PDPs pela Bill and Melinda Gates Foundation, geraram modificações importantes nestes últimos anos.

As PDPs atingiram agora um ponto crítico na sua evolução. A geração bem sucedida de um fluxo robusto de vacinas e fármacos propostos para estudos clínicos apresenta um novo desafio: será necessário um aumento substancial de fundos para que os investimentos já realizados em pesquisa e desenvolvimento (P&D) não sejam desperdiçados. A escala de investimentos necessários agora, para garantir que as melhores propostas prossigam até a fase de estudos clínicos, ultrapassam muito os níveis dos financiamentos proporcinados até agora às PDPs. É importante notar que se trata de uma escala que excede a capacidade de financiamento de qualquer doador dos setores públicos ou filantrópicos e demanda esforços coletivos.

Os desafios, entretanto, não são apenas financeiros. Junto com a expansão do fluxo de possíveis e novos vacinas e medicamentos há a necessidade de garantir que as capacidades das organizações e os recursos técnicos e humanos estejam estabelecidos de forma que o fluxo funcione do princípio ao fim. É também importante criar um ambiente de infra-estrutura legislativa, regulatória e de serviços para garantir que os produtos novos sejam eficazes, seguros, acessíveis e tenham preços módicos para quem deles necessita, bem como que sejam administrados e usados.

Para a publicação de Análises Críticas sobre Parcerias em Saúde *(Health Partnerships Review)* o Global Forum encomendou uma série de capítulos sobre PPPs que cobrem os seguintes temas:

- o desenvolvimento de uma estrutura para a avaliação e comparação do desempenho entre PDPs;
- o estímulo à pesquisa biomédica básica, tanto em países em desenvolvimento como em países desenvolvidos;
- a organização e a avaliabilidade de recursos para estudos clínicos em países com doenças endémicas;
- as abordagens utilizadas por PDPs individuais para a administração *de portfolios* de produtos;
- a gestão da propriedade intelectual;
- as estratégias regulatórias para registro de produtos;
- as inovações nas parcerias para a prestação de serviços da saúde;
- a inovação social para complementar a inovação tecnológica.

Esperamos que Análises Críticas sobre Parcerias em Saúde possa contribuir para as discussões sobre o papel futuro das PPPs e indicar as áreas-chave que necessitam de atenção urgente.

Stephen Matlin
Diretor Executivo
Global Forum for Health Research

Enfocar los esfuerzos colectivos en investigación e innovación para la salud de las poblaciones más pobres

El imperativo ético de reducir las desigualdades en materia de salud, de cerrar la brecha entre la salud de los más vulnerables y de los más privilegiados, exige el máximo esfuerzo colectivo.

Los Partenariados Público-Privados (PPP) han experimentado una popularidad creciente como mecanismos para incrementar el acceso a los medicamentos esenciales. Con la creación de los Partenariados para el Desarrollo de Productos (PDP) tales como la Iniciativa Internacional para una Vacuna contra el VIH/SIDA, Medicinas para la Empresa de la Malaria y el apoyo posterior ofrecido a los PDP por la Fundación Bill y Melinda Gates, se ha producido un cambio importante en el escenario de los últimos años.

Los PDP han llegado ahora a un punto crucial de su evolución. La generación exitosa de una sólida línea de medicamentos y vacunas en preparación que son candidatos a ensayos clínicos, presenta un nuevo desafío. Será necesario un aumento significativo de fondos si no quieren desperdiciarse las inversiones ya efectuadas en investigación y desarrollo (I+D). La envergadura de las inversiones que se requieren ahora para garantizar que los mejores candidatos progresen hacia la fase de ensayos clínicos excede el nivel de financiación que se ha suministrado hasta ahora a los PDP. Cabe resaltar que se trata de una escala que sobrepasa la capacidad financiera de cualquiera de los donantes de carácter público o filantrópico y por lo tanto exige un esfuerzo colectivo.

Pero las dificultades no se limitan al plano financiero. La expansión de nuevos medicamentos y vacunas en preparación, genera la necesidad de garantizar la existencia de la capacidad organizacional así como de los recursos humanos y técnicos para que esta línea de productos en preparación funcione de principio a fin. De igual manera, es importante crear el contexto de infraestructuras legislativas, reguladoras y de servicios que garantice que los nuevos productos sean eficaces, seguros, accesibles y con un precio razonable para aquellos que los necesitan y asegurarse de que sean aceptados y utilizados.

Para la *Revista de Partenariados en Salud* el Global Forum ha encargado una serie de capítulos que examina las características de los PPP que esperan mejorar la salud de la gente más pobre del mundo. Los escritores informan acerca de un amplio espectro de temas críticos:

- el desarrollo de un marco para evaluar y comparar el rendimiento entre diferentes PDP;
- el incentivo a la investigación biomédica de base tanto en países en desarrollo como en países desarrollados;
- la organización y la afectación de recursos destinados a ensayos clínicos en países con enfermedades endémicas;
- los enfoques desarrollados para el manejo de portafolios de productos por PDP individuales;
- la gestión de la propiedad intelectual, las estrategias de regulación para el registro de productos;
- las innovaciones en los partenariados para la prestación de servicios de salud;
- la innovación social como complemento a la innovación tecnológica.

Esperamos que la *Revista de Partenariados en Salud* contribuirá al debate acerca del papel futuro de los PPP y aportará pistas en áreas claves que requieren atención urgente.

Stephen Matlin
Director Ejecutivo
Global Forum for Health Research

The PDP approach

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The new landscape of product development partnerships (PDPs)

Stefanie Meredith
Elizabeth Ziemba

Adapted from 'A new landscape of partnerships', published in *Global Forum Update on Research for Health,* 4:132–136.

Background

Over the last few years, partnerships between public and private sector organizations have become an increasingly common mechanism to address some of the diseases of the poor in developing countries.

The ultimate goal of most of these partnerships is to improve and increase access to treatment, particularly for 'neglected diseases'. Many also express the goal of contributing to the alleviation of poverty through improved health.

The need for such partnerships can be explained by a failure of public health systems – the inability of the public sector to provide public goods entirely on its own, due to lack of resources; competing priorities for the limited resources available; management issues; conflict and post-conflict situations; etc. There is also a failure on the part of the private sector when there is little or no commercial incentive for the development of diagnostics and medicines for most of the diseases endemic in developing countries and affecting mainly the very poor.

"Research targeted on the diseases of the developing world – that account for 90% of the global disease burden – is still woefully underresourced."

Introduction

Approximately US$ 125 billion was spent on health research in 2006.[1] This represents a major increase since the earlier estimates of US$ 60 billion in 1999, but research targeted on the diseases of the developing world – that account for 90% of the global disease burden – is still woefully underresourced. The lack of availability of medicines to people in developing countries results in enormous human and economic costs.

During the past ten years, the global health community has identified gaps in research and development of medicines to prevent or cure diseases that are primarily associated with extreme poverty and the attendant lack of access to clean water, adequate nutrition, and basic sanitation.[2] While diseases such as malaria, tuberculosis – and others that are even less well known – are rampant in developing countries, they are of lesser or no consequence in developed countries.[3,4,5,6]

There is little or no economic incentive to develop pharmaceutical products[7,8] for these diseases. Some of the obstacles to developing these products include distribution challenges in countries with poor infrastructures; lack of awareness about these diseases in more developed countries;[3] liability considerations; an inadequate science base; and underestimation of the disease burden.[9] As a consequence, compared with other diseases, minimal research on diseases affecting the poor has been conducted. The formation of public–private partnerships (PPPs)[10] has been an important and innovate approach to addressing the enormous and widening gap in availability of medicines.

PPPs bring together skills, knowledge, and resources from a variety of sectors including academia, nongovernmental organizations, philanthropists, government and intergovernmental agencies, as well as members of the for-profit private sector such as pharmaceutical and biotech companies to create a unique approach to solving a global health issue. Each partnership has its own separate legal status, broad range of goals, combinations of partners from the public and private sectors, management structures and strategies.[11]

The nature, variety, and individuality of PPPs make definition difficult.[12,13,14] However, one working definition of PPPs for health is: "arrangements that innovatively combine different skills and resources from institutions in the public and private sectors to address persistent global health problems".[15]

Although the philosophy behind PPPs includes shared risk, using complementary skills and expertise from each partner organization and equal input from public and private organizations, the reality is that many of these so-called PPPs would be better described more classically as partnerships or even collaborations due to the traditional division of financial and technical roles of the organizations.

Global health partnerships frequently use the term 'neglected diseases' when referring to a group of diseases affecting developing countries. Although there are several different definitions of neglected diseases, the following broad definition will be used in this context:

"Diseases that primarily affect populations in the poorest areas of developing countries for which there are inadequate or no treatment options and do not constitute a valuable enough market to stimulate private sector research and development."

To redress the imbalance in availability of medicines to developing countries, PPPs are used as a means to gather resources and funding to be applied to addressing this problem. Both the private and public sectors acknowledge that "a pure market mechanism generally does not work"[12] where medicines are involved and new approaches need to be developed.

Globally, millions of people die or become disabled from diseases for which there are inadequate or no medicines. From 1975 to

2004, only 1.3% of the 1556 new chemical entities marketed were registered for tropical diseases and tuberculosis despite the fact that these diseases account for 12% of the global disease burden.[16]

Barriers to access to products and treatments for diseases of the poor

The barriers to access to products and treatment for diseases of the poor that these partnerships have been created to address can be classified under the following six groupings:

1. lack of affordable, effective, safe diagnostics, medicines or vaccines;
2. the cost of the products, medicines and vaccines;
3. lack of a reliable supply of products, medicines or vaccines;
4. weak/fractured health systems;
5. cultural perceptions and beliefs;
6. lack of political will.

Kinds of partnerships

In general, PPPs can be broadly categorized into the following 3 areas: (1) product distribution or disease control programmes; (2) product development; and (3) policy/advocacy for health systems issues.[17] However, categorization is not an exact science as partnerships may deal in any combination with product distribution, product development, and/or policy and health systems issues between or among various diseases.

1. Product distribution/disease control programmes. These PPPs are designed to improve access to treatment in developing countries by improving distribution of medicines or medical products to prevent or treat specific diseases.
2. Product development. The majority of partnerships focus on the development of medicines, vaccines or products for use in the treatment or prevention of neglected diseases[18] such as the Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI) and the Global Alliance for Vaccines and Immunization (GAVI).
3. Policy/advocacy or health systems issues. Most of the partnerships that fall in this advocacy and policy category, e.g. GAVI, the Drugs for Neglected Diseases Initiative (DNDi), the Global Alliance for Improved Nutrition (GAIN), and the Safe Injection Global Network (SIGN) Alliance, also have some technical, access or product development component.

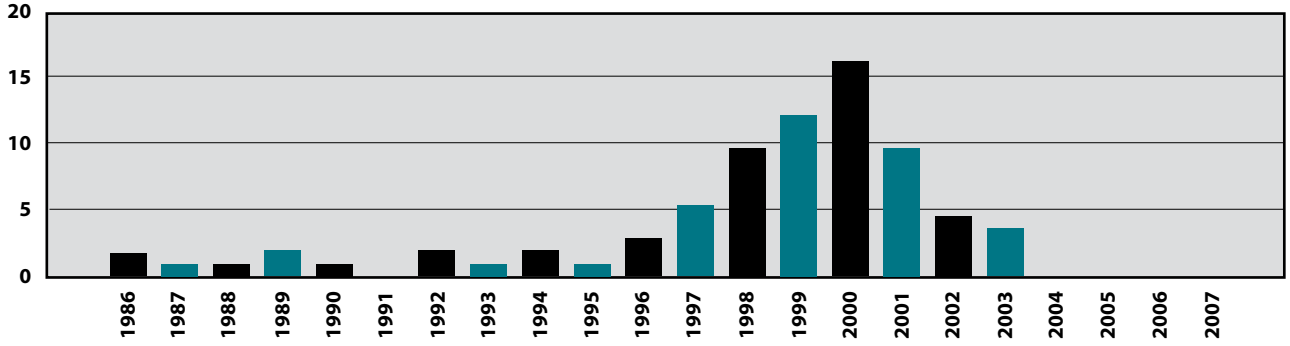
This review focuses on the product development partnerships (PDPs) which we define as "a non-profit organization that builds partnerships between the private, public, academic and philanthropic

Table 1.
Current Product Development Partnerships [23]

Disease	Number of PDPs			
	Drugs	Microbicides	Vaccines	Diagnostics
HIV		2	2	
Tuberculosis (TB)	1		2	2*
Malaria	4		3	
Chagas	2		1	
Dengue fever			1	
Diarrhoeal diseases	1		2	
Human African trypanosomiasis (HAT)	2			
Hookworm			1	
Leishmaniasis	2		1	1*
Onchocerciasis	1			
Schistosomiasis	1			
Pneumonia			1	
Meningitis			1	

* The Infectious Disease Research Institute (IDRI) works on vaccines and diagnostics for TB and leishmaniasis, included in both categories.

Figure 1.
Number of public–private partnerships for product development created by year from 1986 to 2007 [21]



sectors to drive the development of new products for underserved markets". PDPs are created for the public good and the resulting products are made affordable to all who need them.[19]

Currently, 24 PPPs devote their efforts to developing medicines, vaccines or diagnostics for diseases of developing countries including malaria, tuberculosis, HIV, leishmaniasis and others collectively referred to as 'neglected diseases' (see Figure 1).

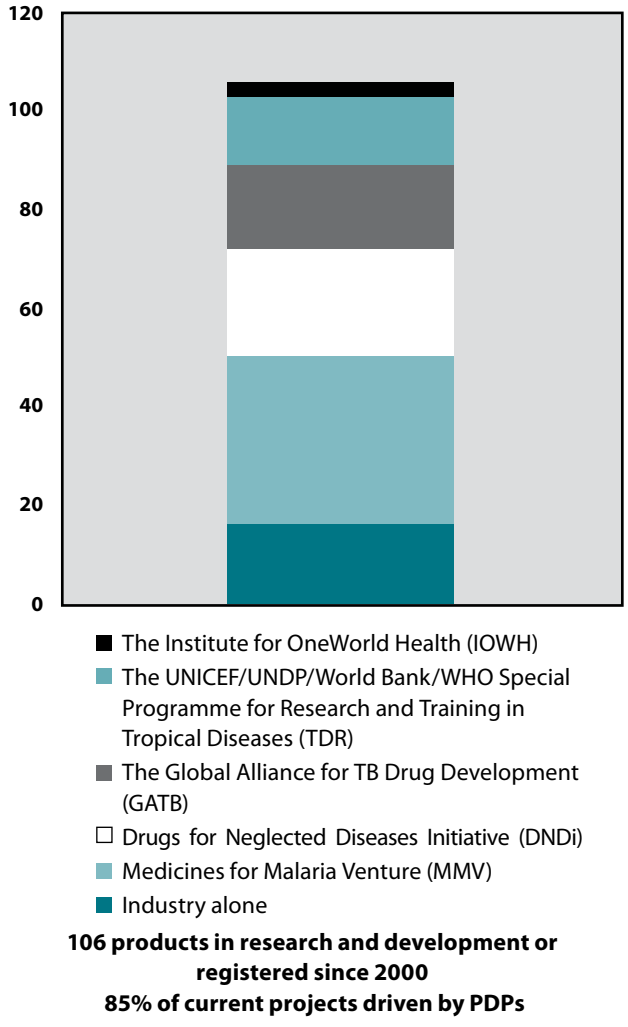
Of these partnerships, 9 are devoted to developing medicines and/or microbicides, 11 are committed to vaccine development, 1 is focused on diagnostic products, and 3 are involved with the development of a combination of medicines, vaccines and/or diagnostics. Five partnerships focus exclusively on reproductive health issues, 5 focus on malaria and 2 are committed to tuberculosis and HIV respectively.

Current situation with regard to PPPs for health

The raising of awareness and stimulation of research and development on drugs/prevention for neglected diseases has certainly changed the field over the last seven years. There is now a very crowded landscape of PPPs, particularly in certain sectors. At least one PPP providing research and development, drugs and technical support and/or some funding is now addressing most of the neglected diseases.

A recent analysis of drug development for neglected diseases[22] has shown that many of the long-held beliefs on drug development for neglected diseases are no longer valid or accurate, and product development since 2000 has increased substantially (Figure 2). However, despite the public–private label, 80% of the drug development is through private philanthropy and the industry institutions are largely self-funding. Moran and collaborators point out that although the product development PPPs have proved to be a good conduit for directing public funding to industry and academia, they could collapse if there is not more public support.[23]

Figure 2.
Products currently in research and development[23]



Partnerships focusing on access to medicines and drug donation programmes have raised the profile of the diseases involved, kick-started national disease control programmes and improved delivery systems to those at 'the end of the road'.

However, there remain many gaps that the partnerships have not been able to address, which raise the concern of sustainability, including systemic problems in health systems and infrastructure, capacity development and human resources, and long-term operational funding. The clinical trial capacity is limited and underfunded at present and mechanisms for 'after research and development' are not being addressed – i.e. how to get the products to the people that need them.

Overall, improved coordination between the partnerships is needed as well as integrated approaches to addressing neglected diseases, which would maximize efficient use of resources.

Conclusion

Public–private partnerships have changed the landscape of drug development for medicines for neglected diseases, and the delivery of medicines for some neglected diseases in the developing world. Stemming from market and government failures as well as ineffective legislative incentives, PPPs have brought together participants from all sectors in an attempt to maximize the skills and resources of those participants to tackle complex issues of drug development and distribution.

While product distribution and disease control programmes are filling a gap and improving access to treatment for specific diseases, many issues concerning long-term sustainability remain.

PDPs are relatively new entities and though the first products have come to the market (the Drugs for Neglected Diseases Initiative (DNDi)–sanofi-aventis new fixed-dose combination of artesunate and amodiaquine (ASAQ) and the Medicines for Malaria Venture (MMV) – Novartis Paediatric Coartem), these were developed from existing compounds, and it remains to be seen if this innovative approach to drug development will really succeed in both delivering the needed new products and doing so at lower costs than the traditional for-profit model. The PDPs have introduced innovative and creative systems and processes for drug development outside the traditional pharmaceutical model and are challenging governments, industry, academia and non-profit organizations to face urgent public health issues.

Product development partnerships face the risks inherent in the costly and time-consuming process of drug development, especially for diseases where basic science and research has been dormant for decades. The cost of drug development is high and PDPs are facing the problem of availability of sufficient funding as drug candidates move through each stage of the development process. Major funding gaps for drug development have already been recognized and thus the challenge will be to secure predictable, sustainable funding.

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Biographies

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Public–private partnerships in health systems

Sania Nishtar

Of the various functions of governments in sovereign countries, the one that stands out in terms of being perceived as reflecting a commitment to meeting the equity objective is the delivery of social services. However, most low- and middle-income countries are finding it increasingly difficult to deliver on this objective due to fiscal constraints and the prevailing regulatory environment, which enables non-state entities to operate in the social sector for profit. This has lent impetus to the realization that strengthening the public–private interface is important in achieving objectives within the social sector. Changes in public–private roles are also interlinked with broader changes in the macro-economy, which promote a package of measures that make the private sector the engine of growth and move back the borders of the state, reshaping the way the government does business. Governments in various parts of the world are therefore increasingly recognizing that a policy, regulatory and legal environment that fosters fairness, social cohesion and transparency, in combination with private sector's resources, outreach, entrepreneurial talent and/or management efficiencies, can assist them in meeting equity-focused objectives. However, the challenge in such 'partnerships' is to balance support to the private sector against safeguards for the poor and marginalized, whose interests governments must be committed to protecting.

Within the health sector, the credit for spotlighting partnerships in health undoubtedly goes to global infectious disease partnerships,[1] which have improved access of populations to a range of products and services, albeit while raising several ethical and methodological challenges.[2,3] These prototype partnerships have sensitized governments to the role of different players in improving health status; however in order to truly tap the potential within the public–private mix, partnerships need to be forged at a health systems level within countries. This is particularly so within contemporary mixed health systems, where public and private entities both provide health care. It is within this context that a viewpoint is articulated in this paper regarding the potential within partnerships at a health systems level.

The public–private mix in service delivery

In mixed health systems, government health-care delivery infrastructure is often compromised both on account of quality and capacity, since health providers have incentives to work in private systems. In such environments, it should appear plausible for governments to leverage the strength and outreach of private sector health-care providers (individual health-care providers, private hospitals and nongovernmental organizations (NGOs)) to deliver essential health services. Governments in mixed health systems should also explore different arrangements – that go beyond contractual roles for delivering services as previously stated – for improving delivery of services through public sector infrastructure by leveraging the private sector's strengths. Many categories of relationships fall within this scope:

- *service contracts,* where the private sector service provider receives a fee from the public sector to manage a particular aspect of public service;
- *management contracts,* where the service provider is responsible for overall management but without responsibility to finance, which remains the responsibility of the state;
- *lease,* where the service provider is responsible for the overall management as well as the public sector's operating assets;
- *build, operate, transfer* (BOT) where a service provider undertakes to design, build, manage, operate, maintain and repair at its own expense but requires the government to pay the service provider a fee for providing services and where the government becomes the owner of the facility at the end of the contract. Other variants of the BOT contract include 'build, operate, own, transfer' (BOOT) and 'build, operate, own' (BOO);
- *concession,* where the contractor collects and retains all service tariffs, assumes the collections risk and pays the public sector a concession fee;
- *private divestiture,* which involves the sale of assets of shares of a state-owned entity to the private sector.

Each of these arrangements of public–private mix in delivering services are only as good as the government's capacity allows. This underscores the need for developing institutional capacity and frameworks, structures for participatory regulation and systems of combined governance, which ensure balanced power relationships. It is also important for governments to develop their own capacities in public–private contract management, commercial transactions and related corporate and legal matters. Governments will also have to develop regulatory frameworks and enhance their capacity in transparent competitive selection processes with careful attention to accountability- and sustainability-related concerns, and with ethical and administrative clarity in operations. In addition, governments need to redefine their new operational and regulatory role in contracted-out arrangements, provide frameworks for service delivery targets and most importantly, the norms and procedures for providing subsidies to hospitals for offsetting costs incurred in treating poor patients. This also entails strengthening frameworks for social protection to make sure that public funding is used to ensure that poor people who access health services are not at a disadvantage or discriminated against. In addition, where decentralized forms of governance exist, such as in many developing countries, this involves linkages with community management structures.

Service delivery partnerships can also be developed with *practitioners of traditional medicine,* who are deeply rooted in many parts of the world. However, in order to utilize this health system the

pathway to care chains and access to care patterns will have to be defined and randomized control trials will have to be conducted on the most commonly used drugs in the system.

The potential for *behaviour change communication* within health systems has been truly untapped and here the private sector can bring significant value to the public sector, in terms of the lessons learned from persuasion, and large group processes such as those employed by advertising agencies and social marketing approaches.

The public–private mix in health financing

The ultimate aim of health financing should be to maximize the role of public sources of financing (public revenues and social insurance), which are more equitable in protection against health expenditure, than private sources (private insurance and out-of-pocket payment at the point of service). Out-of-pocket payments continue to be a major form of health financing in mixed health systems and therefore in health system reforms in such environments, some form of fee structures and user charges are inevitably introduced at point of care in government health facilities as part of *cost sharing polices*. Although user fees are a contentious subject, they can present an opportunity to employ differential financing. This can alter the subsidy going to different segments of the population and can thus be used to promote equity by reducing the amount that the poor must pay through fee exemptions. If these are introduced with appropriate waiver and exemption systems they can form pragmatic solutions to achieving equity through alternative financing. However, in order for that to happen, governments will have to mainstream regulatory and legal reform that fosters responsible citizen participation and creates an innovative public–private mix for enhancing the pool of health financing in mixed health systems.

"The role of the public sector is to create an enabling regulatory environment for (private) insurance agencies, albeit with appropriate safeguards, patient-centred norms in transaction standards and ethical safeguards."

The *private insurance industry* can be a source of health financing in individual or group settings. However, growth of the private insurance industry is related to growth of a country in general, and to increases in the number of employees in the formally employed sector in particular, where employers subscribe to global employment practices. Here the role of the public sector is to create an enabling regulatory environment for insurance agencies, albeit with appropriate safeguards, patient-centred norms in transaction standards, and ethical safeguards. Governments will also have to build appropriate incentives for health providers to subscribe to health insurance given that providers generally do not buy into health insurance because of the tax-related implications.

The interface of public–private roles also occurs in the area of *social health insurance.* Conventionally, social health insurance is applicable to employees in the formally employed sector, where compulsory deductions from salaries at source can enable the creation of insurance pools. In many countries state/quasi-state institutions secure employees in the private sector, as in the case of the Employees' Social Security Institute in Pakistan.[4] Here the state can create incentives for employers to enhance the number of private workers insured in such arrangements through regulation.

Financial contributions from private sources to augment public funds are another form of public–private interface in health financing. There is potential in channelling money from individual philanthropies, community contributions and corporate donations, mobilized through social responsibility programmes, to state funds that have the flexibility to receive such contributions – as in the case of social protection funds and health equity funds. The public sector should explore the possibility of creating a conducive tax configuration to harness the potential within such contributions.

Public–private mix in health governance

The private sector can also play a role in combined forms of governance within the health sector particularly on the boards of autonomous/quasi-state owned institutions, the classical example of this is in the *hospital setting*. Many of the ingredients in the contemporary hospital reform recipe are amenable to hospital autonomy interventions – such as decentralizing hospital management, developing efficient management structures and cost sharing financial arrangements, and building incentive structures for staff. Institutionalizing hospital autonomy means decentralization of hospital management and bringing hospitals under autonomous governing boards, where the private sector can be represented. Other forms of *public–citizen participation in health governance* are relevant to decentralized forms of governance, which governments in many developing countries are now moving towards. In such settings, public–citizen partnerships rather than organizational institutional partnerships can bring value to collective decision-making on grass roots organizational entities such as community citizens boards and village health committees.

The public–private mix at the health systems input level

Ensuring appropriate human resource capacities within a particular health system is a complex task. It necessitates a well-defined policy on human resources; the existence and appropriate implementation of service laws that address qualitative, quantitative and deployment-related concerns; and attention to education and training. In many countries human resources in health are within the state domain; however in countries where the private sector operates in the area of post graduate and undergraduate medical training, governments should assess the potential within the private sector to contribute to national goals and the feasibility of offsetting their cost *vis-à-vis* production through their own system. In addition, the private sector can be involved in contractual roles for in-service training and Continuing Medical Education (CME) programmes.

With reference to the public–private mix in pharmaceuticals, a range of transnational infectious disease partnerships constitutes an empirical ground; most of these have involved a number of stakeholders, globally and within countries and have involved

contribution of resources from commercial entities. Although they have been widely acclaimed for presenting a mechanism for achieving a range of desired health outcomes including improved access to products and services, they have also been the subject of much debate.[5] Lessons learned should be instructive in developing relationships with the corporate sector within country settings.

The way forward

Of the various health systems that have emerged since the late 19th century, the one that demands most attention is the mixed model, which is characterized by the social welfare component, albeit where public service quality and outreach is compromised because of insufficient funding, better incentives for providers to work in private systems and lack of transparency in regulation. In such health systems, it is imperative to explore arrangements for public–private partnerships (PPPs) with the understanding that this would represent a fundamental change in the way the government functions in the social sector. Although PPPs in health have been the focus of attention of global efforts through transnational infectious disease partnerships, a comprehensive health systems focus on PPPs has never evolved globally. Recently, the World Health Organization (WHO) has articulated health systems strengthening as one of its priority areas. In order for this to be streamlined, the public–private interface will have to be a part of this agenda.

In structuring PPPs, a number of ethical challenges constitute an important caveat to be addressed.[6] These include the concerns that PPPs may: reorient the mission of the public sector; interfere with organizational priorities and weaken their capacity to uphold norms and regulations; conflict with the fundamental concept of equity in health; lead to withdrawal of social safety nets; redirect national and international health polices; facilitate access of the commercial sector to policy-makers; and enable NGOs to achieve a range of complex objectives.

It is critical that the driving principles for promoting PPPs are rooted in 'benefit to society' rather than 'mutual benefit to partners' and should centre on the concept of equity in health. Norms must stipulate that partnerships contribute to the strengthening of social safety nets in disadvantaged settings and should be set within the context of 'social responsibility'. PPPs are not intended to put private funds to public use, nor to privatize public responsibilities. Global principles must specify that partnerships should be in harmony with national health priorities; they should complement and not duplicate state initiatives and should be optimally integrated with national health systems without any conflict of interest.[7]

In order to do this, there is a need to establish and strengthen, where appropriate, principles, policies, legislative frameworks and operational strategies for such relationships. Governance and accountability structures need to be defined clearly. Safeguards must be stipulated against potential conflict of interest and processes that weaken and fragment the public system of social service delivery. In many ways, the onus of responsibility falls on governments within sovereign countries to initialize action at this level. Perhaps it is also timely for international agencies to pay attention to this matter.

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Biography

Sania Nishtar *is the founder and president of the nongovernmental think tank Heartfile, the most powerful health policy voice in Pakistan, recognized as a model for replication in other low- and middle-income countries. She is the strongest civil society advocate for health and social policy reform in Pakistan and part of many global health initiatives. She has received many awards, including the Sitara-i-Imtiaz of Pakistan, the European Societies Population Science Award and more than 16 gold medals for academic achievements. She was recently nominated as the International Health Professional of the Year 2007 by the International Biographical Centre in Cambridge.*

Issues in assessing product development partnerships (PDPs)

Lakshmi Sundaram

The past decade has seen an increased recognition of the idea that, when appropriately organized and motivated, players from the public and private sectors can combine their different skills in partnerships to solve problems that have not so far been adequately addressed by independent action. The Millennium Development Goals also lend importance to the idea of developing global partnerships, particularly with Target 17: "In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries". Much of this partnership activity has come in the form of product development partnerships (PDPs), which can generally be described as collaborative efforts between nongovernmental organizations, public and private sector actors to address research and development challenges using innovative methods. The ultimate aim of these PDPs is to develop affordable, appropriate products including drugs, diagnostics, vaccines and others such as microbicides to address neglected diseases in the vulnerable populations of low and middle-income countries. In 2004, Widdus and White described the emergence of these PDPs:

"What distinguishes these new ventures is that they take as their starting point not a ('favourite') specific candidate product, but a survey of the field and then promote the parallel development of a range of different candidate products (a 'portfolio'). Management of a portfolio, borrowed from the pharmaceutical and venture capital fields, is designed to manage the risk of failure accompanying any individual project. Many of these PDPs use a portfolio management approach, similar to that used in the pharmaceutical industry".[1]

"What distinguishes these new ventures is that they take as their starting point not a specific candidate product, but a survey of the field and then promote the parallel development of a range of different candidate products (a 'portfolio')."

Why do PDPs need to be assessed?

The PDPs were set up as a new model, an innovative method of pursuing public health goals, and were accompanied by a high level of enthusiasm. Research published in 2005 by the Pharmaceutical R&D Policy Project (Moran et al.) showed that this enthusiasm was not misplaced; the drug development projects from a sample of PDPs performed as well, or better than, industry standards (see Figure 1).

As many of the projects in the PDP pipelines now enter Phase III clinical trials, however, the funding needs of the organizations are increasing in an exponential manner. Extrapolations from the same study mentioned above on drug development PDPs show that there will be a funding shortfall in the next few years.[2]

In the coming years, current donors may have to make some tough choices on where to spend their money. In addition, new donors will need to be found to address some of the shortfall. Because of their innovative methods of setting up short-term agreements with different sets of partners for different parts of the research and development (R&D) cycles, PDPs have found some difficulty in tapping into more traditional sources of funding, such as the European Union, which often do not have the mechanisms to fund these types of projects. Commonly recognized, comparable measures by which to assess the performance and progress of the different types of PDPs may facilitate targeted longer-term funding for the PDP approach as a whole, and ultimately result in better products for neglected diseases and populations.

There have been some arguments that, since each PDP is different in scope and methodology, and since different donors have different reporting requirements, it is not useful to develop a common set of metrics across PDPs. However, the current state of affairs has led to a situation of ambiguity, where it is unclear to outsiders, and even to some donors, how these PDPs function. This vagueness is unproductive for the PDPs, for the funders, and for the global health community more broadly. The managers of PDPs need to understand what they can do better and more efficiently. Funders need to understand where their money will be put to best use. Furthermore, since these PDPs are a new way of conducting development work, it is in the best interest of the field to use clear metrics of success to entice new donors into an area, which they may be currently reluctant to enter.

Challenges of assessing PDPs

One important point to keep in mind when trying to develop a common assessment framework for PDPs is the following central question:

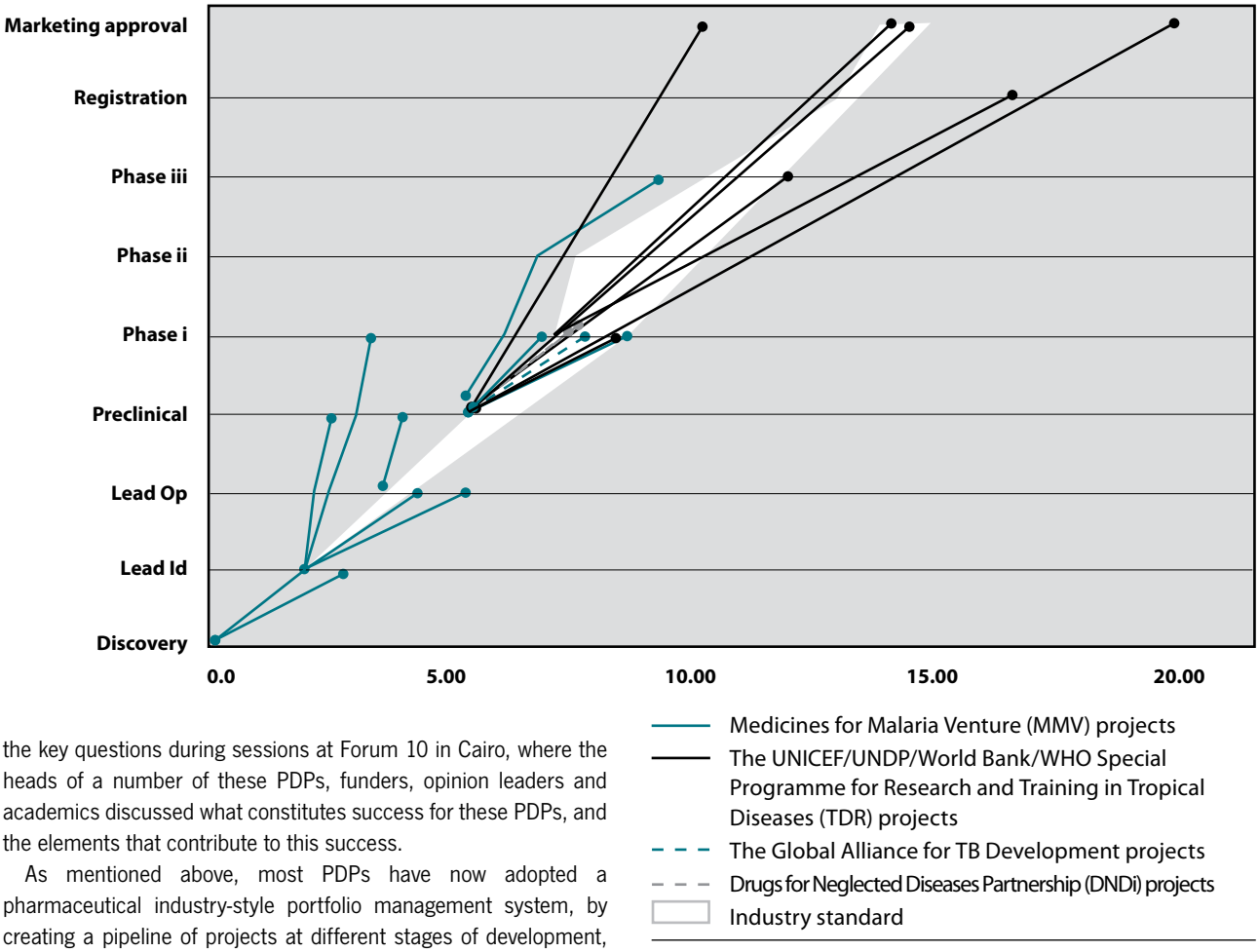
How should and can the performance of individual PDPs be assessed in a way that encourages:

- increases in funding overall;
- greater collaboration between PDPs;
- the best possible products;
- the best possible care for the end-users of these products.

The idea is not to develop a restrictive and punitive set of metrics or to develop a league table of PDPs, but rather to create a dialogue between the PDPs, donors and the global health community more broadly to ensure the best possible use of scarce resources.

The Global Forum for Health Research began a workstream in 2006 to examine some of these issues, and brought out some of

Figure 1.
Timelines for PDP projects [3]



the key questions during sessions at Forum 10 in Cairo, where the heads of a number of these PDPs, funders, opinion leaders and academics discussed what constitutes success for these PDPs, and the elements that contribute to this success.

As mentioned above, most PDPs have now adopted a pharmaceutical industry-style portfolio management system, by creating a pipeline of projects at different stages of development, with different risk profiles. This approach is used to increase the likelihood of developing a viable product, as there is a natural attrition rate in the product development process (i.e. a certain number of projects are statistically bound to fail). A criticism of some PDPs, and their donors, has been that this portfolio approach has not been well understood or managed. Donors may view project failures as being representative of organizational failures. Consequently, the PDPs may keep unpromising projects on board for longer than is optimal. There may also be a tendency to maintain suboptimal projects to give the appearance of a well-filled pipeline.

Thus, one suggestion has been to use a similar methodology to assess PDPs as would be used to assess a classic for-profit pharmaceutical company. This suggestion has met with quite some pushback, however. Unlike in the pharmaceutical sector, PDPs are not in competition with one another in the traditional sense. Many are funded by the same set of institutions, and it is not in the best interest of the field as a whole to see PDPs fail. PDPs work in parts of the world where basic structures do not exist, and where the PDP invariably becomes involved to some degree in developing, for example, the clinical trials infrastructure. Furthermore, the mission of most PDPs involves an element of advocacy for the field of neglected diseases in general; one head of a PDP described the continuum he is involved in as being from the lab bench to the G8[4]. Furthermore, classic industry projects are anchored with the idea of 'return on investment', based on projections of future economic gains from the product, to determine whether a project moves forward or not. There is not currently enough consensus within the global health community on how to calculate the value of future products of PDPs, and this will ultimately be crucial for any common metrics to be seen as anything more than process indicators.

Organizational level

At the level of the PDP organization, there are a number of points to keep in mind when developing an assessment framework. Because the ultimate goal is to develop products which will be used by vulnerable populations in low- and middle-income countries, PDPs need to take into account access issues to some degree, whether this is explicit in their mission statements or not. This by no means implies that the PDP has to be responsible for getting a product developed, registered, mass-produced and delivered to end-users. However, the PDP should be part of ongoing discussions on access issues, and should be linking from the start to partners who will be able to take on the access challenges.

There has been some debate on the importance of involvement of leaders and scientists from low- and middle-income countries in PDPs, as well as the degree of capacity building PDPs should be responsible for. Any assessment framework of PDPs will need to address these issues to some extent. In certain situations, working closely from the start with partners in low- and middle-income countries is seen simply as the most effective method of developing

products for these regions of the world. In other situations, capacity building is seen as a separate function carried out by the PDP. In any case, there needs to be clarity between the PDPs and their donors on the importance of this function, and the most effective process to carry it out.

Portfolio/project level

When examining and comparing the portfolios and individual projects of a PDP, it is again important to remain sensitive. Major scientific challenges, for instance, which may form part of the reason for which no appropriate products yet exist against a specific disease, should not penalize the PDP working on high-risk projects to overcome them. Furthermore, it may be difficult to compare project costs to industry benchmarks, as industry costing information is often highly confidential, and can vary significantly depending on the extent to which quoted figures take into account the cost of failed candidates, as well as peripheral activities such as marketing.

What will be important, however, is to understand the PDP's strategy for portfolio management and its policies for project selection. It may be worth maintaining some projects that 'normal' industry practices might have killed off, if the products are targeting certain specific sub-populations for whom no other safe, effective and affordable alternatives exist.

As more PDP projects reach the stage where they require large pools of clinical trial volunteers in low- and middle-income countries for Phase III trials, there is a growing recognition that more work is required to ensure that the capacity exists to take on these trials. At that point, it will be more important than ever for PDPs to work together to ensure that the same clinical trial sites are not being bombarded with competing projects, ultimately leading to confusion, which will be detrimental to the global health goals of all PDPs. Thus, it will be important for any assessment framework to look at how well a PDP is able to manage the complex and constantly changing environment in which it has to conduct its trials, and how well it can set up constructive collaborations with other PDPs facing similar challenges.

Next steps

Most PDPs were set up to solve very specific problems, and it will be important for them to keep sight of their own overall aims, while increasing collaboration with one another. Since their inception, the PDPs have brought a huge amount of attention to the area of neglected diseases. Clear metrics of success, through a thoughtful assessment framework, will hopefully lead to greater effectiveness among PDPs, and a greater number of new donors entering the field. Further work will need to be conducted to ensure that such a framework addresses the issues described above. The ultimate test of PDPs, however, will be to see how well they are able to manage the requirements of their different constituents, and to ultimately deliver safe and affordable products to those that need them most.

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Technological and social innovation: a unifying new paradigm for global health

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Reprinted from 'Health Affairs', Volume 26, 4:1052–1061.

In colloquial use, the term 'innovation' is often seen as synonymous with 'invention.' To the global health community, 'innovation' may carry baggage associated with patents and the high cost of medicines. However, the definition used by economists is far broader than invention and is highly relevant to considerations of access: it encompasses the entire process–from idea to implementation–for new products, services, processes, practices and policies.[1]

Improving access to essential products and services requires three forms of innovation: technological, to ensure availability of products that are more cost-effective than existing interventions; social, to ensure the distribution of essential goods and services; and adaptive, involving both providers and communities, to contextualize the adoption of goods and services to local settings.[2] Technological solutions in health include new drugs, devices, diagnostics and vaccines. Social and adaptive solutions include new ways to organize human resources, information and decision-making in health systems. In all cases, innovation involves both the solution and its implementation.

Unfortunately, 'technological utopians' and 'systems utopians' seem to speak different languages; at worst, they compete fiercely for finite resources in the global health field.[3] Yet, in our view, technological and systemic solutions are two sides of the same valuable coin. New products always require social and adaptive innovations to ensure their introduction, distribution, uptake and use. New ways to organize funders, producers, distributors, managers, providers, patients and communities often spotlight needs and opportunities for further technological innovation. Ideally, each should enable the other, helping make health systems more effective and equitable.

Economists and business leaders have long understood these different facets of innovation.[4] This inclusive view might help bridge a long-standing ideological divide in the global health community. Ultimately, the only sustainable goal must be to build capacity for local innovation so that developing countries can continuously improve the effectiveness and equity of their own health systems.

Health technology innovation

On their own, innovation systems respond best to the needs of those who can afford their outputs. Therefore, numerous initiatives have been created or proposed over the past decade to 're-engineer' those systems to address the needs of poor people.[5] These interventions affect various components of innovation systems, from research to manufacturing to distribution, predominantly in industrialized countries.[6]

Re-engineering innovation systems

For example, product development partnerships (PDPs) were explicitly modeled after partnerships in the private sector.[7] They have business plans and corporate management structures, conduct market analyses and acquire and manage portfolios of candidate products to speed them through the development process. Several countries are testing industrial policies such as tax breaks, liability protection and expedited regulatory approvals to stimulate product development.[8] Finally, huge procurement funds have been created such as the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

"Advance market commitments (AMCs) have been proposed to create 'pull' incentives for companies to develop new products for neglected diseases."

Advance market commitments (AMCs) have been proposed to create 'pull' incentives for companies to develop new products for neglected diseases. Donors would offer binding contracts to guarantee future procurement. The merits of AMCs are still hotly debated.[9] In a widely respected paper, Mary Moran argues that AMCs would be less cost-effective than PDPs and might actually hinder PDPs' efforts.[10] Yet at least two PDPs have welcomed AMCs in the belief that they would make it easier to attract new private partners.[11]

It seems clear there is a need for implementation research–defined here to include research on policies and practices affecting distribution, adoption and availability.[12] There is a need to document the impact of these policy and programmatic experiments and to gain a better understanding of their potentially synergistic or antagonistic impacts on global health.

Innovative developing countries

Another positive development over the past decade has received far less attention: a handful of innovative developing countries (IDCs) have emerged as world leaders in the manufacture of essential drugs and vaccines.[13] These countries are all adjusting and refining their national innovation systems. However, this process often occurs

through a discourse that is driven more by ministries of industry, trade and science and technology than by ministries of health.[14] We believe that a critical window has opened to share lessons learned among countries (both North–South and South–South) in the development and adaptation of policies that promote both public health and economic development.

Obviously, major differences exist among developing countries. A recent analysis of the 1967–1987 worldwide declines in infant mortality identified "differing rates of technical progress (or diffusion) as the principal source [66%] of the (large) cross-country variation."[15] Although just a few countries can be considered technological IDCs, all developing countries can aspire to develop, adopt and adapt social innovations to implement new technologies.

Growing public and private investments

Public spending on health research by developing countries now exceeds US$ 2 billion per year.[16] Local ingenuity, as well as lower labour costs and overheads, amplifies the purchasing power of these investments (Goldman Sachs estimates that research and development (R&D) in India costs 12.5% of R&D in wealthy countries).[17] Unlike donor funding, this local public investment is, presumably, sustainable. Private R&D investments in IDCs by both local and global drug companies are also growing.[18]

Increasing publications and patents

Over the past decade, the number of highly cited academic papers from Brazil, China, India and South Africa nearly doubled, while the number of United States biopharmaceutical patents increased tenfold.[19] When Carlos Morel and colleagues ranked countries by United States biopharmaceutical patents per gross domestic product (GDP) per capita, the top 15 included not only Organisation for Economic Co-operation and Development (OECD) countries, but also India (third), China (fourth), Brazil (eleventh) and South Africa (fourteenth).[20]

Lost in translation

A recent survey of biotechnology in IDCs highlighted several health product success stories arising from local public–private R&D partnerships.[21] However, it also found a lack of national and institutional policies and experience to manage such partnerships, which suggests that these successes were exceptions rather than the rule. Without such capacity, public investments may produce a multitude of academic jobs and publications but fail to translate new ideas into products.[22]

Low-cost products

Drug manufacturing in India costs 70% less than it does in wealthy countries.[23] Currently, 67% of India's drug exports and 74% of Brazil's go to other developing countries.[24] India is now the world's leading manufacturer of diphtheria-pertussis-tetanus (DPT) vaccine; Brazil, of yellow fever vaccine; and China, of penicillin.[25] The world's first meningitis B vaccine was developed by Cuba, which now exports it throughout Latin America (and recently licensed the product to GlaxoSmithKline).[26] India recently approved a low-cost Japanese encephalitis vaccine, developed and produced in China.[27] Brazil, Cuba, India and Indonesia now meet 64% of the vaccine requirements (excluding oral polio vaccine) of the United Nations Children's Fund (UNICEF).[28]

'Re-engineering' national innovation policies in IDCs

There are mixed views on the likelihood that manufacturers in technological IDCs will engage in R&D and manufacturing to address local needs without external incentives.[29] As a rough starting point, however, some of the 'interventions' noted at the global level could be adapted locally.[30] All countries–even the wealthiest–could benefit from lessons learned as IDCs experiment with national innovation policies to promote economic growth and (ideally) the development of new products to address the needs of poor people.

Social and adaptive innovation: what is needed

Social innovations are needed within health systems to achieve the maximum uptake of essential new drugs, vaccines and diagnostics; to assist public and private efforts to deliver essential services; and to promote healthy behaviour at the community and individual levels. Recent calls by the World Health Organization (WHO) and the Global Forum for Health Research to support health policy and systems research and by others for 'implementation research' are essentially pleas for social innovation to increase the effectiveness and equity of health systems.[31]

New products often involve centralized production and widespread adoption; social innovations almost always require adaptation to local conditions.32 As innovation economist Richard Nelson points out, "Just as with innovation at the frontier of knowledge, organizational innovation involves a lot of trial and error learning, hard work and thoughtful adjustments; while practices used elsewhere may serve as models, almost always there are going to be modifications needed to fit the new context."[33]

"Just as great gaps in our knowledge of health systems require 'health policy and systems research,' enormous gaps in our knowledge of health product innovation systems require 'health innovation policy and systems' research."

Worsening health indicators and slow progress towards the Millennium Development Goals (MDGs) have spotlighted the need to strengthen health systems in developing countries. Numerous nontechnological initiatives have been proposed or implemented to address this challenge.[34] The What Works Working Group has collected examples of such initiatives.[35] These include conditional cash transfers to encourage prenatal visits and vaccinations in Mexico; professionalization of midwives and systematic use of health information in Sri Lanka; involving grandmothers as volunteers to deliver low-cost vitamin A capsules in Nepal; and the 'SAFE' strategy (surgery, antibiotics, face-washing and environmental change) to reduce trachoma prevalence in Moroccan children.

One problem stands out from these examples: very few of them are homegrown.[36] This is not for lack of indigenous ingenuity. Richard Mahoney and Carlos Morel have argued that least-developed

countries themselves can innovate by developing new approaches to train health workers, manage clinical trials, increase procurement and distribution efficiencies, fight counterfeit drugs, improve the governance of national regulatory authorities, improve priority setting, increase the effectiveness of locally adapted education campaigns and ensure that communities and patients have a voice in demand-driven local health systems.[37] Unfortunately, as a Disease Control Priorities Project report notes, "evidence on which approaches work best is limited".[38]

Expert systems

A shortage of health providers in the least-developed countries has evoked calls for more resources to support health workers and for efforts by industrialized countries to stem the 'brain drain'.[39] To date, there has been little discussion of how increasingly common and inexpensive information and communication tools could allow countries to restructure who gets trained, how they get trained, who is needed and where they are needed. To the extent that a new cadre of fieldworkers can work effectively with a small number of professionals in specialist centers or can use expert systems software to aid in diagnoses and referrals, currently extrapolated human resource needs would change.[40]

Business innovation

CK Prahalad has analyzed "breakthrough innovations that dramatically alter cost, quality and delivery standards" for high-volume, low-margin production and service delivery in the developing world.[41] Examples include Aravind Eye Care, the world's largest provider of cataract surgery, and Narayana Hrudayalaya, a leading provider of cardiac care – both profitable Indian businesses that provide low-cost products and services to the poor. The secret of success in such 'bottom-of-the-pyramid' models is a commitment to excellence combined with a hyperspecialized division of low- and high-skilled labour that is unheard-of in costly hospitals of the industrialized world.

Microfranchising is another form of business innovation that combines the best of public goals with small-scale entrepreneurship. BroadReach, in South Africa, uses communication technology to deliver expert medical advice to clinics in remote settings.[42] CFWshops in Kenya are supported by a central nonprofit organization that sets quality standards, uses pooled procurement of generic medicines to lower costs and provides training and medium-scale loans to help local entrepreneurs establish small pharmacies in rural and periurban settings.[43]

Optimism and caution for technological utopians

The field of innovation economics considers the 'healthy' functioning of the components of innovation systems and the dynamic interlinkages among those components, to be essential for a robust system that produces positive outcomes for society.[44] We believe that it is possible to pursue innovation policies with win–win outcomes for both economic development and the generation of essential public goods. At the country level, this will require policy research to guide decision-makers and careful attention to the linkages between innovation policies and health priorities.

Some caution is in order, however, when considering policy interventions. The truth is that we do not yet know which initiatives are most cost-effective, which are synergistic and which may cross-react to produce unwanted side effects. Just as great gaps in our knowledge of health systems require 'health policy and systems research', enormous gaps in our knowledge of health product innovation systems require 'health innovation policy and systems research'.

Some IDCs are beginning to play an active role in helping to address health challenges in the least-developed countries. For example, Brazil's Ministry of Health now provides technical assistance in HIV prevention and care to 11 African countries.[45] In 2003, Brazil signed an agreement to help Mozambique manufacture antiretroviral drugs.[46] And FIOCRUZ, a major publicly funded research and manufacturing centre in Rio de Janeiro, is helping Angola and Mozambique establish new schools of public health.[47]

During a recent meeting convened by South Africa's Council for Scientific and Industrial Research in Tshwane, policy-makers and research leaders from developing countries called "for the IDCs to act collectively and think globally" to harness science and technology for sustainable development.[48] Participants highlighted the need for "close networking of universities, research councils and industry" to facilitate "the creation of affordable ... products and services for poor people."

A new paradigm: agenda for action

Recognizing the need for technological, social and adaptive innovation, as well as the growing capacity of developing countries, represents a potentially unifying new paradigm for global health. Within this context, we believe that three areas require greater attention by both developing countries and donors.

Translation and stewardship

In North America, where more than 40% of biotechnology patent applications are filed by universities and other publicly funded research institutions, effective university-industry partnerships are essential to translate 'academic' ideas into tangible products.[49] We believe that they can also give greater traction to the more than US$ 2 billion in public funds that developing countries invest each year in health research.

Since publicly owned intellectual property (IP) can be used as a kind of currency to achieve public goals, promoting good stewardship of IP in such partnerships can help ensure affordability and access, while also attracting and leveraging private-sector know-how to address the problems of the developing world.[50] Global PDPs have pioneered such creative approaches to IP management in their negotiations with the private sector.

Both the United Kingdom Commission on IP and the WHO Commission on IP, Innovation and Public Health (CIPIH) have called for capacity building in this area.[51] Such work is also consistent with a large body of analysis from the field of innovation economics and represents a logical complement to the efforts of global PDPs. We are aware of only one international organization that is dedicated to such capacity building (the Centre for the Management of Intellectual Property in Health Research and Development, or MIHR).[52]

Implementation research

Total development assistance for health now exceeds US$ 10

billion per year.[53] This includes large vertically oriented disease programmes that are stretching the limits of human resources in developing countries' health systems. Given these huge investments and the complexity of health systems, it is shocking that less than 1% of the total is invested in research to document and understand which programmes work and which do not.[54] A dearth of data to guide policy-makers has led to calls for major increases in implementation and health systems research.

We wish to highlight a complementary need for South-led implementation research on policies and practices affecting the availability, distribution and adoption of health products and services (including conditions that enable local technological, social and adaptive innovation to build more effective and equitable health systems). As the CIPIH report has noted, "South–South networks have often been neglected in the past but may become especially useful now that world class expertise exists in some developing countries."[55]

Morel and colleagues have called for a South–South health innovation network to analyse and promote enabling policy environments to develop products and services and deliver them to poor people.[56] This would complement – not replace – Northern efforts to address health challenges in the South. Specifically, such a network would (1) foster active support by key opinion leaders in developing countries to create an effective policy environment in this area; (2) support research on national policies and organizational practices that affect the generation and implementation of new products and services to improve health systems' effectiveness; and (3) engage in global debates on policies that have national relevance and help shape the global health policy architecture.

A network of this kind would be unique in the public health field but could build upon other relatively new South–South networks highlighted by Morel and colleagues and the CIPIH report (for example, the India–Brazil–South Africa Dialogue Forum and Developing Country Vaccine Manufacturers Network). It could also take lessons from the WHO Collaborating Centres and the Global Health Policy Research Network (among others).

The power of individuals

These first two needs cannot be addressed without the third: individual leadership. To the extent that thought leaders in the global health community – North and South – begin to articulate a broader and more inclusive vision for health innovation, local policy-makers in developing countries will be better equipped to craft national policies that promote both economic development and public health. Donors might also listen and adjust their strategies.

Concluding comments

New international treaties, new trading partners and the challenge of both emerging and chronic diseases call for new strategies to support health innovation in developing countries. An 'innovation systems lens' highlights the need to create and implement both social and technological solutions. It may thus provide a much-needed framework to design the 'architecture of global health' called for recently by health experts.[57] Local public–private R&D partnerships and South-led networks for policy and implementation research could help developing countries play a more prominent role in global health. There is a critical need to maximize outcomes from the substantial investments in health research that some countries are now making and to recognize, help and encourage countries that make deliberate efforts to improve the effectiveness and equity of their health systems.

The authors thank Richard Isnor, Hannah Kettler, Richard Mahoney, Carlos Morel, Richard Nelson and Amitav Rath for helpful comments and suggestions on earlier drafts. The views expressed in this paper are those of the authors in their individual capacities and do not necessarily reflect those of their respective organizations.

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Product development partnerships: public–private partnerships among unequal partners?

Anna Wang

Until a few years ago, hardly any drugs, vaccines, microbicides or diagnostic tests were being developed for diseases that mostly affect the poor. Because investment in new tools research and development (R&D) for these diseases did not guarantee sufficient returns, this section of the market was virtually shunned by the private sector. But towards the end of the last century, without much fanfare, a veritable sea-change occurred: a new mechanism for R&D was established to bring together expertise and resources from multiple stakeholders. This new mechanism – the public–private partnership (PPP) – was developed to translate scientific advances into life-saving products. Today, this model is often called a product development partnership (PDP) to distinguish it from other forms of public–private partnership.

In a speech at the World Economic Forum's 2007 meeting in Davos, Switzerland, Melinda Gates, co-founder of the Bill and Melinda Gates Foundation, applauded this new approach as it "makes the most of the strengths of the private and the public sectors. It lets them work together as partners rather than against each other as competitors. It brings in crucial money and expertise. And it reduces the risk of failure for pharmaceutical companies by giving them access to the best new scientific research.[1]"

"Most PDPs have been in operation for less than 10 years, but their track record demonstrates that this mechanism is already proving to be effective and efficient."

Most PDPs have been in operation for less than 10 years, but their track record demonstrates that this mechanism is already proving to be effective and efficient. With the combined expertise of hundreds of research institutes, pharmaceutical and biotechnology partners, and thousands of scientists around the world, PDPs are working on the most robust product pipeline in history, solely focused on the health needs of those that are least able to afford them. Some products have already been licensed, while many others are entering into late-stage clinical trials. As many as four new fixed-dose combination drugs, developed in partnership by the Medicines for Malaria Venture, will be available to patients between 2008 and 2009.

The PDP model is no longer an experiment. Building pipelines of new products to meet anticipated needs requires cutting edge science, capable scientists and clinicians, high-tech facilities, a supportive regulatory environment, and perhaps most importantly, an increase in resources. Thus far, donor governments have provided a startlingly low proportion of investments in PDPs.

Since the launch of the Millennium Development Goals (MDGs) in 2000, the growing recognition of the link between health and poverty has led to the establishment of various advocacy and funding initiatives. The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) has been successful in raising the profile of the 'big three' and raising funds to support developing countries' disease control and prevention programmes. Although it is dependent on a continuous pipeline of new and effective tools, it does not currently fund their development. Initiatives such as the Roll Back Malaria Partnership, Stop TB Partnership, and the Joint United Nations Programme on HIV/AIDS (UNAIDS) also provide invaluable support to countries and to numerous partners.

Understandably, these groups' priorities are not focused on health innovations but implementation of solutions driven by country needs. Research and development is too often erroneously thought of as a 'nice to have' but not critical to achieving health goals. For example, the Abuja Declaration at the Africa summit on AIDS, TB and other infectious diseases in 2000 optimistically stated that it would take 10 years to turn back the tide of malaria.[2] This short time frame failed to factor in the time needed to develop innovative new drugs, insecticides, vaccines and diagnostics. Today, we know that in the face of resistance to drugs and insecticides, there will be no success without the fruits of R&D. Why then is it so difficult to include R&D on the international agenda? Why does combined government funding of PDPs still fall far short of private philanthropy?

A number of factors contribute to the difficulty in getting neglected disease R&D and PDPs on the international agenda.

The R&D road is long and unpredictable, with many more failures than successes. Investors and funders all realize that there is no guaranteed return on investment. This is one of the reasons the Bill and Melinda Gates Foundation is a major investor in PDPs: they can afford the risk. A government has to be accountable to its constituents and typically may not have the luxury to make a large contribution to such risk-laden investments. Policy-makers often shy away from funding projects that may not bear fruit for a decade, if at all. It is more politically expedient to support projects that offer immediate and easily explained achievements.

During their initial phases PDPs focused on setting up projects with researchers and partners from the industrialized world. Many PDPs did not make a concerted effort to engage developing countries. Although many trials continue to take place in disease-endemic countries, policy-makers in these countries were often not

involved in designing the research agenda. Increasingly, and rightly, many donor agencies including the GFATM are looking for validation from these countries. What use are innovative products if they are not oriented to the environment, conditions and needs of the very countries targeted? However, this search for endemic country validation is not as easy as it sounds, as unfortunately, research and development is not high on their agendas, and in fact is not even a priority.

Many health activists have the impression that we have all the tools we need to fend off these infectious diseases and that the only barrier is funding. Some activists have also been harsh critics of the pharmaceutical industry. From the very start, they have expressed skepticism about the merit of the PDP model, which they see as not only partnering with industry but funding it as well. The PDPs have had to prove that they were not 'in the pockets' of industry, but can work independently, leveraging industry expertise and research facilities. PDPs had to also simultaneously focus on the needs of the public health agenda and build bridges between the public and private sectors. Without the full support of activists, the PDPs had an uphill task to gain popular and government support.

One of the key drivers of success for PDPs is that most of them are focused on a single disease. Until recently PDPs have not considered the sharing of information and collaboration amongst themselves to be a priority. Thus, there is a perception that there are a myriad PDPs pursuing their own missions myopically, all competing for visibility and funding. In fact, it is this perception that propelled the PDPs to join forces on many fronts leading to a much more prominent and credible international presence.

The 2005 G8 summit in Gleneagles was a turning point in placing PDPs on the international agenda. A major focus of the summit was to review the progress made towards the MDGs, and many PDPs planned to advocate individually for what they saw as their own missions: to promote public–private partnerships as a more efficient R&D model for neglected diseases, linking health innovation to poverty alleviation. It soon became clear, however, that their messages were similar and a united effort was needed to make an impact. This resulted in the first joint PDP advocacy initiative calling for G8 members to commit to supporting R&D for neglected diseases and PDPs. Major industry partners, and global initiatives such as GFATM and the Global Alliance for Vaccines and Immunization (GAVI) also signed the joint statement.

This collaborative effort was a major victory. In the concluding communiqué from the summit, the G8 acknowledged the importance of R&D and the value of PDPs. Furthermore, they recognized the need for both 'push' and 'pull' mechanisms as incentives for innovation. As a result, at least one G8 member, the United Kingdom (UK), significantly increased its funding for PDPs and led the creation of the International Finance Facility for Immunization (IFFim). The elevated prominence of neglected diseases R&D and PDPs also led non-G8 members, such as Ireland, to contribute.

The partnership model for product development also generated academic and policy interest. Following the 2005 G8 Summit, the London School of Economics and the Wellcome Trust, a leader in medical and scientific philanthropy, published a comprehensive analysis of the R&D model in *The New Landscape of Neglected Disease Drug Development.* The paper pointed out the surprising lack of policy incentives to support PDPs, which have become the entry point for both large and small pharmaceutical company involvement in neglected disease R&D. It warned that "...continued lack of public support is likely to lead to the collapse of PPPs, leaving governments with little recourse but to fund expensive in-house industry activity from start to finish or to build alternative drug-making capacity.[3]"

This independent and rigorously researched report, clearly demonstrated that the PDP model is effective and efficient. This report and other policy analysis on finance mechanisms also prompted donors to request further analysis of the model, including synergies at clinical trial sites, cost variances, and incentive mechanisms. These analyses not only benefited the PDPs in their operations and future planning, but also helped keep the issue on the international agenda.

"Members of the R&D community are collaborating with each other and adding value to global policy formulation."

The Malaria R&D Alliance's report *Malaria Research and Development: An Assessment of Global Investment* is another example of an important joint PDP effort that has benefited the entire malaria community.[4] For the first time since the birth of the PDP model, this study provided real data on the current landscape for funding of malaria research and development. The report was another indication that members of the R&D community are collaborating with each other and adding value to global policy formulation.

As PDPs moved from the start-up phase to intense activities including clinical trials and policy development, they saw more opportunities for teamwork. Now, collaboration extends beyond advocacy efforts, to sharing information and technical capabilities to capitalize on each others' experiences and knowledge. PDPs regularly share information and experience on issues such as clinical trial site capacity development, management of intellectual property, and advocacy opportunities and strategies.

The key learning in the last few years is that PDPs can be a much stronger force when working together. Increasingly, donors are evaluating organizations not only on individual achievements but also on how well they collaborate and share their experiences with other grantees. Engagement with all parties, particularly in-country research partners, health-care providers, policy-makers and nongovernmental organizations (NGOs) are seen as critical in ensuring that there is the necessary input from the customers of these new products. Stakeholders also want to see that their funding is creating synergies rather than being wasted on duplication of efforts.

Health innovation and PDPs have gained more visibility in the past few years. PDPs are regularly mentioned in G8 communiqués; an international working group was formed by World Health Organization (WHO) Member States in 2006 to devise a work plan for a global R&D strategy; and a forum was convened in 2007 on this topic by the Organization of Economic Cooperation and Development (OECD). However, the flow of government funding remains slow. Of the G8 countries that have signed on to the supporting mechanism for funding R&D since 2005, only the UK and the United States of America (USA) have consistently supported

PDPs. Why has the increased visibility not resulted in more support from governments? This area remains a challenge for PDPs, who continue to strongly encourage governments to increase support for R&D for neglected diseases.

The bottom-line regarding government support for PDPs seems to be inertia. The validity and value of applied research on cures and prevention for infectious diseases through PDPs seems now to be widely acknowledged, the challenge remains that it has no natural institutional home. For example, take the USA. It is the largest investor in medical R&D, both in terms of public funding and industry investment. The National Institutes of Health (NIH), the primary federal agency for conducting and supporting medical research, spends over US$ 28 billion annually.[5] Most of its research is focused on expanding the frontiers of scientific exploration and knowledge, not turning this knowledge into innovative products. NIH expects the pharmaceutical industry to be the product developers. This model works only for diseases that affect the rich because the market is lucrative enough to attract the for-profit private health-care industry. This is not an effective model for diseases of the poor. The PDPs with such a focus currently do not receive core funding from the world's largest publicly funded medical research institute. A few PDPs, instead, receive funding from the United States Agency for International Development (USAID), though the amount is often less than that provided by other much smaller countries such as Ireland. A leader in foreign aid assistance and global health initiatives, such as the President's Emergency Plan for AIDS Relief (PEPFAR) and the President's Malaria Initiative (PMI), USAID spends many thousands fold more on product roll-out, systems support and capacity building projects. This is not surprising. In the foreign assistance agencies in many donor countries, their expertise lies in development aid and implementation, not research. This is the same for funding from the European Union (EU). A few PDPs have received small project funding from the EU Research Directorate. The International AIDS Vaccine Initiative (IAVI) is the only PDP that has received core funding from the EU Development Directorate. Finding a natural funding source for PDPs has not been easy.

Today, largely thanks to private philanthropy, principally the Bill & Melinda Gates Foundation, PDPs are able to sustain their momentum and continue to accelerate product development. However, the critical support of philanthropic foundations is a double-edged sword. It seems to give some governments a reason to shift the burden of responsibility, as they have come to accept that R&D is the business of private philanthropy and industry, while their mandate rests on implementation.

Medical innovation with the ultimate goal of developing a 'public good' is a 'public responsibility'. It should not rest largely on the shoulders of private foundations, however visionary and wealthy they might be. Indeed, one foundation's wealth will not be able to support the development of an entire arsenal of weapons to fight the diseases that predominately affect the poor. Governments too must share this responsibility.

If PDPs have demonstrated one thing especially well, it is the power of partnership. With the launch of PDP-developed drugs for malaria and leishmaniasis, and many more soon to emerge from the pipeline, they have begun to prove that they can deliver cutting-edge scientific advances to those who cannot afford them in the developing world. However, without enhanced public sector engagement and support, these life-saving innovations will stay in the pipeline, out of reach of the countless people who need them. PDPs and their global health partners must hold governments accountable for their previous commitments. Their increased visibility in the international arena is not an end in itself. It must lead to concrete support that will drive the development and delivery of urgently-needed cures, diagnostics, and preventive measures.

PDPs are demonstrating that they can bring groundbreaking advances in health care to the developing world by extracting the best from the public and private sector. It is time that the public sector become an equal partner in this partnership.

Notes and references

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4 Malaria R&D Alliance, *Malaria Research & Development: An Assessment of Global Investment.* http://www.malariaalliance.org/

5 NIH website : http://www.nih.gov/about/budget.htm

Biography

Anna Wang *is the Vice-President for Public Affairs at the Medicines for Malaria Venture (MMV). She has been a leading advocate for product development partnerships and the critical role research and development (R&D) plays in global health. She also led the Malaria R&D Alliance's study of global investment in malaria R&D, a widely referenced benchmark study.*

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Facing the dual challenge of developing both products and research capacities for neglected diseases

Piero L Olliaro
Steven C Wayling

This paper is about developing products and relevant sustainable research capacities at the same time, based on the intimate conviction that one cannot exist without the other. Lack of both adapted products and the capacities to develop and test these products[1] in the countries most affected characterizes many neglected diseases.

In the short period available for the preparation of this paper, the organizations and individuals contacted were generally unable to quantify and detail needs and investments for setting up, strengthening and maintaining capacities and facilities on top of funding research itself. Tedious and prosaic an exercise it may sound, collating this information from a variety of actors (including donors, developers and recipients) would be relevant and worthy as it would allow better appreciation of the process and its costs towards identifying ways of streamlining and improving synergies and efficiencies of the system. Further, there is no clear or accepted methodology for quantifying the costs for setting up a research project or site and what each group recognizes as a contribution to the development process. For example, in the case of clinical trials, this may range from the provision of a drug under study and the placebo, extending to the construction of physical facilities and the provision of all primary and ancillary training.

"All agencies and programmes working in this area are faced with the problem of underdeveloped research capacities in endemic countries. Investing in capacities offers less visibility than funding research."

The types of capacities required to cover the whole spectrum of research and development (R&D) – from product discovery research to post-registration studies – are varied and diverse. In particular, product development towards registration is submitted to demanding international regulations, and as such, requires special skills and investments, and is costly. For ease, here the authors will focus on clinical research.

The need for local capacities is in some instances unavoidable (clinical trials are done were the disease is most prevalent), but should also be viewed as a genuine way of empowering countries, and thus breaking the cycle of dependency on foreign aid and leadership.

All these factors call for a coordinated effort towards developing both products and the capacities to develop products for neglected diseases in affected countries.

For various reasons, all agencies and programmes working in this area are faced with the problem of underdeveloped research capacities in endemic countries. Investing in capacities offers less visibility than funding research, however, so it is less appealing to donors and other agencies – although traditionally some have consistently invested in capacities at large. These investments are also more difficult to quantify and to relate to specific advances in science or health.

The issue of what a trial site is and the time required to develop a site is an important one.[2] For a one-off trial, the investment may be minimal and include only an informal alliance of projects at the site. The resources from projects fund the core costs and the life-span of the site is generally short-term and not sustainable. Any investments beyond the conduct of the specific trial are lost or not accounted for.

An evolution from this short-term commitment is to move from the idea of a field site to one of a project site. This would include some infrastructure development useful beyond the trial with a usually limited amount of core funding and resources. This generally permits a small number of projects, but allows additional or different diseases or interventions to be pursued in addition to the original trial or intervention. Sustainability is medium (3–5 years) and establishes the basics that outlive the individual trial or intervention.

The final evolution is a fully established research centre that provides all scientific infrastructures to engage in long-term research. Some permanent core funding is established with new projects also contributing to the core funding. Research is now undertaken on different interventions and/or different diseases. Development is long-term, often exceeding 10 years, but the centre can be maintained over time with projects each paying a share.

The Special Programme for Research and Training in Tropical Diseases (TDR) was set up some 30 years ago when research regulations and requirements were very different from today's standards, yet it was mandated with both research and capacity building from the outset. Indeed, the type of activities and the interaction between research and training programmes has evolved

to better serve this dual mandate. In particular, the programme has evolved towards producing more efficient mechanisms of integration between building/strengthening capacities and the priority research areas. While TDR's mandate is broad – encompassing upstream and applied research, different disciplines and diseases – organizations with a narrower scope are equally concerned.

With more political attention and more money, the past few years have witnessed the blooming of public–private partnerships (PPPs) and other organizations involved in activities related to, otherwise, neglected diseases. This has resulted in a bewildering array of older and new organizations, many of which need different sets of local capacities to execute the work they are poised to do. Of these organizations, some are more specifically concerned with product research and development (R&D) and are often referred to now as product development partnerships (PDPs) – some 20 multi-candidate/portfolio-based, not-for-profit ventures developing products for a range of diseases have been identified.[3]

While this has generated a boom in the number of products in the development pipelines for some of these neglected diseases, sites and researchers that meet international requirements and can organise and manage trials remain limited and are now in great demand (Box 1).

Taking tuberculosis (TB) as an example, there are today six new candidate drugs in preclinical and six in clinical phases of development (from products entering Phase I to others in Phase III). Assuming an average for each product of some 300 patients in Phase II and 2000 patients in Phase III trials, if all products were successful, nearly 14 000 TB patients will have to be recruited at good clinical practice (GCP)-compliant sites. The world is unlikely to have the capacity today to absorb all these studies. Availability of GCP-compliant trial sites is likely to be the bottleneck slowing down developments. Drug developers have either to compete for the current GCP-compliant sites (needing minimal investments) or strengthen weaker institutions (in which case significant investments may be needed, timelines affected and programmes delayed).

Some of these diseases occur in remote areas well outside the coverage of the health sector or in displaced or migrant populations. Studying diseases like African trypanosomiasis is particularly problematic as cases occur focally in remote areas and foci tend to be unstable. The lack of access to patients in numbers large enough to conduct sufficiently representative clinical trials in adequate facilities has traditionally been a hindrance to studying interventions for this disease. In this case, a broad spectrum of investments is normally required, covering everything, starting with bricks and mortar and basic equipment.

Whether patients are seen at health system facilities or by nongovernmental organizations (NGOs), converting structures and personnel, who are overwhelmed with routine work and do not have a culture of research, into productive research settings is often problematic. In some cases, research outfits are created next to the health post to draw the patients off. Paradoxically, strengthening research capacities may jeopardize already weak systems by diverting scarce human resources and disrupting work. The migration of personnel initially trained for trials and site development can occur in two ways. First, South–North migration in search of higher salaries and better job security: increasingly, this migration may also be public–private where the individual does not leave the country or region but does move to international or

Box 1.
Lessons from the field[4]

1. **Preamble:** the degree of compliance with GCPs varies across the range of trials, settings and purpose of the study.
2. **General timelines:** total duration from identification to site preparedness depends on availability of trial sites for a given disease/indication. In general it takes 12–18 months from identification to site preparedness implementation, including (1) site identification (approximately 6–9 months); (2) infrastructure and equipment (3–6 months); (3) personnel employment and training (1–2 months).
3. **Costs:** vary considerably depending on the type of study, disease, site, etc. Organizations account for costs and investments differently. For instance in regulatory-type pivotal studies, significant costs are often related to the use of Contract Research Organizations (CROs) to organize and monitor the trial.
4. **Main deficiencies/biggest challenges faced:**
   - variable on-site level of good clinical practices and good clinical laboratory practices;
   - practical in the lab: in country expertise for maintaining and servicing lab equipment, reagent supply, cold chain, power supply;
   - communication with trial sites in some areas, customs clearance;
   - management and administration: underestimated need for good financial practices;
   - ethics review process;
   - staff motivation for not-for-profit research.
5. **Incentives and support needed to keep going:**
   - ongoing training, additional training opportunities towards career development;
   - improved communication (including phone lines, internet, etc), meetings;
   - frequent site visits;
   - between-studies support.

northern-funded groups in their home countries. In both cases, trained human resources are lost to the project and possible future research centre. Contributing to the 'brain drain' issue is the associated issue of career development possibilities. Lack of core support, infrastructure and trained colleagues can result in a feeling of isolation, accelerating the departure of trained research staff.

One of the major issues facing development of trial sites and research centres is that many of the current 'big funders' including the Bill and Melinda Gates Foundation and the Global Fund to Fight AIDS, Tuberculosis and Malaria are reluctant to support initiatives to develop and sustain capacity. Until these groups (and indeed bilateral agencies) are persuaded of the importance of building sustainable indigenous capacities, it is questionable whether many of the new and existing products can be effectively tested and introduced.

Conversely, where there are investments in trial site development, there may be a lack of coordination between funders resulting in multiple independent investments when a coordinated action would be more productive and efficient for both the funders and the sites. This lack of coordination, or perhaps competition for the top settings, may also result in the site not being able to decide on their own priorities and subsequently reduce any feelings of local ownership in the activities undertaken. Investments in capacity strengthening should empower the local research community through dialogue and opportunities to assume leadership roles.

Notes and references

1 Here, a product is defined broadly as any tool (drug, vaccine, diagnostic or other) requiring regulatory approval for marketing authorization or intervention (e.g. bednets, ways of delivering tools, etc.).

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Biographies

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Steven C Wayling *has spent the past 17 years with the Research Capability Strengthening (RCS) programme area of TDR. He supports research capacity building within disease endemic countries by promoting and monitoring research grants for institutional strengthening and through numerous activities aimed at human resource development. Over the past decade, he has managed the activities of TDR related to research training, including formal degree training, short-term courses and the development of academic and distance learning programmes including exploring methods to evaluate the outcome and impact of TDR's research capacity strengthening activities.*

The portfolio approach to successful product development in global health

David Brown

Introduction

The range of medicines available in developed countries for treatment or prevention of disease has expanded rapidly over the past half century. These products are a factor in the steady improvement in health and the increase in longevity of people with access to these products. Lessons learned in the successful development of these medicines can be applied at least in part towards product development for neglected diseases in less developed countries.

The process of drug discovery and development is arduous and risky. Many more potential drugs fail than eventually achieve success. However, with a thorough understanding of the process of drug discovery, of probabilities of success at each stage of the process, and of the major factors that govern success or failure, then the enterprise can be approached with confidence. It is particularly important that for each disease a portfolio of drug research and development (R&D) projects is constructed in such a way that the probability of success is maximized in relation to the funds available.

This overview summarizes key factors in the construction of portfolios addressed to neglected diseases, building on learning from the pharmaceutical industry but also factoring-in any special circumstances. The focus is on the discovery of small molecule drugs, however, the key points may be equally applicable to development of vaccines and other products.

The drug R&D process

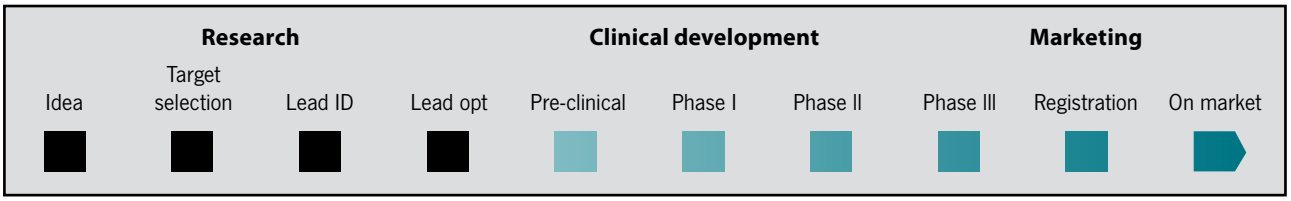
Drug development follows a number of steps that have evolved through experience over the past century. Dynamic interplay between the pharmaceutical industry and country-specific regulatory authorities has led to a process and system that is still evolving. This process is equally applicable to the development of drugs for neglected diseases and is indeed that followed by those currently focused on this goal. The stages of the process are outlined in Figure 1.

In the preclinical research phase, a target mechanism is selected, usually on the basis that basic science indicates its involvement in the underlying disease process or development of symptoms. Alternatively, a mechanism may be selected that compensates for the disease process or symptomology. In some diseases the underlying mechanisms may be poorly understood and therefore a more empirical approach may be adopted, in which random screening is used to detect potential drugs that can modulate the effects of the disease. In all these approaches large numbers of compounds are often screened, somewhat randomly, in order to find a chemical starting point for drug discovery. Occasionally, a more favourable situation, a drug already in use for another disease, is suspected to have a second utility. This early phase of drug discovery is usually divided into 'target selection' and 'lead identification' phases.

Resulting lead molecules then enter the 'lead optimization' stage during which they are modified chemically to build in drug-like properties. This is an arduous multi-dimensional optimization process; addressing such properties as potency, selectivity, safety, pharmacokinetic properties for drug absorption and distribution within the body, drug elimination, cost of goods etc. At the end of this phase, one or two selected molecules will undergo extensive, rigorous testing against a wide range of parameters, including many specified by regulatory authorities, to ensure suitability for entry into clinical trials in humans. This is known as the 'pre-clinical' or pre-IND phase.

Once a suitable molecule has been identified, then the drug sponsor notifies the appropriate regulatory authority, such as the European Medicines Agency (EMEA) or the United States Food and Drug Administration (FDA), of its intention to conduct clinical studies on human subjects. This is called filing an 'investigational new drug' (IND) application and is an essential step before Phase I clinical trials can begin. There follows a detailed review process by the regulatory authority before clinical studies can be sanctioned within its territory.

Figure 1.
The stages of drug R&D



Clinical development typically involves three phases:

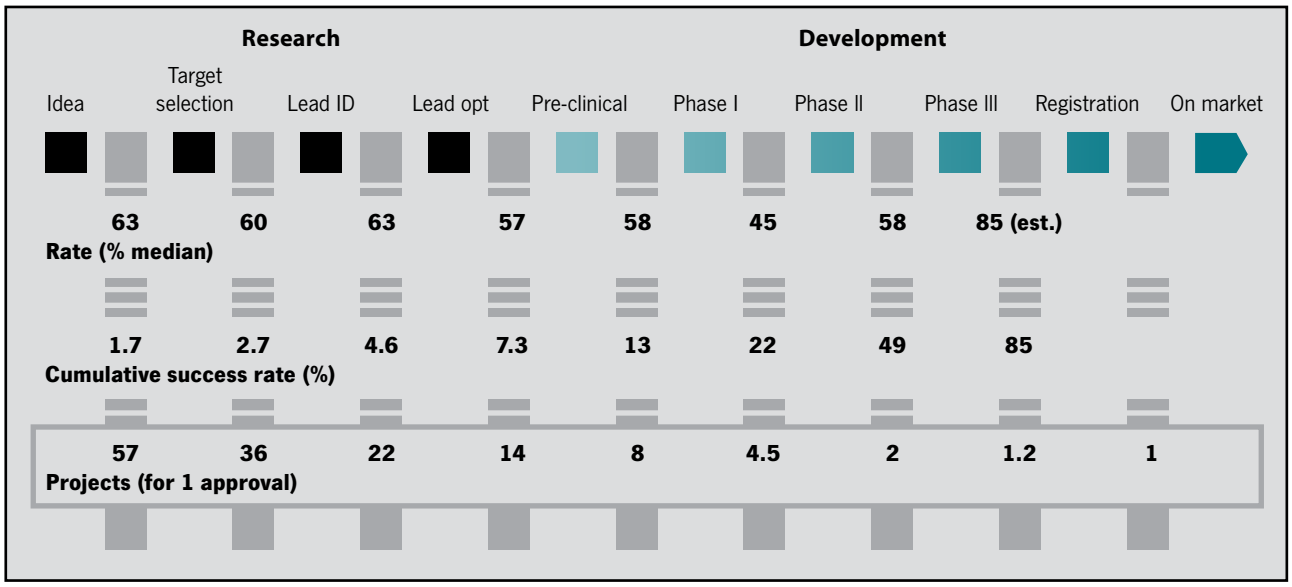
Phase I studies are usually conducted in healthy volunteer subjects. They are primarily designed to determine the tolerability and pharmacokinetics of a drug, i.e. whether it is well-tolerated by the volunteers, and how the drug is absorbed, distributed, metabolized, and excreted by the body. In favourable circumstances it may be possible to achieve some assessment of the pharmacological effect of the drug, which may give early evidence of effectiveness.

Phase II studies are designed specifically to assess the effectiveness of the drug versus the target disease. They may also highlight any side-effects associated with the drug. Phase II studies are closely monitored and conducted in a relatively small number of patients, usually no more than a few dozen. Phase II studies may be expanded (Phase IIb) to a larger number of patients to gain increased confidence in the effectiveness and safety of the drug, and also to ascertain the appropriate dose of drug for larger scale Phase III trials.

cumulative attrition in the discovery phase is approximately 80%; only about 1 in 5 projects gets as far as selecting a compound for clinical trials. In clinical development, attrition between selecting a compound to enter Phase I studies and completion of Phase III studies followed by marketing is >90%. This means that less than 1 in 10 clinical projects gets a product to market. Overall, throughout the R&D process, less than 1 in 50 projects succeeds in getting a drug to market.[1]

For those involved in constructing drug R&D portfolios for neglected diseases, it is critical to thoroughly understand the reasons for project failure in pharmaceutical companies. Only then can portfolios be constructed rationally such that productivity goals have a good chance of being met. We must learn how to construct portfolios with a much higher chance of success rates than these averages indicate. Special circumstances pertaining to neglected diseases make this possible, as will be discussed later.

Figure 2.
R&D success rates of major pharmaceuticals. The average success rate at each stage is shown, together with the cumulative success rate.[1]



Phase III studies involve larger numbers of patients to gain statistical confirmation of the safety and effectiveness of the drug. Comparison with placebo is usually essential, and in addition an active comparator (an established drug) may be included for comparison in a parallel set of patients. Phase III studies provide information that eventually will go on physician labeling.

The number of human subjects involved progressively increases from phase to phase, with Phase III studies typically including several hundred to several thousand people.

Learning from the pharmaceutical industry: the major reasons for project failure

The failure rate during the drug discovery and development process is quite high. Independent analysis, and also figures released by pharmaceutical companies (Figure 2), indicate that the

There are several published analyses of the reasons for project failure. These suggest that there are 4 or 5 main reasons:[2,3]

- Choice of target – the key issue is that the chosen target mechanism fails to produce the required beneficial effects in animal studies or in human clinical studies.
- Choice of leads – there may be a total failure to find a lead that can be optimized, or a lead is found that ultimately proves to be non-optimizable.
- Drug safety – the final drug candidate selected from the lead series fails to pass regulatory toxicology requirements.
- Adverse events or poor pharmacokinetics in humans – not predicted by animal studies.
- Late failure of compounds in Phase 2b and Phase 3 clinical trials – due to failure to demonstrate the efficacy expected from earlier smaller trials (has greatest impact in terms of cost).

Lessons for portfolio construction and management in public–private partnerships

Based on these findings, what are the lessons for portfolios targeted at neglected diseases?

a) Before selection of individual projects

Best practice in all major pharmaceutical companies has evolved through experience and usually requires at least three factors to be clearly defined before a project can be considered for inclusion in a portfolio. These are: analysis of the medical need and potential market; and writing of both a 'target product profile' and a 'molecule profile'. These are described below:

i) Market analysis/medical need

This is the primary driver of all drug discovery projects. In the global health arena such factors as global death rates and DALYs (disability adjusted life years) will be key information, and the potential pharmacoeconomic benefit of treatment is increasingly taken into account. In addition, in global health one must consider factors such as the perception of governments and the World Health Organization (WHO) that the disease is a high priority; and the availability of partners on the ground for clinical trials, safety monitoring and to deliver medicines.

ii) Target product profile

The target product profile (TPP) describes the key attributes of the product that is to be produced. It describes the benefits to the patient and the key registerable claims. Often both a 'desired' and a 'minimum acceptable' profile will be defined. Clarity on these issues, and particularly on the 'minimum acceptable' profile, can help avoid project drift: If the laboratory or clinical data being generated on a potential drug indicates that it will fall short of the TPP then the decision may be made to cease development and focus money and resources elsewhere.

iii) Molecule profile

The molecule profile is a partner to the TPP. It defines the properties that a molecule must have to deliver the product profile. It is an essential guide to the scientists, particularly the chemists, working in the discovery phase of a project to optimize a potential drug molecule. It may include such criteria as potency, selectivity, pharmacokinetic properties, safety margins, cost of goods etc. Note that these are the very same factors described earlier as responsible for the failure of many drug R&D projects, which highlights the importance of the molecule profile.

b) Selection of individual projects

For small portfolios, which are unable to balance risk across a large number of projects, it is critical to select projects with a high probability of success. In practice this means those that are relatively late-stage, preferable Phase IIb or later.

At these later stages of development much de-risking has already occurred in that the drug has already circumvented the issues listed in the first four reasons for failure, cited above.

Additionally, if discovery projects are to be included within a small portfolio, it is critical to reduce risk as much as possible, as follows: i) select projects for which there is clear evidence already from another drug that the mechanism will work in the clinic (to reduce target risk), and ii) select projects for which there is at least one, preferably two, high quality chemical leads already in hand (to reduce lead identification risk).

Of course, such projects may be in short supply, particularly in neglected diseases with historically low investments into R&D. For larger portfolios it may be possible to include projects that do not completely fulfill these criteria. The key point is that the portfolio should be constructed with acknowledgement of the likely probability of success for a project at each stage of the R&D process. This can be achieved using the pharmaceutical averages as a baseline, but with productivity projections modified for any special advantageous circumstances specific to neglected disease R&D in general, or the specific disease under consideration. What might these advantages be? The following points may work in favour of neglected diseases:

- The pharmaceutical averages cover a broad range of disease areas. Success rates for individual disease areas can vary significantly from the averages. Most neglected diseases are infectious diseases and success rates for drug development can be significantly higher for anti-infectives than for 'all diseases', which include difficult, high failure areas such as psychiatric diseases.
- There may be 'low-hanging fruit' to exploit with respect to neglected diseases, especially over the next few years, due to relative neglect in the past. For example: existing drugs may be suitable for recycling into a new disease indication, with expected high probability of success. Combination products may be required to overcome resistance.
- The failure rates exemplified by pharmaceutical companies include projects dropped for commercial reasons. These may include changing market dynamics due to competitors getting ahead, or erosion of patent life due to slower than expected progress through R&D. These factors are likely to be less significant for development of medicines for neglected diseases.
- Organizations involved in global health are smaller and therefore tend to specialize in particular disease areas. This has significant advantages which could improve success rates above those attained by pharmaceutical companies.

"For small portfolios, which are unable to balance risk across a large number of projects, it is critical to select projects with a high probability of success, namely those that are relatively late-stage, preferable Phase IIb or later."

This point is worthy of expansion. To maximize probability of success it is essential that organizations involved in development of drugs for neglected disease become specialists in the diseases they are targeting. This will generally mean that each organization, due to small size, must concentrate on a single disease or a cluster of related diseases. Even in the very largest pharmaceutical companies there has been a trend towards specialization in specific disease areas. This is due to recognition that each disease area brings its own challenges both in R&D and marketing. Therefore, while global health R&D organizations may wish to build a diversified portfolio of projects to balance risk and ensure ultimate success, success is more likely if that diversified portfolio is built within a single disease area. Thus it seems wise to pursue projects within a single disease

area or at least within related fields in order to exploit spill-overs and economies of scope in R&D.[4]

One final point about portfolio construction should be made. In most disease areas in global health there will be a need to create a rolling stock of new drugs entering use. This will be especially true for treatment of infectious diseases, during which drug resistance will eventually arise. For each disease it will be necessary to assess the precise need for rolling out new drug entries over time, and then to assess the optimum portfolio size required. Each organization involved will need to build up the appropriate portfolio size, then maintain it by taking in new projects/compounds periodically to keep the portfolio size relatively constant. The portfolio size will differ from disease A to disease B if the latter needs complex multi-drug regimes. Those disease areas that require constant replenishment of drugs for resistance reasons will need to invest in, for example, translational research to ensure the necessary supply of targets and lead molecules.

c) Decision-making during management of the portfolio

Successful portfolio management is a skill that must be developed by all organizations engaged in product development, including those in global health. Returning to Figure 2, this diagram portrays the stages of drug R&D. The grey bars between each stage represent the 'gates' at which decisions should be made whether to transition to the next stage. Effective decision-making at each of these gates is the number one determinant of the overall probability of success of the portfolio. Just as activities within each 'stage' should be carefully defined, so should the precise criteria ('gating' criteria) for progression to the next stage. Rigorous decision-making at each stage, including the decision to stop a project totally if necessary, form the backbone of effective portfolio construction and development. Each organization involved in drug R&D should have carefully considered criteria for each of these decision points, and a skilled review board. This should preferably include people external to the project and most preferably external to the organization.

Of particular importance is the decision to select a molecule to enter human clinical trials. Every drug R&D company must have very carefully considered criteria for this decision point, decided well in advance, and these criteria must be understood by the project team as the goal to which they must aspire. Quantitative metrics should be defined for each criterion whenever possible, and compounds failing to meet these criteria are unlikely to be progressed. The criteria may differ on a case-by-case basis, for instance a drug safety criterion may vary according to the severity and life-threatening nature of the disease being addressed; and pharmacokinetic criteria may differ according to the proposed route of administration of the drug and the duration of effect required.

Conclusion

The extensive experience of the pharmaceutical industry provides a very valuable guide to construction of a portfolio of projects for successful R&D in the global health arena. Above all, companies engaged in this noble enterprise should avoid repeating the mistakes of the past by capitalizing on these lessons and on advantageous factors specific to global health R&D.

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Biography

David Brown *has over 30 years experience in the pharmaceutical/biotechnology industry. He has served with Zeneca, Pfizer, GlaxoSmithKline and Hoffman-La Roche and also as President, Chief Executive Officer and Board member of Cellzome AG, a biotechnology company. Whilst at Pfizer, he was named co-inventor on the patent for Viagra, a treatment for male impotence. He was also instrumental in the discovery of Relpax, a treatment for migraine. Since 2005, he has been Senior Advisor and a member of the Executive Team at OneWorld Health, San Francisco, where his work is dedicated to bringing medicines to the poorest of the poor in the world.*

The role of the health system in biotechnology in Brazil and Cuba

Halla Thorsteinsdóttir

Developing countries have become increasingly active in health biotechnology development. In recent years they have had the largest growth rates in health biotechnology publications of all the countries in the world;[1] their residents are increasingly filing health biotechnology patents in the United States;[2] and they are successfully developing and manufacturing health biotechnology products.[3,4] Governments in developing countries have prioritized the biotechnology sector, built up infrastructure and allocated resources towards its development in the hope that the sector will be successful in developing health products and services and in providing economic gains.[3] In several developing countries, the private sector has also become active in the health biotechnology field with an escalating number of firms focusing on and commercialising health biotechnology.[4] The new-to-the-world innovation record of developing countries in health biotechnology is still modest, however, but there are indications that suggest that their innovation potentials are being strengthened.[3, 4]

"It is important for developing countries to strengthen their local health systems and ensure that they are closely linked to public and private sector organizations in their countries in order to cultivate innovation."

This paper examines the health biotechnology innovation in two developing countries, Brazil and Cuba, with special reference to the role of the local health systems in health biotechnology development. It argues that it is not enough to allocate public and private sector resources for health biotechnology development, but it is equally important for developing countries to strengthen their local health systems and ensure that they are closely linked to public and private sector organizations in their countries in order for the necessary knowledge flow to take place to cultivate innovation.

User-producer interactions fuel innovation

Analysis of innovation in science- and technology-intensive fields has generally placed a heavy emphasis on users of new knowledge, where innovation is said to take place through the interactive learning between the users and producers of the technology.[5, 6, 7] It is therefore surprising what limited attention has been given to the role of health systems in the innovation process, both in industrialized and developing countries.

Research has pointed towards important factors and conditions that shape health innovation such as the role of governments, universities, intellectual property rights arrangements, linkages with the large pharmaceutical firms etc. but with few exceptions has ignored the effects of the demands from the health system.[8] The exceptions include the work from Gelijns et al. which emphasises the roles of health practitioners in, for example, identifying the cardiovascular benefits of aspirin years after it had been introduced to the market;[9, 10] and the work from Porter and Teisberg[11] and Martin and Milway[12] pointing out how lack of user-producer relationships in the United States and Canada have restricted health innovation.

In literature on health innovation in developing countries, health systems have, at best, been seen as rather passive recipients of health innovation. There has been strong emphasis on the supply side with, for example, the Global Forum for Health Research doing important work in advocating for increased resources for health research in developing countries.

Increasing health research is without doubt an essential step towards developing health solutions for people in developing countries; but, as we have seen in industrialized countries, putting resources into basic research alone is not likely to cultivate innovation. As several papers on this issue discuss, a number of public–private partnerships have been established to promote the development of health solutions for developing countries' diseases. They certainly will encourage the important knowledge flow between the public research systems and private sector firms, but they don't systematically try to involve the health system in the innovation process and thereby forego the important insights the health system can contribute to innovation in this field.

To delineate the potential role local health systems can play in health biotechnology innovation, this paper considers the results of case studies focused on the health biotechnology innovation in Brazil and Cuba, where local experts in the field were directly asked to discuss the roles of their health systems in health biotechnology innovation.

Case studies on health biotechnology innovation in developing countries

To examine health biotechnology innovation, 33 experts in Brazil and 32 experts in Cuba, were interviewed in face-to-face settings and were asked to answer a number of questions about health biotechnology development in their respective countries. The respondents played various roles in the health innovation systems in the countries studied. They were policy-makers, entrepreneurs, academics, regulators etc. and their answers reflected this diversity.

Brazil – Great knowledge production but lack of alignments

Brazil actively publishes papers in health biotechnology in international peer-reviewed journals and is very successful in

publishing in relatively high impact journals, compared to other developing countries. In Brazil the experts interviewed identified a recombinant human insulin product developed in the 1990s by the Federal University of Minas Gerais and the Brazilian biopharmaceutical firm Biobrás as one of the best examples of Brazilian innovation in this field. Diabetes is a significant health problem in Brazil and the country ranks number eight in the world in terms of the number of diabetes cases. A recombinant human insulin is therefore highly relevant to the Brazilian health system.

Brazil also has a relatively strong diagnostic sector and has, for example, developed a recombinant antigen test for Chagas disease. That is another example of the focus on local health needs by the health biotechnology sector as Chagas disease has been endemic in Brazil.[13]

The interview evidence pointed out that Brazilian researchers and entrepreneurs have attempted to address local health problems in their health biotechnology endeavours. This is also supported by an analysis of health biotechnology publications from Brazil that shows high specialization indices in tropical medicine and parasitology. Brazilian research is therefore more likely to be relevant to diseases of developing countries than of industrialized countries, typically located outside the tropics.

Still, the interview evidence did not report that users–producer relationships involving the health sector have been strong in Brazil, but rather suggested that the knowledge flow between those directly involved in health biotechnology research and development (R&D) and the local health system in Brazil has been limited. Knowledge from the health sector was, for example, not singled out as being an important source of new innovative ideas, and clinical practices were not a particularly important source of innovation. On the other hand, public procurement policies seem to have had detrimental impacts on health biotechnology development in the country.

In Brazil, the public procurement policies require that the lowest cost products are purchased by the public health system. This policy led the health system in Brazil to choose recombinant insulin from the multinational firm Novo Nordisk over the local recombinant insulin produced by the company Biobrás (also discussed by Sutz)[14]. The difference between the prices of these two products was small but the decision to purchase led to the downfall of the Brazilian biotechnology company and ultimately it was acquired by Novo Nordisk. This demonstrates that, despite good intentions to focus on meeting local health needs, the policies influencing health biotechnology development may not be well aligned, which can interfere with local development.

Cuba – Health biotechnology systematically harnessed for public health

Whereas Cubans have been successful in developing new-to-the-world innovation in the health biotechnology field, their publication rate in the internationally peer-reviewed literature is rather modest. The Cuban interviewees emphasized that the main driving force for the health biotechnology sector was solving health problems of the Cuban population. The government has directly harnessed the potentials of the research system to come up with health solutions. That was, for example, the case when a meningitis B vaccine was developed by Cuban researchers.

In the late 1970s, there was an outbreak of meningitis in Cuba. It was due to serogroup B for which no vaccine had been developed and therefore the Cubans could not import a vaccine to prevent the infection. Meningitis had become the primary health problem in the country, so the government established a multidisciplinary, multi-institutional group to develop a vaccine candidate. The group managed to develop a vaccine candidate in 1985 and clinical trials, which started in the same year in Cuba, proved it to be effective; thus, the incidences of meningitis have since dropped down to lower levels than before the outbreak.

This is one of the best examples from developing countries of how the focus of the research system has been on local health needs, and the health biotechnology sector has directly contributed to measurable improvements in the health of the population. Other more recent Cuban innovations in this field include the world's first synthetic vaccine against *Haemophilia influenzae*, which is expected to decrease the cost of the vaccine significantly,[15] and both a cholera vaccine and a therapeutic cancer vaccine, which are now undergoing clinical trials.

Cuban procurement policies favour local health products over imported ones. They rely on local products whenever possible, partly because of a lack of resources to import more expensive ones. There also seems to be an active knowledge flow involving the health system in health biotechnology innovation in Cuba. The health system is heavily involved in the whole research process. A researcher in a public research institute said, for example: "We have feedback from the clinical trials to the lab. This is not a linear process. The cycle is a good ground for innovative thinking. It has definitely improved our products." This fits very well within innovation literature discussed above, which stresses that innovation takes place through interactive learning, involving users and producers of the technologies.[5, 6, 7] In Cuba, the health system is not only a recipient of innovation, but also a contributor to the whole development.

"In the late 1970s, there was an outbreak of meningitis in Cuba. This is one of the best examples from developing countries of how the focus of the research system has been on local health needs."

Knowledge flow between the users and producers of health biotechnology is also facilitated by the so-called West Havana Scientific Pole, a cluster-like entity that was established in 1991. It has around 40 participating institutions, representatives from all the major research institutes, universities in Havana and five hospitals. The various ministries in the country are also involved. The Pole organizes regular coordination meetings and working groups on applied topics, and includes a wide spectrum of participants. The strong interactions between the health and the research systems in health biotechnology in Cuba are therefore shaped both by a clear focus on local health needs and emphasis on building linkages between the different types of organizations involved, which are facilitated by the Scientific Pole.

Key implications involving developing countries' health systems

Both interview data with experts from developing countries and data on publication patterns in health biotechnology suggest that the health biotechnology sectors of the developing countries examined here are aimed at local health needs rather than solely the needs in the lucrative markets in industrialized countries. This is also supported by research on other developing countries.[3, 4] In instances where domestic procurement policies have not averted resources towards the purchase of imported alternatives, the role of the health systems has therefore been as the ultimate users of products and services produced by their health biotechnology sectors.

As we observed a clear focus on local health problems, the key implication of the research reported here is to highlight the relevance for international organizations and philanthropic organizations to support health biotechnology endeavours in developing countries when promoting innovation to address health problems of poor people in the developing world. There are significant pockets of research and other expertise on developing countries' health problems in these countries and proven potential to develop health products and services that are well aligned to local health needs and conditions. Instead of giving the bulk of their support for innovation activities carried out in industrialized countries, these organizations should identify promising groups in developing countries and support them, even though they may have more modest international reputation.

"Instead of giving the bulk of their support for innovation activities carried out in industrialized countries, these organizations should identify promising groups in developing countries and support them, even though they may have more modest international reputation."

The research reported here also shows that close ties between those involved in R&D in this field within the health system are key to cultivating innovation in health biotechnology. Even though a number of developing countries have been innovative in the health biotechnology field, the developing country with the strongest record so far is undoubtedly Cuba.

As stressed above, Cuba has an active knowledge flow between its health biotechnology R&D system and its health system and has developed new-to-this-world innovations that are widely used by the Cuban health system and exported to several other countries. Innovation is a complex process and we cannot attribute the Cuban successes solely to the tight linkages between those involved in R&D in this field with the health system. However, the observed success of the Cuban health biotechnology sector and the repeated message in the Cuban interviews, which stressed that the ties to the health system were a key to their innovation, points to the importance of encouraging close knowledge flow between the health sector for health biotechnology innovation.

A second implication of the research reported here is that governments in developing countries should encourage linkages and knowledge flows between organizations that are active in researching and developing health biotechnology solutions and their local health system. This implication fits particularly well with innovation systems literature, which has emphasized user-producer interaction in the innovation process. From the Cuban experience, it seems to be important to have a vehicle for exchanging ideas. This is done with the cluster-like West Havana Scientific Pole, which includes both users and producers of the technologies. The vehicle is low cost and consisted mainly of establishing a forum for knowledge exchange.

The important role of health systems for health biotechnology innovation highlights that developing countries that have not stressed establishing a strong public health system are, as a result, at a disadvantage when engaging in health biotechnology development. When a large part of the population is not likely to be able to afford the products/services of the local health biotechnology innovation system, the innovation potentials can be seriously compromised.

Promoting health innovation cannot be taken out of context from promoting a society which emphasizes access of the poor to health products and services. Health innovation policies need to be closely entwined with economic policies but they are dependent as well upon policies for public health and other social policies. Health biotechnology is in a symbiotic relationship with the health system; it is a tool that can improve public health, but its products and services need to be accessible to a large segment of the population in order for innovation to flourish.

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Acknowledgements

The author wants to thank all the collaborators in the study on Health Biotechnology Innovation in Developing Countries, published as a special issue of Nature Biotechnology in December 2004, for their research and discussions that helped conceive this paper. Particular thanks go to Marcela Ferrer who worked on the case study on Brazil and Tirso W Sáenz for discussions on the Cuba case study. Thanks also to Science Metrix for their scientometric analysis of health biotechnology publications in developing countries and to all the experts interviewed for the case studies who generously shared their expertise and time. Any errors in this paper are the responsibility of the author. The McLaughlin-Rotman Centre for Global Health, Program on Life Sciences, Ethics and Policy is primarily supported by Genome Canada through the Ontario Genomics Institute, the Ontario Research and Development Challenge Fund, and the Bill and Melinda Gates Foundation. Other matching partners are listed at http://www.geneticsethics.net. The author is supported by a Canadian Institutes of Health Research New Investigator Award.

Biography

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Sustainable (vaccine) development: the International AIDS Vaccine Initiative (IAVI) and capacity building

Joanna Chataway
Rebecca Hanlin

Product development partnerships (PDPs), of which the International AIDS Vaccine Initiative (IAVI) is one, are being developed to bridge the gap between scientific and technological potential and the needs of the poor in developing countries. Consequently, PDPs are now the recipients of large amounts of development donor funds. Although the primary concern of many involved in PDPs is to generate products to address neglected diseases and illnesses that affect people in developing countries, donors are also keen that initiatives work with partners in the global South and increase scientific and technological related capacities in the south. This has implications for the way PDPs are assessed and performance is measured. Based on case study fieldwork carried out by IAVI over the last four years,[1] then authors argue that PDPs can provide a means of moving forward sustainable development objectives, highlighting the importance of what is referred to as 'social technology', the creation and transfer of institutional capacity, particularly local ownership of vaccine development resulting from advocacy activities.

"Partnerships are seen as an opportunity for increased access to new ideas and best practices, technical expertise, and resources, and wider coverage and impact of research benefit."

Partnerships for new product development…

Development of vaccines to prevent infectious diseases does not often occur within the private pharmaceutical industry. The argument put forward to explain this situation is usually couched in terms of market failure as a result of both a lack of purchasing power in developing countries where demand is greatest, as well as the 'public good' nature of vaccines. Partnerships between the public and private sector are put forward as a means to create incentives for vaccine development in this area.

One such PDP is IAVI. IAVI is a large international not-for-profit public–private partnership devoted to the creation and delivery of a preventative HIV vaccine. Its headquarters are in New York, United States and it works in approximately 23 countries, building local research capacity primarily to undertake local vaccine trials, and building awareness and 'demand' for an HIV vaccine.

… and improving developing country science and technology capacity

Although it is a long way off achieving its core goal of creating and distributing an HIV vaccine, IAVI has achieved three main things. Firstly, it has raised large sums of money, over US$ 340 million to 2006. This money has been used to fund the development of promising vaccine candidates and to raise awareness about HIV and the need for a vaccine. Secondly, and intimately connected to the first achievement, it has created widespread awareness of the potential impact of vaccines and the role that cutting edge science and technology can play in the fight against HIV in developing countries.[2] IAVI has put the possibility of an HIV vaccine, and awareness of the need for very considerable investment, on the agenda of every bilateral donor. Thirdly, it has created capacities in developing countries both to carry out advocacy in relation to HIV and also to participate in the actual development of vaccines and conduct clinical trials.

It is around this third issue that IAVI has focused most of its attention. With growing recognition of the importance of building local health research and science and technology capacity,[3] partnerships and networks are emphasized as a means of developing this capacity. Partnerships are increasingly seen not only as important for new product development by bringing together the right combination of actors and resources, but also, and related, as necessary for good knowledge generation and health research activities. In particular, successful innovation and knowledge generation is seen as occurring in a 'mode 2' networked format rather than a 'mode 1' exercise that takes place in a linear fashion and excludes opportunities for feedback loops and systemic learning opportunities.[4] Partnerships are therefore seen as an opportunity for "increased access to new ideas and best practices, technical expertise, and resources; wider coverage and impact of research benefit; and an increased probability of sustainability recognition and leverage of the research partnerships."[5]

IAVI and capacity building

The challenge of creating an AIDS vaccine is enormous and given IAVI's mission, one might think it obvious that it would choose to work only with the best scientists in developed country environments and to focus on scientific excellence exclusively. Although working with excellent scientists in leading research centres is of course a priority, IAVI has taken a more multifaceted approach to its mission.

For example in Africa, substantial amounts of money have been invested in infrastructure and in training.[6] IAVI has worked with speed and efficiency, combining focused activity with real evidence of capacity building and engagement with southern partners. Importantly, interviewees from Kenyan, Rwandan and Ugandan facilities all feel that largely as a result of engagement with IAVI, they have the potential of turning their units into clinical trial centres of excellence, dealing not only with HIV vaccines but with a range of drug and vaccine development projects. This is then an unusual story of capacity building activity. Although capacity building in developing countries is not part of IAVI's vision or mission statements, IAVI makes significant achievements in this area. In a previous paper the authors have labelled this 'development by not doing development'[7].

An interesting question is why IAVI pursued this strategy? Why did it not just focus on creating a vaccine in the best labs in the world and in the shortest time? Given the urgency of the challenge IAVI confronts there would have been an argument for taking that approach. The answer is not simply that IAVI decided to be a good citizen in developing countries. The very hefty investment, the enormous effort involved in creating partnerships in developing countries, is not an 'add on' to other efforts so much as it is a consequence of taking communications extremely seriously and in some sense letting the communication concerns drive the work. IAVI is an organization driven and dominated by its concern with communication. And that has led it in interesting directions with some very interesting results.

"The strategy of combining advocacy, communication and more participative approaches appears successful. Close relationships have been forged with community groups and nongovernmental organizations."

Innovation driven by communication

IAVI began its work on vaccine development in Kenya. These efforts were in partnership with the Kenyan AIDS Vaccine Initiative and the Oxford Medical Research Council Laboratory. IAVI did not have a regional office at that time and could well have been characterized as a US or 'western' led effort. This danger was highlighted by an independent review.[8] It quickly became apparent to IAVI that if it was to develop local support (which is absolutely essential if a vaccine is to be distributed effectively) it would have to work in such a way that it had local partnership at its core and prioritized local communications as well as lobbying efforts at the international level.

As a consequence of this desire to build political demand and support from the grassroots level upwards, IAVI needed to make sure that efforts were seen as locally appropriate endeavours. The HIV vaccine initiative needed to be owned by developing countries, and as a result compromises and concessions to capacity building in developing countries had to be made. IAVI committed to that effort and let it influence the work it does in fundamental ways.

Commenting on the way in which operations were established in India, where a memorandum of understanding was signed with two government bodies at the outset, one IAVI interviewee said: "It's a partnership with governments and we always accept that... it's a three way partnership, NACO [the National AIDS Control Organization] and ICMR [the Indian Council of Medical Research] and us – we are the junior partners and we accept that".

The strategy of combining advocacy, communication and more participative approaches appears successful in this case. Close relationships have been forged with community groups and nongovernmental organizations (NGOs) and the emphasis on advocacy and relationship building was noted by an independent reviewer as having been particularly strong. One informant noted that, "If IAVI had not come, India would not have taken a vaccine initiative so soon and so strongly".

Apart from commitments to developing infrastructure in developing countries, IAVI's communications focus has also had other consequences. For example in Africa, IAVI conceptualizes the vaccine trials themselves as an advocacy programme. The trials provide a lot of publicity, drive state engagement, and provide people with the opportunity to begin to engage with issues around their fundamental needs, their rights with respect to biomedical ethics, and essentially drive African demand for a vaccine, at a political if not an economic level. This is an important component of IAVI's work on ultimately promoting access to a vaccine, should it become available. One interviewee from the East Africa regional office stated: "I bet you that is what he [interviewees' boss] is doing right now, that's why he is not in the office. He's sensitizing the community, and we define community very broadly, and sensitizing the community so that people are aware – and people understand that people are aware – and people understand that the vaccine does have a place in HIV prevention, and when it becomes available they will demand it from their governments and their governments will demand it at the United Nations, whatever forum is available to them to make these demands for an HIV vaccine. And it's not stored on the shelf somewhere."

The interviewee went on to say that this view of advocacy and trials as building demand was related to decisions to locate trial sites in different African countries rather than just concentrating efforts. "Just being on the ground does create this awareness and hopefully... in the end, it will create demand."

Vaccine development or sustainable development?

Whether or not IAVI succeeds in its overall mission or is judged over the longer term as a success will of course depend on many factors. The sources of risk and uncertainty are both scientific and social. Even if a vaccine is developed, the ability to deliver and distribute it may well depend on having viable health systems in poor countries, which do not currently enjoy even the basics of health-care provision. We would certainly not want to suggest that the IAVI approach is a blueprint or that it guarantees success.

However, the authors study of IAVI shows that it is an example of a PDP that does new product development but also builds significant local science and technology capacity. More particularly, its partnership activities do not just result in transfer of technology

through the provision of infrastructural resources and training, but also transfer what we term 'social technology', the institutional and organizational capacity needed to conduct successful clinical trial level vaccine development activities. This is not because IAVI has a specific mandate to build institutional capacity but because it ends up 'doing development without doing development' – focusing strongly on advocacy and communication activities. The result, as we have pointed out elsewhere,[9] is that IAVI is becoming increasingly decentralized in the way it deals with activities in developing countries, which differs from how it is increasingly acting internationally, particularly in terms of basic science research. These changing roles and different institutional and organizational forms are important to assess and understand (see Cacciatori and Brusoni).

The kind of solution that IAVI offers, which involves it acting as an innovation 'integrator', directing scientific and technology development agendas, and a development 'broker', bringing together diverse development actors around a particular agenda, may not ultimately succeed and may not be replicable. But, acknowledging what works in terms of building science and technology capacity and assessing attempts to create new social technology (i.e. new institutional and organizational spaces) is crucial to international development efforts and the process of assessment of PDPs such as IAVI. Assessing how they work (i.e. how they build capacity) towards the production of a new health product is important and necessary beyond simply assessing their activities in terms of product development outcomes.

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1 Our case study of IAVI comprised an extensive literature review and over 50 interviews with IAVI staff, IAVI partners, collaborators and funders in India, Kenya, New York, Rwanda, South Africa and Uganda. These interviews were semi-structured and the majority tape recorded. We also interviewed independent analysts, informed managers from other PDPs and policy-makers in the relevant countries. A workshop held in Edinburgh in December 2004 helped clarify ideas and perspectives.

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Beyond market failures: IAVI and the organizational challenges of vaccine development

Luigi Orsenigo
Stefano Brusoni
Eugenia Cacciatori

The organizational landscape of vaccine development has changed significantly over the last thirty years. The pharmaceutical industry, which has traditionally neglected vaccines, is now showing a growing interest.[1, 2] This new interest follows major shifts in both the knowledge bases and the organization of the industry as a consequence of the emergence of biotechnology.[3] At the same time, the public sector institutions traditionally involved in vaccine research, primarily universities and public research centres, have been under increasing pressure to demonstrate their productivity, in terms of both publications and patenting. These changes have taken place in a context in which the systems that govern the processes of discovery, development and delivery of vaccines have been increasingly criticized for both their inability to deliver, in comparison to expectations, and for the long delays with which existing vaccines become available to the citizens of developing countries. It is against this background that product development partnerships (PDPs) for the development of vaccines for diseases affecting primarily developing countries have been emerging and gaining importance.

This paper argues that the rise and diffusion of these 'new species' of organization suggests that the problems of vaccine development, particularly for neglected diseases, go beyond the 'market failures' argument, around which much of the current policy debate is centred. The turbulence that characterizes the organizational arrangements of vaccine development suggests that there is considerable uncertainty about how to distribute activities to organizations or groups, monitor them, evaluate their results, and integrate such results with those of other organizations or groups.

Building on ongoing research on the International AIDS Vaccine Initiative (IAVI), this paper argues that the difficulties in devising a way to organize the quest for new vaccines are linked to the complexity, interdependencies and fundamental uncertainties characterizing the bodies of knowledge underpinning the task.[4] While appropriate incentives may give a motivation to solve these problems, they do not *per se* guarantee that the players in the field possess the necessary competencies to address the challenges posed by managing vaccine development across an unstable and expanding set of bodies of knowledge. Therefore, the development of policies that will successfully address the problems of vaccine development requires an improved understanding of how the scientific, technical and social dimensions of vaccine development can be mapped into complex arrangements of actors, each of which possesses only a part of the competencies, and the motivation to use them, required to solve the overall task.

Organizational challenges of innovation in complex environments

Innovation studies have consistently emphasized that innovation, understood as the successful commercialization of a new product, requires complex processes of integration between research and development (R&D), manufacturing and marketing activities.[5] If one considers drugs, for instance, despite the growing trend towards outsourcing and inter-organizational collaborations, large pharmaceutical companies play a central role in coordinating the different elements of the innovation process, including managing increasingly demanding regulatory approval processes across a widening spectrum of actors.

"Innovation studies have consistently emphasized that innovation, understood as the successful commercialization of a new product, requires complex processes of integration between research and development (R&D), manufacturing and marketing activities."

A robust body of research on innovation has shown that this configuration, in which a relatively large company acts as the 'hub' coordinating the activity of a widely distributed network of innovators, is prevalent for science- and engineering-intensive products. The reasons for the prevalence of this configuration are various, and may reflect a long-standing balance of power among industry participants rooted in history or tradition. However, this configuration has also been shown to be particularly suitable to enable problem solving in a context in which the underlying knowledge bases (e.g. scientific disciplines) are rapidly evolving and differentiating. In this situation, a networked approach enables adjustment of the configuration, adding, deepening, weakening or deleting the ties between different organizations as the knowledge bases evolve.[6]

Why then can we not simply rely on many small specialized organizations joining forces as needs arise? The non-linearity and non-sequential nature of the relationships between the different elements of the innovation process means that the development of products that are technically and socially complex entails numerous

feedback loops. The management of these loops, as well as the identification of critical interdependencies in novel products, is a non-trivial process of trial and error, which requires highly specific competencies. Therefore, networks centred round a hub have the advantages of both a wide search space and some degree of central coordination.

Vaccine development since 1945 has, however, largely followed a different organizational model. The level of involvement of the private and public sector has changed but, on the whole, an overview of the development of vaccines after the second world war shows two regularities.[7] The first is that the 'invention' element of the innovation process (discovery) typically takes place in public sector institutions (particularly universities). The second is that at a certain point along the development process, there is a hand-over to industry. In very few instances it is possible to identify a single institution, whether public or private, acting as the hub across the whole process. PDPs seem to have evolved to fill this space in the organizational ecology of vaccine development. However, while the nature of the problem suggests that the development of vaccines may benefit from the birth of new institutional actors acting as 'hubs', the identification of the precise set of activities and competencies that they need in order to carry out their task is far from clear and will require time and (costly) experimentation. We now turn to the case of IAVI to illustrate the organizational dilemmas faced by PDPs.

The International AIDS Vaccine Initiative (IAVI)[8]

IAVI was founded in 1996 with the objective of making an HIV vaccine available for developing countries. Today, IAVI operates in approximately 23 countries, employs about 190 staff and has raised over US$ 340 million. IAVI was set up because, after initial enthusiasm, by 1993 efforts to produce an HIV vaccine had dwindled as a consequence of the scientific difficulties that surround the tasks.

IAVI's activities initially concentrated on policy-making and advocacy with two objectives: stimulating the search for ways to provide financial incentives for the development of the vaccine; and stimulating the search for a vaccine that would work against the strains prevalent in developing countries. This second objective brought the need to set up clinical trials in Kenya. In 1998, IAVI approached this issue by setting up a partnership which, by its own admission, encountered significant problems. As one of the managers of IAVI put it, "We understood very early that we could not simply parachute in a country, run the trials, and parachute out."

Similarly, IAVI understood very early the importance of political support for vaccine demand in developing countries.[9] This understanding has led to the development of in-house competencies in managing its relationships with developing countries, which, after the success of the trials in India, has brought the development of an independent department devoted to the task.

Initially, IAVI saw its mission primarily as 'product development'. Again, as an interviewee put it, "We realized that there were lots of good ideas that were not proceeding into trials." In this field also, IAVI has been learning. "A lot of the small biotech firms that we work with do not have the ability to see the big picture – so we decided that we needed a broad-based scientific staff in house to do that, and project management capabilities to bring it all together." Furthermore, this broad-based staff plus project management skills were also felt to be needed in order to evaluate the quality of contribution of their partners.

Over the years IAVI has become increasingly critical of the state and priorities of scientific research, arguing that avenues that should be explored are not. Furthermore, IAVI has seen the disappointing results of the efficacy trials of early candidates as an indication that the current 'empiricist' approach to vaccine development may not be successful and that a more 'rational' approach to vaccine design (based on a fuller understanding of the basic mechanisms of HIV infection and of the immune response to it) is needed as a back up, should the current pipeline of vaccines prove to be ineffective. As a consequence, IAVI has once again remoulded its activities, starting to promote and fund basic research, for instance on broadly neutralizing antibodies. However, this required the development of a range of complementary tools, such as assays, which were difficult to contract out. IAVI consequently began to set up its own laboratories – so that its activities "would not be hostages of the timetable and price structure of other laboratories."

This brief overview of IAVI, although still preliminary and incomplete, suggests that IAVI has been changing both its internal organization and the type of ties it has with external partners as the dimensions of the problems, and their interrelations, have become clearer. In a trial and error process, IAVI has become more of a broker in its relationships with partners in developing countries, more of an integrator in its product development activities,[10] and still a facilitator/broker in the relationships and projects it funds in basic research. Notably, however, in order to sustain both these roles, IAVI has felt the need to develop in-house competencies that its partners do not possess, in both social and scientific fields.

Conclusions

The evolution of IAVI in its quest to develop an HIV vaccine is an exemplary case of how successes and failures are defined not simply by the 'nature' (i.e. public versus private) of the organizations involved, nor by the incentive structure, but rather by the specific relationships within networks of heterogeneous organizations. Two sets of issues seem to be particularly relevant. The first set is related to the type of role that PDPs will play. The question is the extent to which these new actors will act as facilitators or take a stronger leadership role. In other terms, are successful PDPs more 'knowledge brokers', simply connecting distant partners, or more 'integrators' that use the knowledge provided by partners as inputs to a complex process of re-evaluation of knowledge in order to direct future developments? Will they need to take a brokering role in certain contexts and an integrator role in others? Initial evidence from IAVI suggests that the latter is indeed the case. The second set of issues has to do with the extent to which PDPs will need to bring in-house activities and competencies in order to perform their role. Notably, it has been shown that, in order to coordinate innovative activities of partners, system integrators typically maintain a spectrum of in-house competencies that is wider than their range of in-house activities.[11] The answer to these questions is therefore not simple, but certainly very important for the development of effective vaccines.

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Clinical trials

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Clinical trial site capacity for malaria product development

Mary Moran
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Research and development (R&D) of new malaria products has increased significantly over the past 15 years due to increased philanthropic and government funding. As a result, several promising new drugs and vaccines are now moving through the research pipeline and will need to be trialled in endemic populations in Africa. Although there is a widespread perception that trial site capacity in Africa is insufficient to cope with current R&D activity, there is little understanding of what the real trial site demand and supply for malaria licensure trials is. This paper aims to answer this question and to provide a clearer picture of what funders and product developers can reasonably expect in the next five years.[1]

Trial site demand and supply

Overall, trial site demand is driven by the number of products moving forward and the number of trials each of these products will require to support registration. However, additional factors such as the type of product to be trialled (drug or vaccine) and the age group in which trials will be conducted (adults, children or infants) are also of crucial importance to understanding the presence, size, nature and timing of trial site capacity gaps. For instance, malaria drug trials predominantly require sites capable of small trials with access to modest numbers of adults and children. Malaria vaccine trials, on the other hand, initially need small safety and immunogenicity trials in adults, then large safety and preliminary efficacy trials in children, and finally they need sites able to access and manage very large numbers of infants – the target population for vaccination.

Demand for licensure trial sites for malaria products in Africa

The likely collective demand on licensure sites in Africa, generated by the current global malaria drug and vaccine portfolios going forward to 2012, is illustrated in Table 1.[2] For ease of reading, the total enrolment figures noted in Table 1 are also shown graphically in Figure 1.

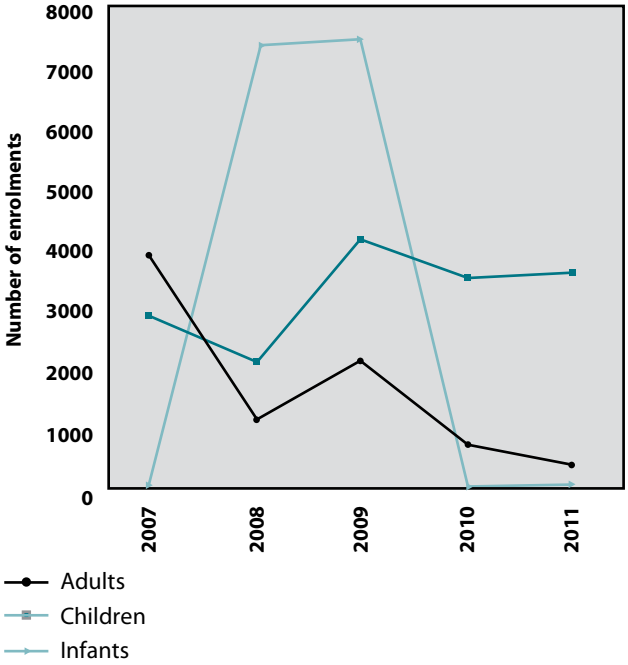
These figures might appear high, and in order to be meaningful they also have to be contextualized and matched against current supply of licensure trial sites.

Table 1.
Number of malaria drug and vaccine trial enrolments in Africa projected to 2012

	2007	2008	2009	2010	2011
Drug trial enrolments					
Adults	2370–4580	700–1290	1670–3240	1020–1740	020–1740
Children	1230–3150	530–1250	400–1000	150–300	350–600
Vaccine trial enrolments					
Adults	200–230	230–310	170–270	200–280	90–140
Children	250–280	1040–1120	2610–3520	1820–3530	2520–4200
Infants	900*	7380*	7480*	0	60–120
Total enrolments					
Adults	2570–4810	930–1600	1840–3510	1220–2020	1110–1880
Children	1480–3430	1570–2370	3010–4520	1970–3830	2870–4800
Infants	900*	7380*	7480*	0	60–120

*These figures are based on clinical development plans for RTS,S as current in Nov 2006

Figure 1.
Total enrolment demand for malaria product licensure trials in Africa projected to 2012[3]



Supply of licensure trial sites in Africa

The key factors that determine a site's ability to match trial site demands are its technical capacity, operational capacity and geographic location in terms of overall site distribution.

Technical capacity

Technical capacity can be defined as the on-site skills and physical facilities needed to conduct 'licensure standard' drug or vaccine trials. Currently, there are 18 sites technically competent to conduct these trials for malaria products and an additional five are being upgraded to reach licensure standard by the end of 2008.[4] The 18 technically competent sites can further be divided into 12 all-purpose sites (five 'mature' and five 'young') and five drug sites (see Figure 2).

'All-purpose' sites have the capacity to conduct a wide range of licensure trials, be these for drugs or vaccines, large or small. Half of these sites are well established and can be considered 'mature'. They have collectively conducted 85% of malaria vaccine trials in Africa (35 out of 41), with a minimum of three malaria vaccine licensure trials each, and have also run multiple drug licensure trials in parallel.[5] The other half are considered 'young' since, although they can all conduct drug and vaccine trials, they have substantially less vaccine experience than the mature sites. Most have moved up to vaccine trial capability recently due to Malaria Clinical Trials Alliance (MCTA)/Malaria Vaccine Initiative (MVI)-funded upgrades linked to large RTS,S Phase IIb malaria vaccine trials, which were the first vaccine licensure trials for most of the sites in this category.

'Drug sites' have the capacity to conduct drug licensure trials. They have each conducted two or more drug licensure trials, but none have malaria vaccine licensure experience. However, two sites (the Tropical Diseases Research Centre (TDRC) in Zambia and the Blantyre Malaria Project Research Clinic in Malawi) have already committed funding for upgrading to malaria vaccine-licensure standard.

As mentioned above, five additional non-licensure sites are now being upgraded to reach licensure standard by end of 2008

Figure 2.
Technically competent licensure sites in Africa

6 mature 'all purpose sites' vaccine and drugs

1. US Army Medical Research Project Kenya (USAMRU-K), Kisumu (Kenya)
2. Wellcome Trust/KEMRI Kilifi: Kilifi, Pingilikani, Junju (Kenya)
3. Malaria Research and Training Centre (MRTC) Bancoumana, Bandiagara, Doneguebougou (Mali)
4. Centro de Investigación en Salud de Manhica (CISM) Manhica (Mozambique)
5. Bagamoyo/Ifakara Health Research & Development Centre, IHRDC (Tanzania)
6. Medical Research Council (MRC): Basse, Banjul/Fajara, Farafenni (The Gambia)

6 young 'all purpose sites' vaccine and drugs

1. Hospital Albert Schweitzer (HAS): Lambarene, Libreville (Gabon)
2. Agogo Clinical Trial Centre, Kumasi Centre for Collaborative Research (KCCR) in partnership with the School of Medical Sciences (SMS), Kumasi (Ghana)
3. Kintampo Health Research Centre (Ghana)
4. National Institute for Medical Research (NIMR) Amani/Tanga (Tanzania)
5. Navrongo Health Research Centre (Ghana)
6. Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Oubritenga/ Ouagoudougou (Burkina Faso)

6 drug sites Drugs

1. Centre de Recherche en Santé de Nouna (CRSN), Nouna (Burkina Faso)
2. Blantyre Malaria Project Research Clinic, Ndirande, Blantyre (Malawi)
3. QE Hospital Malawi – Liverpool – Wellcome Trust Research Programme (MLW) (Malawi)
4. Malaria Institute at Macha, Choma (Zambia)
5. Tropical Diseases Research Centre (TDRC), Ndola (Zambia)
6. Komfo Anokye Teaching Hospital (KATH), Kumasi (Ghana)

Figure 3.
Trial sites being upgraded to licensure standard in Africa

5 sites being upgraded ▶

1. CDC/KEMRI (Kenya)
2. Malaria Research Laboratory (MRL) University of Ibadan (Nigeria)
3. Noguchi Memorial Institute for Medical Research Clinical Trials Facility (Ghana)
4. Service de Parasitologie, University Cheik Anta Diop, Dakar (Senegal)
5. Niakhar Institut de recherche pour le developpement, Niakhar/Dakar (Senegal)

Figure 4.
Potential capacity: trial sites that have conducted licensure standard drug trials with external support

14 potential sites ▶

1. Faculté des Sciences de la Santé, CNHU (Benin)
2. Faso Institute Superior des sciences de la santé, Université Polytechnique de Bobo-Diolasso (Burkina Faso)
3. Institut Pasteur, Abidjan (Côte d'Ivoire)
4. School of Public Health, University of Kinshasa (Democratic Republic of the Congo)
5. Moi University, Eldoret (Kenya)
6. State Specialist Hospital, Maiduguri, Borno State (Nigeria)
7. University of Nigeria Teaching Hospital, Enugu (Nigeria)
8. Lagos State University Teaching Hospital (Nigeria)
9. Obafemi Awolowo University Teaching Hospital, Ile-Ife (Nigeria)
10. Plateau State Specialist Hospital, Jos, Plateau State (Nigeria)
11. University of Calabar Teaching Hospital, Calabar (Nigeria)
12. Centre de Santé Roi Baudoin, Guediawaye, Dakar (Senegal)
13. Kivunge Public Health Care Centre Zanzibar (Tanzania)
14. MSF Epicentre, Mbarara (Uganda)

(three to become malaria vaccine trial sites; two as drug trial sites). These sites are very close to being ready to take on licensure trials and nearly all have recent relevant large-scale, non-licensure trial experience due to IPTi, IPTp or ITN trials.[6]

It is important to note that 14 additional sites have also conducted licensure-standard drug trials with external support from the Medicines for Malaria Venture (MMV), and represent potential capacity in the future.

These sites have participated in multi-centre drug trials but might not be able to conduct licensure trials on their own, as the trials they participated in had close supervision and centralized trial and data management. They will, however, have a head start on reaching licensure-standard due to the increased experience of the Principal Investigator, the 'good clinical practice' (GCP) training of site staff and general site improvements.

In conclusion, there will be around 23 African clinical trial sites with the technical capacity to conduct licensure-standard malaria product trials by end-2008.[7]

Operational capacity

We refer to operational capacity for malaria product licensure trials at two levels: the general management and financial skills needed to successfully handle projects; and the site's ability to access sufficient patients to support efficient trial enrolment. Our analysis shows that different sites are limited by different operational capacity constraints.

Mature sites are more constrained by inadequate patient access and lower malaria rates than by management or financial incapacity. These constraints may be associated with reduced local malaria burdens caused by bednet use or indoor spraying (Manhiça Health Research Centre (CISM) and Wellcome Trust/Kenya Medical Research Institute (KEMRI) Kilifi); with lack of access to specific patient subsets (e.g. infants); or with 'over-use' of the resident population due to frequent product trials. In practice, this is more a problem for malaria product developers than for the individual sites since most have diversified into other disease areas to improve their chance of sustainability and/or because malaria (or malaria work) was not sufficient to keep them busy.

Young, all-purpose licensure sites, on the other hand, have continuing high malaria incidence and large infant populations but are generally constrained in the short-term by management and financial limitations as well as by limited experience in accessing newborns. These sites generally have sufficient malaria and sufficient patients, but they may not have the management capacity to conduct or to schedule multiple simultaneous trials, particularly if these are very large vaccine and intervention trials. For instance, Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) and Kintampo in Ghana, and the National Institute of Malaria Research (NIMR) in Tanzania estimated that the planned Phase III RTS,S trial will fully occupy their current capacity, even with the site expansions and support linked to such a trial.[8]

A further limiting factor for some young sites was poor local infrastructure, even allowing for trial-specific upgrades such as construction and expansion of paediatric wards and vaccination

centres. For instance, the National Centre of Research and Training on Malaria (CNRFP) site in Oubritenga/Ouagoudougou (Burkina Faso) lacks public water and electricity, which has hampered its potential as a high infant enrolment centre for malaria vaccine trials.

Geographical spread

The final factor determining site suitability for a licensure trial is its location with respect to other trial sites in the network. Trial demand cannot be said to be fully satisfied unless the available trial sites collectively represent a reasonable geographic, political and epidemiological cross-section of Africa's malaria-endemic countries.

Drug and vaccine licensure trial sites, both young and mature, are well distributed throughout East and West Africa, including in both Francophone and Anglophone countries. However, Central Africa has very few trial sites (e.g. there are no trial sites in Angola, Chad or southern Sudan) and there is also a marked absence of vaccine trial sites in Nigeria.

Capacity gaps

Based on the above analyses, we can now match supply figures to demand projections in order to determine the presence, nature and size of trial site capacity gaps going forward to 2012.

Capacity gaps for malaria drug trials in Africa

Adult and child enrolment in drug licensure trials, as seen from the above forecasts (see Table 1), will decline markedly after 2009 as the current wave of late-stage products comes to an end, and will remain at well under 2000 adults and 1000 children per year thereafter. These figures reflect a panorama with many small drug trials (around 10 trials per year of less than 100 patients), few medium-size trials (3–5 per year enrolling around 300 patients) and even fewer large trials over the next five years (see Figure 5).

On the supply side, there will be at least 20 licensure sites available to meet this demand, including 18 current sites (12 'all-purpose' sites and 6 specific drug licensure sites) plus an additional 2 currently being upgraded for drug licensure trials. Additional capacity will be available at the 14 sites currently capable of conducting assisted trials. With the exception of the central conflict states, these 34 sites are well distributed throughout Africa's malaria zones, including in Nigeria.

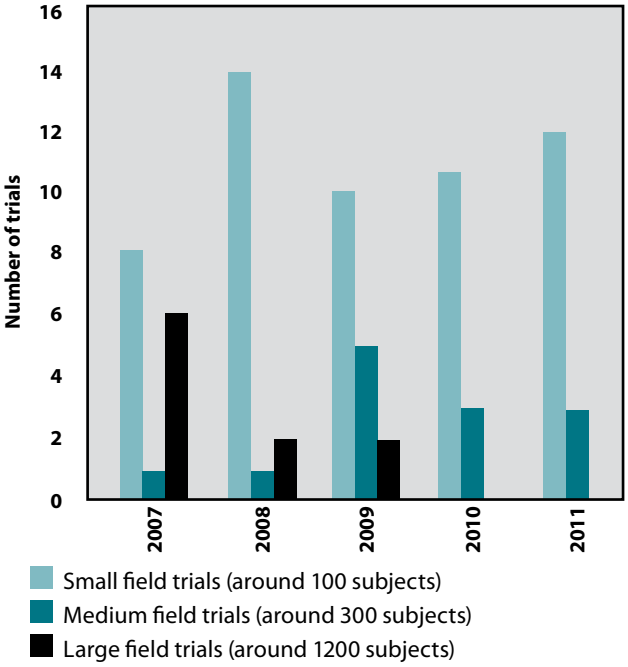
This combination of relatively moderate enrolments in malaria drug trials in the next 3–5 years, and the plethora of licensure-standard sites able to conduct such trials, means there is no unmet demand for licensure-standard malaria drug trial sites nor will there be in the foreseeable future.

Capacity gaps for malaria vaccine trials in Africa

As seen in Figure 2, the situation for vaccine trials is not as straightforward, with significant divergence in demand between trials in adults, children and infants. Adult enrolment demand is minimal and peaks at around 300/year but child and infant enrolment show quite a different picture.

Child vaccine enrolments will start to rise rapidly after 2008 mainly associated with Phase IIb trials (around four such trials per year). As these trials generally enrol all subjects at one site (usually around 400–800 subjects, but sometimes up to thousands), and follow them for two or more years, these child enrolments will have to be allocated to sites capable of handling large-scale vaccine trials.

Figure 5.
Projected total number of clinical malaria drug trials over five years by type of trial



The largest hurdle, however, will be short-term infant enrolments associated with the RTS,S phase III vaccine trials, which will create an unprecedented peak demand for vaccine licensure sites capable of large-scale infant enrolments in 2008–2010. This level of demand is a one off event as no other candidate is likely to reach Phase III before 2012.

On the supply side, as noted above, there will be 16 vaccine licensure sites available to meet this demand: six mature 'all purpose' sites with substantial experience in child and adult vaccine enrolments, but most with limited experience enrolling infants; six young, 'all purpose' sites with modest vaccine experience and no history of infant licensure enrolments; and three sites currently being upgraded, two of which (Blantyre Malaria Project (BMP) and Centers for Disease Control (CDC) Kemri) are being groomed for large-scale Phase III infant enrolments as their first licensure trial experience.

Ten of these sites will be tied up with large Phase III RTS,S infant trials from end-2008 to the start of 2011. This means that anticipated Phase IIb trials in children during this time (estimated at around four per year) will have to be conducted either in the five vaccine licensure sites that will not be used for RTS,S or at 'mature' sites able to conduct two large vaccine trials simultaneously. This combined pattern of child and infant enrolment demand in 2009/10 will create strains on the existing site network. Careful management will be needed to avoid either prematurely overloading young sites, or missing out on mature sites that may be occupied with the large-scale non-malarial trials that constitute an increasing part of their work. Close attention will also be needed to avoid spare capacity once the RTS,S trials are completed at end 2010.

Conclusions

Trial site development is an area where funders and sites can justly afford to congratulate themselves. The malaria licensure site network has grown substantially in the past decade and will reach around 23 sites by end 2008.

This new network is not only bigger than before, but its structure is a better match for projected product trials than anything we have seen to date. More sites are capable of more types of trials than previously; and current Phase III site expansions are making new patient groups available at existing sites, which will increasingly allow sites to 'segment' patients into different disease, age and product trials.

According to our demand projections, this network will be sufficient for malaria product trials out to 2012. However, although we believe the current licensure site network is sufficient in terms of numbers, there is still work to be done. The focus on the six 'mature' sites as the linchpin of trials will decrease as their malaria rates drop and/or as they continue their expansion into other disease areas. Increasingly, the future of malaria trials will lie with the new young sites, whose high malarial populations and birth rates and (at least for the moment) primary focus on malaria, make them ideally suited to malaria product trials.

This presents two new challenges to policy-makers and funders. The first will be to sustain these young and new licensure sites and provide the right kind of support to bring them to their mature potential. The second challenge will be to manage the flow of product trials to all sites over the next five years in a way that is synergistic with, rather than counterproductive to, site growth.

We hope that this picture of the malaria product field, and of where and how it could be advanced, will prove useful to those funders whose contributions offer ongoing hope to the many millions suffering from malaria.

Notes and references

1 This paper focuses on trial site supply and demand for malaria product licensure trials. It does not include post-registration or Phase IV trials aimed at assessing a product's profile in real-life health systems and populations.
2 These enrolment projections are only for African trial sites, as this is our area of interest (i.e. drug enrolments in Asia are excluded).
3 Mid-point enrolment numbers have been used instead of ranges for ease of reading.
4 Assessment and assignment of sites to these categories was based on trial site interviews, product developer interviews, expert opinion, audits conducted by others where available (Wellcome Trust, the TB Alliance, European and Developing Countries Clinical Trials Partnership (EDCTP)), and analysis of licensure experience at each site.
5 The only exception is the United States Army Medical Research Unit Kenya (USAMRU-K) site.
6 The only exception is the Noguchi Memorial Institute for Medical Research Clinical Trials Facility (Ghana).
7 The Malaria Institute at Macha, Choma (Zambia) may soon drop off the list as decreasing local malaria rates make it increasingly unsuited to conduct malaria product trials.
8 The exception was Navrongo, which has a large patient population, a keen desire to expand its scope, and proven management capacity to run multiple trials. For example, it simultaneously conducted a large IPTp study, two Phase II/III drug trials for Pfizer, and a meningitis vaccine trial for GlaxoSmithKline.

Biographies

Mary Moran *trained as physician, working for 13 years in Emergency Medicine in Australia but embarked upon a diplomatic career following a degree in international relations and politics at the University of New South Wales and Monash University. She subsequently worked with Médecins Sans Frontières (MSF), on a range of issues relating to access to medicines. In 2004, she founded the Pharmaceutical R&D Policy Project (PRPP) at the London School of Economics and Political Science, and subsequently moved the unit to Sydney, Australia, where it was consolidated as the Health Policy Division (HPD) of The George Institute for International Health.*

Javier Guzman *trained as physician and then planned and implemented primary health-care projects in the Colombian countryside, mainly working on early detection and treatment of endemic infectious diseases like tuberculosis and Chagas disease. In 2002, he moved to the Royal London Hospital, United Kingdom. In 2004, he obtained his MSc in Health Policy, Planning and Financing from the London School of Economics and the London School of Hygiene and Tropical Medicine (LSHTM). In August 2004, he joined the PRPP and subsequently moved to Australia, where he now heads the HPD research team at The George Institute for International Health, Sydney.*

Anne-Laure Ropars *completed her Masters degree in political economy and international relations at the University of Chicago and went on to work as a consultant specializing in European and developing country health systems and policies. Her clients have included the European Union-based pharmaceutical industry, philanthropic organizations and government bodies. Her project experience spans drug procurement policy in sub-Saharan Africa, market-based mechanisms to reduce the price of essential drugs in Ghana, and drug reimbursement policies in European countries. She joined the PRPP at its creation in 2004 and now heads the HPD research team in the London office of The George Institute for International Health.*

Margaret Jorgensen *joined HPD in 2006 after working for Eli Lilly Australia as a Clinical Project Manager. Here she facilitated the development, data management, reporting and analysis, and scientific communication of clinical trials. Prior to this, Margaret worked as an Infectious Disease Analyst and Consultant for the US-based health-care consulting firm Decision Resources. Margaret obtained her Bachelors degree from the University of Sydney, where she majored in Infectious Diseases. She completed her PhD at the University of New South Wales School of Microbiology and Immunology and received postdoctoral training at the Harvard University School of Public Health.*

Sarah Potter *has been studying malaria for more than eight years. She completed her Bachelor of Science Honours year and PhD, researching the neurological processes of cerebral malaria, at the Department of Pathology, University of Sydney. In 2003 she completed her Masters degree in International Public Health, also at the University of Sydney. From 2004 until June 2006, Sarah was an INSERM post-doctoral fellow at the laboratory of Laurent Renia, Institut Cochin, Paris.*

Alina McDonald *undertook training in science and law at the University of Sydney. She majored in medical sciences, health law and international law. She completed her study of international law at the University of Utrecht in the Netherlands. After contributing towards an EU-funded bioethics research project based in Berlin, she joined The George Institute for International Health in January 2005 to work on a series of health policy Roundtables with the Chinese Ministry of Health. Alina contributed to two Roundtables, held in Beijing, on issues including patient safety and access to basic health care where she conducted background research and prepared policy reports for the Ministry of Health. In early 2006, she had a short-term secondment to the World Health Organization in Geneva to work with the secretariat for the Framework Convention on Tobacco Control. Alina joined the Health Policy Division in Sydney in June 2006 and in her current role conducts research and analysis including for the project "Malaria product pipeline: planning for the future". She began postgraduate study in intellectual property law in 2007 at the University of Technology, Sydney.*

Hiwot Haile-Selassie *joined the London Based HPD team as a researcher in 2006. Prior to joining the HPD, and during and after completing her masters' degree at the LSHTM, Hiwot worked as a researcher on projects in HIV/AIDS, malaria drug policy, and sexual and reproductive health. Her experience includes conducting large systematic literature reviews and providing analytical research support for the development of national vaccination policies as part of the multi-agency HIB vaccine Initiative (WHO-LSHTM-CDC Atlanta-John Hopkins); providing research and programme support for Interact Worldwide's HIV/AIDS programme; and monitoring and evaluating Zanzibar policy on intermittent preventive treatment in pregnant women (IPTp).*

Issues surrounding the implementation of multiple product development partnership clinical trials in developing countries

Gita Ramjee

As the global burden of the HIV pandemic grows, there is an urgent need to develop strategies that will provide a systematic analysis of the burden of disease in developing countries; countries that experience a vicious cycle of poverty leading to disease, and diseases leading to poverty due to its impact on the socioeconomic status of the individuals. This cycle of disease progression in developing countries has led to discussions around innovative strategies of addressing the health needs of low- and middle-income countries as it has been realized that no single sector – for profit, not-for-profit or the government agencies – has all the skills and resources needed to make an impact.[1]

It is clear that new interventions such as biomedical technologies will be needed to address the HIV pandemic as the ABC approach (abstinence, being faithful and using condoms) may not always be feasible. The urgent need to accelerate research and development (R&D) of new products has led to the formation of product development partnerships (PDPs). Many PDPs have emerged in the past decade with the aim of developing health technologies to meet the needs of developing countries. These include product design focused on developing country needs, clinical trial partnerships with countries where the products are expected to be tested, and ensuring access and affordability in these countries. The International AIDS Vaccine Initiative (IAVI),[2] the International Partnership for Microbicides (IPM)[3] and the Microbicide Development Programme (MDP)[4] are examples of such initiatives where the goal is to lead the discovery, development, testing and accessibility of technologies such as vaccines and microbicides.

Clinical trial sites

Clinical trials sites in developing countries are important partners in meeting the goals of PDPs. In order to ensure successful testing of the efficacy of products, key criteria of site performance have to be met. This includes site leadership, adequate infrastructure, site capacity, community partnerships and support of the intervention being tested; support and partnerships with the local health providers; a

Table 1.
Summary of Medical Research Council, HIV Prevention Research Unit clinical trials (as of June 2007)

Study	Start date	End date	Status
MIRA: The latex diaphragm to prevent HIV acquisition among women: a female-controlled, physical barrier of the cervix	September 2003	Complete	Results released July 2007
HPTN 035: Phase II/IIb study to assess the safety and efficacy of BufferGel and 0.5% PRO2000/5 gel in the prevention of HIV among women	February 2005	June 2008	Enrolment complete
Population Council: Phase III study of the microbicide Carraguard in preventing HIV seroconversion among women	October 2004	Complete	Results expected early 2008
Microbicides Development Programme: Phase III study of 0.5% PRO2000/5 gel and 2% PRO2000/5 gel in preventing HIV transmission among women	November 2005	June 2009	On-going (Enrolment to complete June 2008)
CONRAD: Study of cellulose sulphate in preventing HIV infection among women	July 2005	Terminated	Study terminated

certain threshold of HIV incidence rates, and mechanisms to ensure ethical conduct of clinical trials through local ethics committees and other regulatory bodies.

The South African Medical Research Council (MRC), through its HIV Prevention Research Unit (HPRU) was involved in testing five products in Phase IIb/III trials simultaneously (Table 1). This included one Phase III trial of a vaginal diaphragm in the prevention of HIV (University of California, San Francisco);[5] three Phase III microbicide trials testing Carraguard (Population Council),[6] PRO2000 (0.5%) and BufferGel (Division of AIDS, National Institutes of Health (NIH));[7] PRO2000 (0.5% vs. 2%) (Microbicide Development Programme);[4] and Cellulose Sulphate (CONRAD)[8]. The trials were funded through various organizations such as the Bill and Melinda Gates Foundation, the United States Agency for International Development (USAID), NIH and the United Kingdom Department for International Development (DFID).

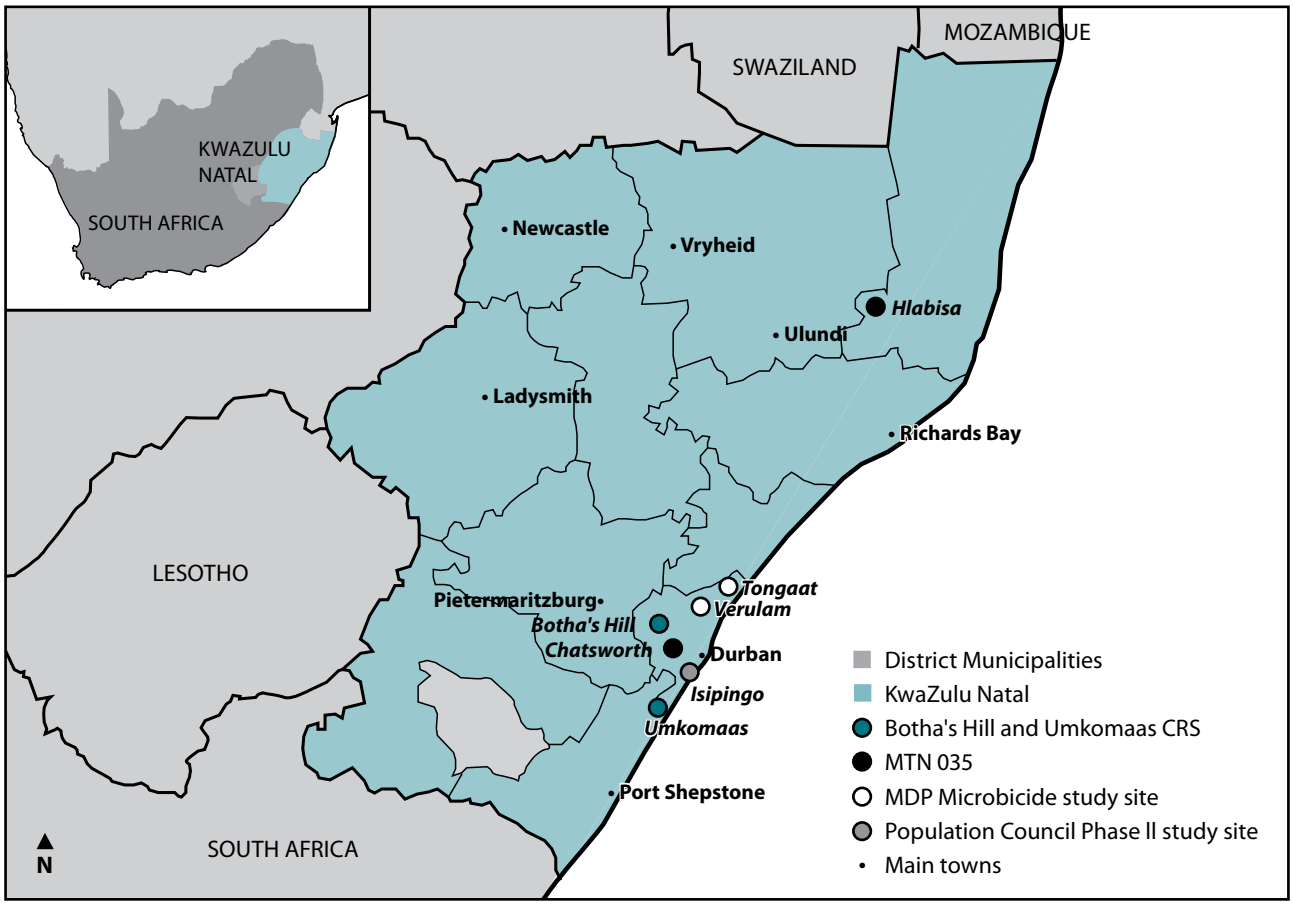
Implementation of multiple clinical trials

Implementation of all the trials required a high level of coordination with each trial being led by a team of 35–40 staff members trained to conduct trials as per good clinical practice (GCP) guidelines.[9] The multidisciplinary team consisted of project leaders (PhD level scientists), project coordinators, clinicians, nurses, HIV counsellors, outreach staff, community liaison officers, data managers, quality control and quality assurance (QA/QC) managers, research assistants, laboratory technologists and pharmacists. Most importantly, each collaborative partnership required an independent implementation team dedicated to specific protocols. However certain core groups such as clinicians, nurses and HIV counsellors are cross-trained in a maximum of two projects to provide oversight in case of staff shortage.

One of the greatest advantages is the enormous amount of clinical trial capacity that is developed at trial sites. All sponsors ensure that trial staff have the opportunity for scientific writing and presentation at local and international conferences. Furthermore, development of standard operating procedures (SOP), GCP and good laboratory practice (GLP) guidelines training, quality assurance/quality control (QA/QC) systems, pharmacy guidelines, and standardization of laboratory procedures, can be shared with all sponsors. Best practices regarding recruitment, retention, clinic flow and participant education materials are also shared or adapted for use across trials and trial sites.

The unique ability to conduct and coordinate multiple PDP protocols simultaneously has resulted in various sponsors and donors inadvertently benefiting from best practices and feasible operating procedures across trials.

Figure 1.
Medical Research Council, HIV Prevention Research Unit clinical trial sites



Community entry

Each of the respective trial sites is located within communities surrounding the greater Durban area (Figure 1), each with their respective political and traditional leadership structures. Community needs and acceptance of research are tantamount to the development of clinical trial sites contributing to the recruitment and retention efforts. A good participatory approach with provision of extensive HIV education, together with regular updates on clinical trial conduct, is absolutely essential to ensure community trust and acceptance of research. Each community may require different levels of HIV prevention education. Community health needs assessments, together with assessment of health-care availability and provision in the area, are essential prior to implementing clinical trials.

Partnerships with local health service providers

There are several layers of partnerships that need to be considered during implementation of clinical trials. Each of the trials has to be registered on the National Department of Health clinical trials registry. At a provincial level, approval from the local Department of Health is essential in order to ensure access to health care services for trial participants. At the community level, partnership with local hospitals and clinics is essential for referral of trial participants for study related and unrelated health care and for accessing participant hospital records.

Partnerships are invaluable in ensuring provision of care for research participants, especially those who are found to be HIV positive at the initial screening period or those who become HIV positive during the course of the trial. One of the greatest challenges is facilitating access to antiretroviral (ARV) treatment to those in immediate need. Many hospitals have long waiting lists and access to treatment may not necessarily be immediate.

Creating partnerships with the President's Emergency Plan for AIDS Relief (PEPFAR) partners has relieved some of the burden at the sites with 'screened out' participants and families having access to care through this programme. The PEPFAR sites have enabled assistance to be given to local care providers in scaling-up of HIV care and treatment efforts.

Unfortunately, the current initiative was not able to access PEPFAR funds directly but partnership with a PEPFAR grantee allowed for care provision at two of our clinical trial sites with a referral mechanism set up from other sites. Ensuring continuum and sustainability of care is an essential component of the clinical trial implementation process. Effective country-to-country coordination is required by PEPFAR to ensure that there is better integration of prevention and care programmes funded by US resources.

"Partnerships are invaluable in ensuring provision of care for research participants, especially those who are found to be HIV positive at the initial screening period or those who become HIV positive during the course of the trial."

Some sponsors, depending on their public–private partnership and funding status, were able to provide funds for care of HIV sero-converters in clinical trials. This included support for providing capacity at community referral hospitals. A package of HIV-related care is determined and funding is used to provide care for research participants and the community at large.[10]

It is essential that sponsors support local investigators on the issue of care service provision. Implementing multiple PDP trials has enabled us to develop many strategies around care that can be accessed by all trial sites. Most importantly, it has to be realized that conducting research in high HIV prevalence areas requires effective and sustainable integration of HIV prevention, treatment and care.

Challenges

Many of the trial sites of the HPRU were developed for the conduct of large-scale Phase III trials. However, with the diminishing product development pipeline in HIV prevention technologies, especially microbicides, these sites may become redundant, with loss of trained clinical trial staff.

It is essential that high performing sites with adequate HIV incidence, staff capacity and community support are sustained. Given that HIV prevention is the common goal of all the sponsors of various technologies, clinical trial sites should be shared between partners with the best and most promising products going forward into large-scale trials.

As trials come to an end, communities do express concerns regarding the loss of voluntary counselling and testing services provided by trial teams, including the provision of safe sex and condom counselling. At an international level, each of the PDPs need to have a shared database of clinical trial sites in developing countries that could be available for testing new products and interventions. This will ensure that existing trial site infrastructure and capacity is sustained.

Negative outcome of trials and its impact on clinical implementation

One of the greatest challenges faced at the site level is the early termination of clinical trials. These negative outcomes not only affect the community where the trial is conducted, but also other clinical trials participants and communities. This is one of the most daunting challenges of implementing multiple PDPs.

The recent termination of the cellulose sulphate (CS) trial[11] had a devastating impact on other trial sites as inaccurate media reporting suggested that all microbicide gels being tested were unsafe.[12] Loss of community trust and support was evident from the substantial reduction in the interest to enrol and/or remain in other microbicide trials or other HIV prevention trials in South Africa. Teams at each of the trial sites had to hold urgent community meetings to explain the interim analysis and outcomes, and to regain community trust and support.

The process of regaining community and participant trust has been a long one, and continues to be challenging. For multiple PDPs implemented in one country, albeit microbicides or vaccines, one needs to be cognizant of the impact of product failure or inaccurate

media reporting on other ongoing trials. This challenge underscores the need for a collective group of HIV prevention scientists to support and dialogue with each other.

Effectiveness of intervention

Although all communities are well informed on the clinical trial methodology, lay public have limited understanding of clinical trial design. Many communities lack the understanding that the only way we can measure the effectiveness of the intervention is by comparing the number of new HIV infections that occur in each of the randomized arms (intervention versus placebo). Hence when trial results are announced and when large numbers of HIV infections are disclosed, there is a sense of uncertainty regarding the ethical conduct of clinical trials. For example, if the product has a negative impact, it is assumed that we perhaps increased the risk of participants to become HIV infected. A concerted effort needs to be placed on educating the community and lay public at the outset explaining that determining new HIV infections is the only way we will be able to ascertain the effectiveness of the product.

"PDPs and other bodies may need to develop improved guidelines to justify conducting trials in areas where there is insufficient and/or unreliable HIV incidence data for an unequivocal outcome."

Another issue is that of level of effectiveness. As scientists we are aware that for many of these new biomedical interventions, we are not expecting 100% effectiveness, or to replace the male condom in the near future. However, it is difficult to convey this message to communities in the developing world who are really looking for a product that will replace the male condom – as many men dislike using condoms, and women find it difficult to negotiate condom use with their partners.[13]

PDPs need to develop clear messages around scientific expectations of a particular product, as well as developing mechanisms to convey this to the broader public. Future regulatory registration and acceptance of products will depend on these issues.

Adherence to product use

There is considerable ongoing investment in the development and testing of novel biomedical tools. However, the efficacy of many of these products relies on coital dependency. These are products that are used immediately prior to sexual intercourse (condoms, diaphragms and microbicides). Other user-dependent interventions include pre-exposure prophylaxis such as daily administration of the antiretroviral drug tenofovir. Recent outcomes of a diaphragm trial and of tenofovir trials suggested lower than anticipated compliance rates.[14, 15]

Poor compliance reduces the power to determine effectiveness. Similarly high pregnancy rates also impact on the power of the study, as participants are taken off the product once pregnancy is determined, due to the unknown teratogenic effects of the product on the unborn fetus.[15] Many trial sites are now providing contraception. However, future protocols could do more to ascertain whether participants are using reliable contraception prior to trial enrolment. Adherence to product use and the high incidence of pregnancy remain concerns of current microbicide trials.

HIV incidence rates

Given the urgency to reduce the number of new HIV infections, PDPs need to extend to trial countries where HIV incidence is high enough to determine the effectiveness of new products. Also, in light of some declining HIV incidence rates reported recently,[16] prevention trials have become large, lengthy and expensive. PDPs and other bodies may need to develop improved guidelines to justify conducting trials in areas where there is insufficient and/or unreliable HIV incidence data for an unequivocal outcome. Furthermore, given the large clinical trial site capacity that has been developed in many countries testing microbicides in Phase III clinical trials, mechanisms need to be put in place to share these sites for testing new interventions. It will be futile to initiate new sites when existing ones are available, assuming that HIV incidence rates are high enough to warrant supporting the site for future trials.

Summary

Every product advancing through to large-scale clinical trial testing requires partnerships in countries where the products will be tested and eventually be licensed for use. The extensive partnerships required at clinical trial site level underscores the complexity of conducting large scale trials in developing countries.

The success of PDPs in the developed world will depend on successful partnerships with scientists and governments in developing countries, to ensure that the disease area to be tackled is also a priority in a given country. Building scientific capacity in protocol development, laboratory capacity, quality assurance programmes and ethics, ensures that the goals of PDPs are met. The importance of site-level partnerships with nongovernmental organizations (NGOs) and community-based organizations cannot be overstated, as without these partnerships, implementation of research and eventual product licensure is unlikely to be a success.

Most of all, PDPs need to collectively push for a broad, and more structured funding mechanism for continued development of novel products, capacity and other achievable goals. This collective aim will be important to help endure the long process from basic science to product development; clinical testing through multiple clinical trials; and most importantly, to finding an HIV prevention option that is safe, effective, accessible and affordable for the people who need it the most: men, women and children in the developing world.

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Biography

Gita Ramjee *is the Director of the South African Medical Research Council's HIV Prevention Research Unit and Director of the HIV/AIDS lead programme. In 1988, she joined the Department of Paediatrics at the University of Kwazulu Natal, South Africa, to complete a Masters degree studying fungal diseases in malnourished children. She went on to complete her PhD in kidney diseases of childhood. In the early 1990s, she joined the Medical Research Council to work on HIV, in particular women-initiated HIV prevention options. She has authored over 50 peer-reviewed publications and serves as a reviewer for numerous international journals and research organizations.*

Collaborative approach to clinical trials

Charles S Mgone
Pascoal Mocumbi

Scientific research often tends to be driven by opportunity rather than purpose. Many scientists consciously or subconsciously conduct research on issues that are presumed to be topical merely because they are either popular, controversial or are attractive to funders. The results of such research studies tend to be duplicative, repetitive and even outright wasteful. Such outcomes can be avoided by conducting tailor-made research programmes designed to answer specific questions prioritized according to public health needs.

Several public–private partnerships (PPPs) and product development partnerships (PDPs) have been founded to promote the conduct of focused research and development to solve specific health problems.[1] Many of these partnerships have concentrated on diseases of poverty.[2] However, such custom-built and purpose-driven research programmes are also not free of peril since the centralization and control of research may lead to the suppression of competitiveness and creativity. This approach is quite often tied to a top-bottom strategy, where the funder defines the research agenda, sets the priorities and conducts the research activities. This approach often bypasses or minimally involves partners at the bottom, which in this case happens to be researchers and policy-makers in developing countries, where the diseases being investigated are endemic. Such an approach should be avoided at all costs. A situation where 'he who pays the piper calls the tune' must never arise. All stakeholders, especially those from developing countries, must be fully involved in the planning of clinical trials.

"Scientific research often tends to be driven by opportunity rather than purpose. Many scientists consciously or subconsciously conduct research on issues that are presumed to be topical merely because they are either popular, controversial or are attractive to funders."

The European and Developing Countries Clinical Trials Partnership (EDCTP) was founded to accelerate research and the development of new or improved intervention tools against diseases of poverty, specifically HIV, malaria and tuberculosis (TB), through the conduct of clinical trials. To achieve and sustain this, the partnership must be genuine with equal commitment and full participation, including planning and implementation by both sets of partners. However, to achieve true partnership, the capacity of developing country partners to conduct clinical trials according to international standards, and using best practices, must be built and strengthened.

Purpose-driven capacity development

In the past, capacity development was generally considered to be a waste of resources. To a lingering few, this is still the case. However, it is encouraging to note that this view is gradually changing as we become increasingly aware that to ensure the success and sustainability of many North–South collaborative programmes, developing country partners must be empowered to fully participate and co-own these programmes. One of the ways EDCTP is encouraging this is by integrating capacity development and networking components into clinical trial grants. The capacity development component is used to ensure the successful completion of the clinical trials and serves as a practical exercise through 'learning by doing' thus enabling the developed capacity to be utilized immediately, enhancing skill retention and sustainability. The networking component allows for technology transfer and, through South–South mentorship, proliferation of capacity among the participating developing country partners.

Joint planning and prioritization of research needs

To better coordinate and focus clinical trials, joint planning and prioritization of the research agenda by all stakeholders is essential. This is particularly so when it involves international collaborations, especially in North–South partnerships, where there is a diversity of needs, expectations and capacities among partners. Where the investigated diseases are endemic, usually in the South, the southern partners must give their input early in the planning of such programmes. They should also be responsible for identifying the capacity gaps that need to be filled in order to conduct the necessary clinical trials. It is, after all, 'the wearer of the shoe who knows where it pinches'. In addition, this joint planning approach will help to address the general misconception that the North is the provider of ideas and funds whereas the South is simply a passive recipient.[3]

One approach to a joint strategy could be planning a series of distinct but complementary clinical trials each asking different questions. In the end, the answers will complete the big picture, in much the same way as fitting together pieces of a jigsaw puzzle. For example, as a means of better understanding a particular vaccine, different groups of researchers may work separately but cooperatively in various clinical trials aimed at elucidating different aspects of the research question, such as the immune correlates of protection, interaction with other vaccines, acceptability and utilization. The answers generated will lead to the acquisition of more comprehensive information about the vaccine. Such joint projects

may also include a standardized methodology to allow pooling of information, which may be useful, especially if the parameters that are being investigated may be from small population samples or are uncommon.

Joint planning may also allow head-to-head studies. It is often a challenge to convince discrete groups to perform comparative clinical trials. This problem may be overcome by prior agreement when working jointly within a consortium. This would provide the opportunity to compare different interventions and pool data.

Product development plans

The rapid progress made by many PDPs is largely a result of prior product development plans. A product development plan is a detailed and focused strategic roadmap that charts the pathway of a product through various stages, such as market approval, licensing and deployment. This roadmap may include a series of interrelated and coordinated clinical trials with predetermined 'go, no-go' criteria. A good product development plan, like any good roadmap, is cost-effective and provides clear direction. It assures the best course of development by minimizing time to development and optimizing use of resources.[4] It is long overdue for policy-makers from developing countries to insist on such product development plans when confronted with requests to conduct clinical trials. Additionally, the expected benefits for the final end-users must be made clear.

"To better coordinate and focus clinical trials, joint planning and prioritization of the research agenda by all stakeholders is essential."

Coordination of efforts

In the past decade, the increasing number of PPPs and PDPs has brought into play well over a hundred different organizations with diverse interests and aspirations.[1, 2] With such diversity, there are bound to be many differences in philosophy and approach. To enhance synergy and avoid duplication, fragmentation and incompleteness, the activities of these initiatives must be coordinated. This applies to both capacity development and the conduct of clinical trials as well as to other major activities.[5] The various global health initiatives should collaborate and meet regularly to discuss matters of mutual interest. These meetings should include the exchange of ideas on what works or does not; what is the best way of doing things; and what can be done together. Additionally, there must be an inventory of all major activities including clinical trials. Such information should be made widely available, could be web-based and open to all.[6]

EDCTP has established an international registry of HIV, malaria and TB clinical trials in sub-Saharan Africa. It is linked to the World Health Organization (WHO) registry and can be used by other initiatives. The registry is an open-source repository that provides information on completed and ongoing clinical trials as well as research gaps that need to be addressed in future trials. Such information is useful for all stakeholders including funders, planners and researchers.

The coordination of efforts should also include capacity development activities. This may include infrastructure improvements, personnel training and supporting an enabling environment in terms of functional health research, ethics review committees and a competent national regulatory framework. For the results of any clinical trial to be credible and the safety of the research participants safeguarded, the researchers must be well-trained and follow good clinical practice. Their protocols must be approved by competent ethics review boards and relevant authorities. Global health partnerships must jointly support the development of this capacity, which is invariably lacking in many developing countries.

Another approach to coordinated clinical trials is to have a common advocacy strategy among various initiatives and relevant stakeholders. This may prove useful when negotiating with funders, political leaders and even between stakeholders. A good example is the strategy that is being developed for the research and development of preventive HIV vaccines in Africa by the African AIDS Vaccine Programme (AAVP) in partnership with WHO, EDCTP, the International AIDS Vaccine Initiative (IAVI) and others. Their strategy is to have a common advocacy approach for the incorporation of research and development of HIV vaccines into national HIV control programmes. Speaking with a common voice is more effective and minimizes confusing the target audience. It also paves the way for coordinated and integrated interventions, including conduct of clinical trials.

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Biographies

Charles S Mgone *is the Executive Director of the European and Developing Countries Clinical Trials Partnership (EDCTP). He has considerable experience in research and research administration and holds a PhD in Medical and Molecular Genetics. Professor Mgone has worked as Deputy Director, later as Acting Director of the Papua New Guinea Institute of Medical Research, advising especially on malaria, HIV, child and public health. Before joining EDCTP, he was Network Director of the African Malaria Network Trust (AMANET) where he was responsible for coordinating the African response to the malaria burden.*

Pascoal Mocumbi *is the High Representative of the European and Developing Countries Clinical Trials Partnership (EDCTP), and was Prime Minister of the Republic of Mozambique from 1994 to 2004. Prior to that, he headed first the Ministry of Foreign Affairs and then the Ministry of Health. He received his medical degree from the University of Lausanne, did his internship in Switzerland, and practiced obstetrics and gynaecology in hospitals throughout Mozambique. As Prime Minister, he led the establishment of Mozambique's National AIDS Council. He served from 1989 to 1998 in the World Health Organization's (WHO) Task Force on Health and Development.*

Running clinical trials in partnership with communities

Anjali Gopalan

Introduction

Researchers the world over have realized that conducting clinical trials in partnership with communities is one of the most effective strategies for ensuring the smooth conduct of the trials, as well as promoting better science. In fact, most studies today give as much consideration to community engagement as they do to protocol design and to regulatory and ethical clearance.

It is important to understand that clinical trials involving human subjects are complex and have the potential to violate the rights of the individuals. This is particularly true in developing countries where it is often easy to enrol participants from marginalized, poor communities, who may have lower levels of literacy. It is well known that there has been a history of misconduct in clinical trials throughout the world, in which individuals have been exploited. However, clinical trials with humans are essential if they are to be the end users of the product. The unfortunate reality is that most of the infectious diseases afflicting humanity are concentrated in developing countries. This paper aims to address this issue in reference to recent experience observing HIV vaccine clinical trials conducted in India.

"The complex ethical and human rights issues involved in all trials are best addressed through engagement with the community."

Community involvement and mobilization are necessarily at the very centre of all trials because the complex ethical and human rights issues involved are best addressed through engagement with the community. Open discussion between researchers and communities about these issues is essential to develop a process that is mutually agreeable to both parties.

Typically, clinical trials raise issues related to informed consent, confidentiality, gender discrimination, care and treatment for trial participants, autonomy to withdraw, undue inducement, access to accurate information, redress of grievances, and understanding the risks and benefits of the trial. Although these issues are universal, they sometimes assume more significance in developing countries. To redress these issues it is essential that we build bridges of communication between the community and the researchers, so that they understand one another's needs and objectives. Simple as it may seem, the process of integrating the needs of researchers, scientists, and other stakeholders with communities can be extremely challenging.

The first step to bringing communities on board with clinical trials is to build awareness through accurate information dissemination and to ensure transparency throughout the trial. This helps the community members to engage in an informed manner and protect their rights from being violated.

This paper highlights some of the specific community concerns that came up during the course of the HIV vaccine trials in India that are broadly relevant to vaccine trials anywhere in the world. They illustrate the importance of consistent, open communication and transparency with communities.

Informed consent

In the context of developing countries like India, obtaining informed consent from individuals who are often non-literate can be difficult for a number of reasons: language and cultural differences between participants and trial organizers; participants' lack of understanding of the concept of consent; and the lack of individual autonomy, because decisions are often dictated by family and social hierarchy (such as the head of the family or community elders). The informed consent process should be designed to empower participants to make appropriate decisions for themselves. The autonomy of the participants is fundamental – whether in relation to their decision to participate, or to withdraw. Informed consent should be obtained from each individual to be enrolled in the trial and their consent should be voluntary – not coerced or unduly influenced in any way.

Effective partnership with communities can smooth out the process of obtaining informed consent, especially from non-literate or poorly educated populations and socially marginalized groups or individuals, who may not be able to adequately articulate their own interests. When the informed consent template was developed for the HIV vaccine trials in India, these issues were of central consideration. A group of stakeholders including community representatives ensured that the informed consent template was made culturally sensitive, locally relevant and protected the rights of the participants. Issues such as the possible risks were outlined clearly and mechanisms for redress were set up.

Care and treatment

It is equally important to develop guidelines for the care and treatment of people enrolled in trials as it is something that is often not adequately addressed. It is important to get the community involved in defining a basic minimum standard of care that would be acceptable, especially when the attainable standard of care may not be on par with that of the developed world. This process also ensures that there is an awareness of the health-care services available on the ground and how the available resources can be consolidated and made available for the trials. This process also creates an opportunity for the researchers to strengthen health-

care facilities and build the capacity of health-care providers so that it benefits the communities in the long run.

Redress of grievances

In many trials the participants do not have ready recourse to voice their grievances. The existing legal systems in many developing countries are difficult to negotiate and extremely time-consuming. There is an urgent need to establish a mechanism for redress that is neutral in nature, easy to access and can respond quickly. For example, if trial participants feel that their problems are vaccine-related and the researcher disagrees, they would benefit from having access to another avenue, e.g. a committee, where they could air their grievances and establish some resolution. Communities in which trials are conducted should participate in selecting the members to serve on such committees.

Gender considerations

Gender imbalances are very common in countries where trials are frequently conducted, and women are seldom in a position to independently negotiate their decisions. In most cases, the husband or indeed the whole family will decide on behalf of the woman. In recent years, there has been widespread recognition of women's biological, social and economic vulnerabilities. It is essential that women participate in clinical trials, as they stand to benefit from the products being tested. Researchers need to understand the social norms and responsibilities that these women live with and ensure that they are provided facilities that will make it easier for them to participate. All of the above requires the understanding and cooperation of the community so that the women can exercise their choice of participation without coercion.

"The informed consent process should be designed to empower participants to make appropriate decisions for themselves. The autonomy of the participants is fundamental."

Access and intellectual property rights (IPR) issues

Ethically, communities have the right to expect that they will gain access to the product that has been trialed in their country and on them. However, very often developing countries do not have the manufacturing rights and therefore cannot afford the product, due to its prohibitive costs. In India, we have witnessed cases where essential drugs have only been made available 10 years after their introduction in other countries and even then at extremely high costs. This is an issue that needs to be addressed right from the time that the country initiates the process of clinical research. Communities involved in the process should be made aware of these issues and have the opportunity to question them from the very start of the research process in order to ensure their future access to the product.

In the Indian HIV vaccine trials, it was evident that the issues mentioned above and other complex details including the cultural context and concerns of the communities, were best resolved with community understanding and partnership. The history of trials like the Tuskegee trials in the USA or the cancer drug trial in India in 2001, involving M4N and G4N, bear testimony to the fact that we need to be vigilant in the defense of community needs. Mechanisms such as expert panels and advisory boards with community representation are now the norm; these mechanisms ensure active participation, informed consent and support of local communities.

One of the ways to address these issues is the formation of community advisory boards (CABs) where they do not already exist. There is also a need to empower existing boards to act as strong links between the scientific researchers and the community. After all, the boards are meant to represent the interests of the community.

Recruitment of volunteers through community mobilization is enabled by such local institutional arrangements. They function as a link between the trial organizers and the community, intervene in problems pertaining to the clinical trials, and bring local contexts and knowledge to bear upon the trial process, especially ethical issues and matters relating to the rights of volunteers.

The prospective resource organizations for facilitating community mobilization and engagement include local institutions for self-governance; self-help groups; women's organizations; nongovernmental organizations working in the field of health; workers' and farmers' associations; health-care providers and representatives of the participating population. Equally important in this mobilization process is the role of well-informed political representatives, policy-makers, and religious/community leaders. They can play a vital role in influencing the communities' prevailing perceptions, addressing the possible social stigma against trail participants, and providing moral and emotional support to the participants.

To date, two Phase I HIV vaccine trials have been conducted in India, in Pune and Chennai. These trials were initiated after a consensus of concern among stakeholders on issues related to appropriate care and treatment for the trial participants, informed consent issues, gender equity, and community involvement.

Phase II and III trials are far more complicated because of the large numbers of volunteers required from vulnerable communities. With this in mind, consultations have already been initiated to understand the nuances of these differences and what process will best accommodate them.

Developing a vaccine or drug is clearly a long process and it could take up to a decade to find one that works. The length of this process is another reason why it it is important that communities gain access to all available information at each given step.

Conclusions and lessons learned

- Communities can work in partnership with researchers to help overcome initial suspicion and create opportunities for dialogue across the diverse groups involved.

- All relevant concerns and vulnerability issues must be integrated into the research programmes to make sure that the specific needs of the population being recruited are addressed in the process.
- Community consultations must be conducted locally as well as nationally. It is important to consider regional differences when reaching out to local groups.
- Constant sharing of information with partners on the progress of the research programme helps sustain interest and keep stakeholders engaged.

Biography

Anjali Gopalan *is the Founder and Executive Director of the Naz Foundation (India) Trust, a Delhi-based nongovernmental organization dedicated to fighting HIV in India. Frustrated by the lack of government and social response to the burgeoning HIV epidemic in India in the 1990s, she founded Naz India with the mission of supporting stigmatized and vulnerable communities affected by the virus. Today, her main concern is providing quality care and support to people living with HIV, which she has done through founding and managing a care home for HIV-positive children and women.*

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Getting diagnostics into countries

Vinand M Nantulya

Diagnosis – an integral part of the solution

Life-saving medicines are increasingly being made available in the developing world for the treatment of major diseases, in particular HIV, tuberculosis (TB) and malaria, through funding mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States President's Emergency Program for AIDS Relief (PEPFAR), the World Bank and UNITAID. However, focusing on the delivery of medicines is by itself not enough. Diagnosis is an integral part of the solution that must not be overlooked. The patients who are to be placed on treatment need to be promptly identified and the treatment outcome needs to be monitored to gauge success. This is all the more important as the new medicines are considerably more expensive than previous remedies, and should not be dispensed blindly to treat inappropriate conditions.

Two major obstacles stand in the way to getting diagnostics into countries. First, we need simple, accurate and affordable diagnostic tests that can be applied as close to the patient as possible. The tests available in the developing world, such as microscopic examination, are often out-dated and ineffective, while newer and more accurate tests, already available in industrialized countries, are either not affordable or are not designed for use in resource-constrained settings in the developing world.

Second, we need to address the poor state of laboratory services in low-income countries, where logistical and infrastructure weaknesses, both in the public and the private health sector, are pervasive. This is of greater urgency in sub-Saharan Africa where the laboratory services' infrastructure and management in many countries in the region has been neglected for a long time. Weak laboratory services may well be the single greatest limiting factor to introducing new and better tests into national disease control programmes. This factor, along with poor organization, also influences the overall cost of diagnostic tests, especially instrument-based tests, due to the increased cost of customer support services, or the so-called 'cost to serve'. The cost to serve is dictated by the status of the laboratory infrastructure, how well organized and networked it is, and the quality and quantity of laboratory human resources, for example. The cost to serve can account for up to 30% of the overall cost of instrument-based diagnostic technologies.

The high cost of poor diagnosis

A point must be made that poor diagnosis or inability to diagnose also carries high costs. The costs are at several levels: for the patient, poor diagnosis or no diagnosis leads to inappropriate treatment, chronic ill-health, high household expenditure on health care and loss of economic activities; for the laboratory staff it means frustration, time wasted and job dissatisfaction; for the clinician it means a loss of faith in laboratory results, an ever-increasing patient load, and resorting to 'polypharmacy' prescription practices; and for the health system it means a high wastage of scarce public resources on ineffective treatments and the loss of economic productivity due to chronic illness and substantial loss of life. These pathways are well captured in Figure 1.

Take the cases of TB and malaria. The world spends US$ 1 billion globally on the diagnosis of TB, but the return on this investment is disappointing: fewer than 25% of the nearly 9 million new cases of TB each year are diagnosed. For a TB patient in Malawi, for example, it takes up to 15 working days (i.e. 15 days of lost income) to be diagnosed.[1]

As shown in Figure 2, the long journey to TB diagnosis involves repeated visits by the patient to the clinic, and expenditure on travel, antibiotics and drugs for symptomatic treatment. The diagnosis is made late in an advanced stage of the disease when the patient is coughing large numbers of bacilli in sputum. Sputum microscopy is not sensitive enough to detect the disease in the early stages of the infection. All the while the patient will have been coughing out bacilli into the environment, transmitting the infection to family members and others he or she is in close contact with, as well as having been economically unproductive for the duration of the illness.

Figure 1.
Cost of poor diagnosis

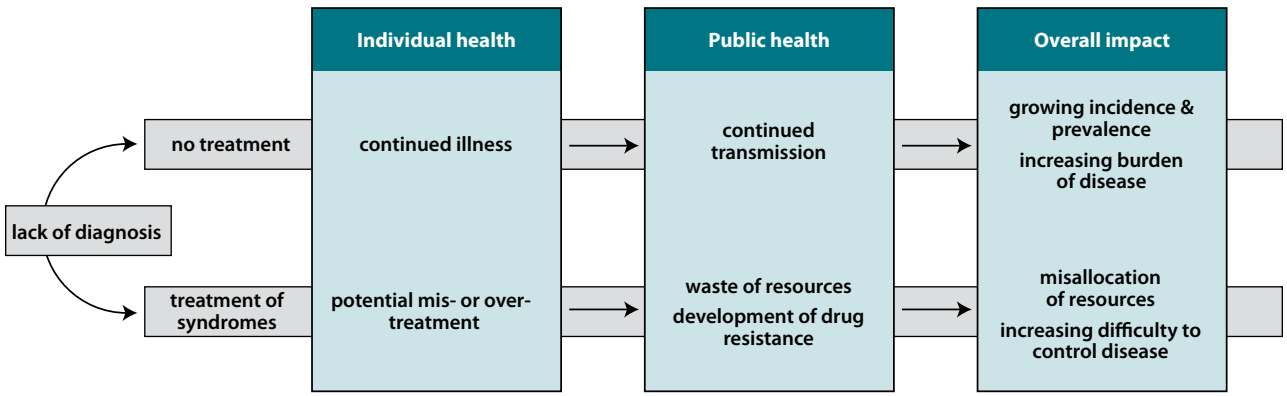
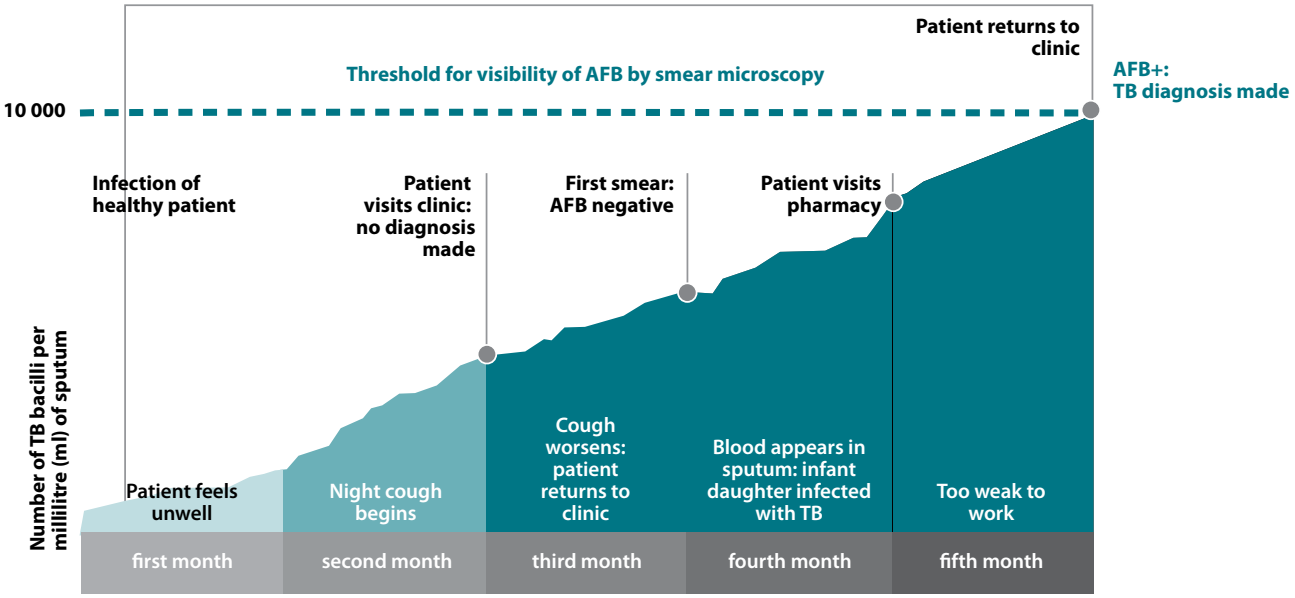


Figure 2.
The slow road to diagnosis of pulmonary tuberculosis (TB) when sputum smear microscopy is used



Over-reliance on clinical signs and symptoms for diagnosis is yet another problem. In malaria, 50–80% of the fever episodes treated on the basis of signs and symptoms are not due to malaria but to other causes.[2] Simple, accurate, robust and affordable point-of-care (POC) tests are not available for most patients seen in community clinics. The lack of simple and accurate tests leads to delayed treatment, multiple clinic visits, and misdiagnosis, all of which result in direct health and financial costs that developing world patients and health systems can ill afford. In pursuing this goal, the Foundation for Innovative New Diagnostics (FIND) is keeping a twin-focus on creating simple technological platforms for diagnosis of several poverty-related diseases, while strengthening the laboratories in low-income countries with high-disease burden.

Critical role of partnerships

New technologies have revolutionized the simplicity, speed, and accuracy of diagnosis of diseases of the developed world. This technological revolution is yet to benefit the diagnosis of diseases endemic to the developing world. What is needed is a robust partnership between the public and the private sector, which can link industry to the diagnostic needs of patients and health systems of the developing countries. A public–private partnership model has gained significant credibility over the past 5–10 years. An evaluation study has shown that such partnerships deliver more efficiently and with less risk than private or public sector-only approaches (Figure 3). The growth in credibility has been matched by a growth in popularity, as evidenced both in sheer numbers (having grown 12% yearly for more than 10 years) as well as funding (having more than doubled research and development (R&D) spending in the past 5 years).[3]

FIND, a non-profit, public–private partnership is a leader in the diagnostics development arena. FIND provides a bridge, as an honest broker, that facilitates industry, academia and disease control programmes of developing countries to work together to develop new tests, without any commercial interests. Through this bridge, industry and academic researchers gain access to clinical trial sites and reference clinical specimens. In exchange, industry assigns all their rights to FIND for use of their technologies in the public and non-profit heath sectors in the developing world, while they retain all rights on these new technologies for the more lucrative for-profit private sector. This provides industry with a strong incentive to generate profit within the private sector worldwide, while allowing the public and non-profit sectors in the developing world royalty-free access to the same technology.

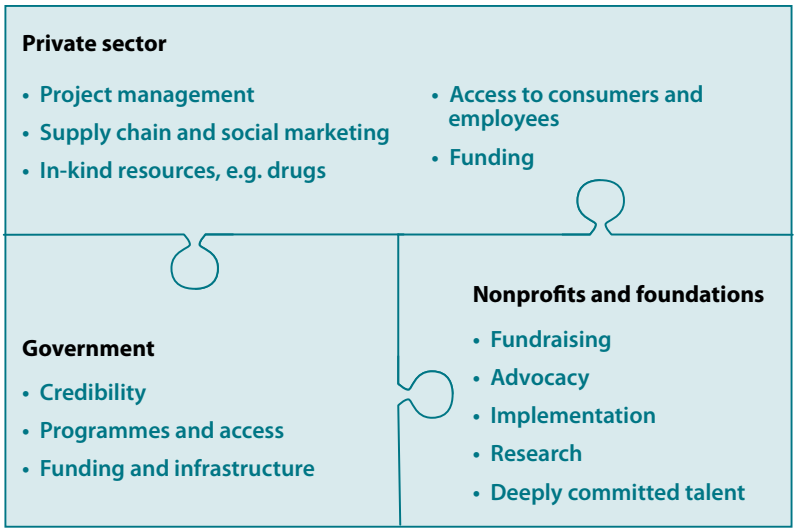
Partnerships are also needed at country level for the adoption and implementation of new technologies in national disease control programmes. At this level, FIND plays the role of a catalyst, as has been shown in the recent introduction of liquid culture for TB diagnosis in the national reference laboratory in Lesotho. This involved the full renovation of the laboratory, acquisition and installation of equipment, establishment of standard operating and quality assurance procedures, and re-training. The partnership involved FIND; Partners in Health (PIH), with funding from the Open Society Institute; the Lesotho Ministry of Health and Social Welfare; and the World Health Organization (WHO) Stop TB Department. The conventional culture and Drug Susceptibility Testing (DST) procedures were streamlined, and liquid media for culture and DST introduced. The South African Medical Research Council, a WHO supranational reference laboratory, ensured external quality assurance for drug susceptibility testing. Through this collaboration, Lesotho now has capacity for diagnosis of multidrug-resistant TB, at a standard previously only obtained in top-level laboratories in the developed world.[4]

The challenge of uptake of new tests

Renewed interest in diagnosis has led to high expectations that tests are being developed that will provide disease control programmes

Figure 3.
In a partnership, each player contributes skills in a critical and distinctive way

A **public–private partnership** is "a continuum of loose-to-tight arrangements that **combines different skills and resources** from institutions in the public and private sectors with the aim of **effectively tackling** socio-economic problems like education and health that persist in the face of independent action"



Such a relationship has important dimensions:

- It is a cross-sectoral and innovative alliance between the public and private sector sharing a common goal.
- It pools the best of different sectors together, working with a shared vision and decision-making, mutual contribution of resources and some shared accountability for results.
- It plays a value-added role to achieve impact that no single player could have managed independently.

with easier, simpler and more accurate tools for case detection. It is also anticipated that better diagnostic tests will improve quality of care and strengthen overall health systems. However, the availability of new tests will only have an impact if laboratories and the health system overall are ready to embrace them. Past experience with the introduction of new tools in developing world national health programmes has shown that there is often a significant delay between availability of evidence that the tools are efficacious and their eventual introduction into use.

Four critical challenges stand in the way. First, the new technologies must be matched to the specific diagnostic needs of a particular disease. If we take the example of TB, the need is for tests that are capable of diagnosing active tuberculosis (both pulmonary and extra-pulmonary disease) with a high degree of sensitivity and specificity. Other high- priority needs include tests that can diagnose TB in children; tests for detection of multidrug- and extensively drug-resistant TB; and tests that could predict progression of disease in patients with latent TB infection, as these might allow targeted preventive treatment.

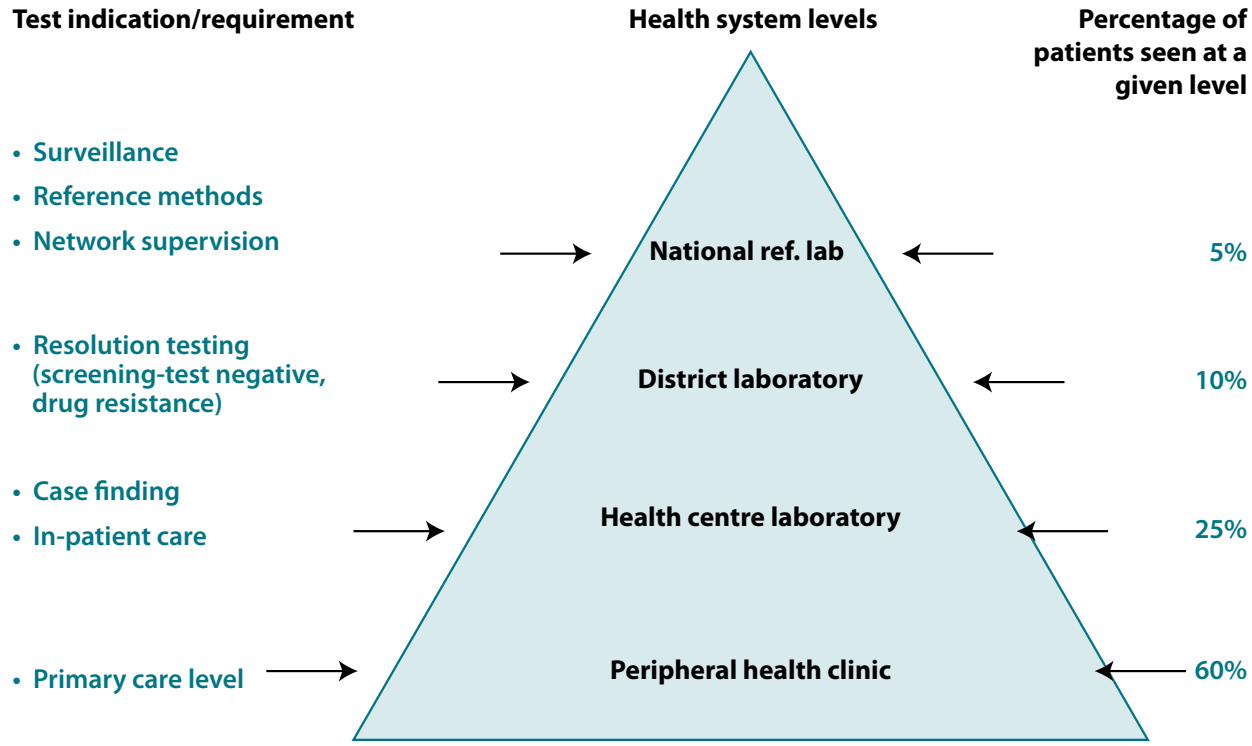
Second, the tests must respond to the operational needs of the health systems, i.e. what the health providers want. The needs of health-care providers lie at different levels. At the lowest level of the health system, where the majority of patients first seek health care, the need is for simple, accurate, and qualitative case-detection tools for point of care (POC) testing, where early treatment and transmission interruption could have the greatest public health impact. FIND currently devotes 75% of its resources to the development of tests for this health system level, for TB, human African trypanosomiasis and malaria. At national referral levels, the need is for higher resolution tools for such indications as multidrug- and extensively drug-resistant TB testing. The differential needs at different levels of the health system are captured in Figure 4.

"With renewed interest in strengthening their health systems, low- and middle-income countries today can receive funding from financing mechanisms like the Global Fund, inspired by the countries' own priorities."

Third, the state of readiness of the health system for change requires special mention. Health systems have to be positioned to embrace rapid integration of new tests as they become available. The introduction of new tests into national disease control will involve stakeholders at both the global and national levels. Engaging stakeholders in the process from start to finish is critical for success. The process will need to overcome many challenges: weak or non-existent legal and regulatory frameworks; inadequate capacity to manage laboratory and diagnostic services; inadequate capacity to manage supplies; inadequate infrastructure, equipment, and support services; human resource constraints in terms of sufficiency and adequacy of health workers, particularly in the public sector; resistance to change; potential misappropriation of resources; country-specific regulatory requirements; lack of leadership; lack of capacity to manage change; and financial constraints.

Fourth, financing the introduction of new tests into control programmes is the single most important limiting factor, in the absence of funding through financing mechanisms like the Global Fund. With renewed interest in strengthening their health systems, low- and middle-income countries today can receive funding from such sources, inspired by the countries' own priorities in strengthening infrastructure, to support uptake of new technologies.

Figure 4.
Diagnostic needs at different health system levels



This is particularly applicable to the low-income, high disease-burden countries in Asia and sub-Saharan Africa, where the dominant source of funding for laboratory infrastructure, equipment, and supplies is through external donor support. For emerging economies with high disease burden, where 80–100% of funding for laboratory equipment and supplies in the public health sector is provided through national budget allocations, this is not an issue. The laboratories in these countries are better equipped, and regulatory in vitro devices (IVD) compliance is being streamlined with international regulations. In these countries, the issue is of local requirements for evaluation and development of the tests in order to obtain registration and access to the public health sector.

Other funding opportunities include PEPFAR, the President's Malaria Initiative, the World Bank and UNITAID, an international product purchase facility established to help scale up access to high-quality drugs and diagnostics to fight AIDS, malaria and tuberculosis. This new initiative, promoted by Brazil, Chile, France, Norway and the United Kingdom, is funded primarily by innovative financing mechanisms such as tax on air tickets.

Affordability of new tests

The issue of affordability of new tests is critical. FIND has an interesting intellectual property policy that assures access by lower-income, high-burden countries at special negotiated prices. This is achieved in a variety of ways, depending on the nature of the project, maturity of the technology, size of the company, and extent of FIND's total investment. When there is significant intellectual property (IP), FIND typically seeks an irrevocable, royalty-free license to the IP for the public sector in developing countries. If necessary, FIND may purchase the IP outright to ensure access. In other cases, when IP is either irrelevant or not negotiable, negotiated product pricing may be the primary mechanism to ensure affordability.

It is to be understood that in the long term the countries themselves should be looking at the day they will be able to foot the full bill of the diagnostic services from domestic resources. This will not be possible if tests are not affordable.

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Biography

Vinand M Nantulya *is Senior Policy and Implementation Officer at the Foundation for Innovative New Diagnostics (FIND), which he joined in February 2006, having previously been Senior Health Advisor at the Global Fund to Fight AIDS, Tuberculosis and Malaria. Before that, he served as Senior Research Scientist in International Health at the Harvard School of Public Health. He has also worked as Senior Research Scientist and Head of Programmes at the International Laboratory for Research on Animal Diseases (ILRAD) and as Director for Strategy at the African Medical and Research Foundation (AMREF). He is Professor of Health and International Relations at the Geneva School of Diplomacy, University of Geneva.*

The control of neglected tropical diseases using access to available medicines through public–private partnerships

Alan Fenwick
Peter J Hotez
David H Molyneux

In Africa it is estimated that two thirds of the population (approximately 500 million people) are harbouring one or more infections among the list of 'neglected tropical diseases' (NTD) detailed in Table 1.[1, 2] This list could easily include several other diseases such as dengue fever, foodborne trematodes and scabies. Significantly, most of those infected are from the poorest populations in rural communities, and yet the burden of disease suffered is unnecessary because the five most common infections (soil transmitted helminths (STH); lymphatic filariasis (LF); onchocerciasis (river blindness); schistosomiasis; and trachoma) can each be controlled with an annual treatment. There are five drugs to be used: albendazole or mebendazole (against STH) ; albendazole and Mectizan (ivermectin) in combination against LF; Mectizan against onchocerciasis; praziquantel against schistosomiasis, and Zithromax (azithromycin), against trachoma, which when administered appropriately will immediately alleviate symptoms and eventually control or eliminate the diseases.[3]

STH are the most common of these infections with over one billion individuals estimated to be infected worldwide. STH are often considered asymptomatic, yet all infections are debilitating, and moderate to heavy infections of *Ascaris sp.* (hookworm) in children can cause significant malnutrition, anaemia, intestinal blockage, stunting, cognitive deficits, and other symptoms. LF causes the most horrific disfigurements when adult worms induce a cascade of pathology associated with lymphatic system malfunction and bacterial and fungal infection of the limbs in particular. This has an extremely detrimental effect on the lives of infected individuals as their limbs, genitals and breasts swell to gross proportions. If uncontrolled, onchocerciasis can lead to unbearable itching and discomfort, and in the longer term, to blindness. Schistosomiasis affects an estimated 200 million people worldwide, over 80% of these cases in Africa, causing symptoms from blood in urine and stool, anaemia, retarded growth, liver damage, calcification of the urinary tract, cancer of the bladder and haematemesis. Although rarely recognized as the cause of death, schistosomiasis probably causes over 200 000 premature deaths per year.[4] Trachoma is the world's most common cause of preventable blindness, a disease of poverty and lack of hygienic water.

Individual NTDs do not hit the radar screen of disease burden. The combined burden due to all NTDs is now realized to cause an estimated 56.6 million 'disability-adjusted life years (DALYs), more than malaria (46.5) and tuberculosis (TB) (34.7), and more than half the burden attributed to HIV (84.5).1 In short, NTDs are important infections that cause significant morbidity and mortality, and yet many are easy to treat.

The disease burden caused by NTDs is preventable. A single annual dose of albendazole will effectively deworm children and prevent serious debilitating disease. An annual dose of Mectizan combined with albendazole will arrest transmission of LF if 70% coverage of the total population is achieved. Six years of mass drug administration in infected areas is sufficient to eliminate new cases of infection. Regular washing of limbs will also alleviate symptoms of lymphodema of the limbs. An annual dose of Mectizan will rapidly stop the itching caused by onchocerciasis microfilariae (larvae), and will prevent further eye damage and blindness, provided only the anterior segment of the eye is affected. An annual dose of praziquantel kills schistosomes, stops immediate symptoms in children and prevents children from developing serious sequelae in later life. Meanwhile an annual dose of Zithromax will cure active *Chlamidia* infections that cause trachiasis, and prevent blindness. Damaged eyelids can be operated on to prevent the blindness caused by scratching of the cornea.

"The Mectizan Donation Programme (MDP) was established in 1988. The realization that Merck manufactured a drug which could save the sight and alleviate the symptoms of people in onchocerciasis-affected areas, who were otherwise unable to pay for it, led Merck to embark on a long-term programme of donation."

The cost of these drugs, the fact that those in need have little or no income, and the recommended strategy for mass drug administration (MDA) to whole populations place the treatments beyond the reach of the poorest individuals, and of the governments

of the poor countries in which the diseases mostly occur. This is where the public–private partnerships (PPPs) can play such a vital role.

Ministries of health and education need to be convinced of the value of treatments. Nongovernmental organizations (NGOs) and other implementing agencies need to be funded to offer support in training and delivery. But most of all, the pharmaceutical industry is needed, because a donation of the appropriate drugs is the only way for these diseases to be controlled.

Why should MDA be the preferred strategy? Diagnosis is expensive and in some cases less than definitive. Sometimes, whole populations need to be treated, or certainly whole generations of pre-school or school-aged children. The drugs are administered orally and only annually, and are safe enough not to require medical supervision. The constraints to embarking on MDA are continuity of drug availability and funds for training and delivery. The cost of delivering these drugs has been estimated at just US$ 0.50 per person per year when delivered at scale – the best buy in public health – provided the drugs can be donated.

"A window of opportunity exists to offer better health to the poorest of the poor and give children in Africa a healthier start to life by using pharmaceutical industry donations in the most appropriate way."

The first pharmaceutical company to meet this responsibility was Merck & Co., Inc. The Mectizan Donation Programme (MDP) was established in 1988 to provide medical, technical and administrative oversight of the donation of Mectizan by Merck for the treatment of onchocerciasis. The realization that Merck manufactured a drug which could save the sight and alleviate the symptoms of people in onchocerciasis-affected areas, who were otherwise unable to pay for it, led Merck to embark on a long-term programme of donation through a broad partnership involving the World Health Organization (WHO), the World Bank, national governments and NGOs.[5] Ten years later in 1998, the MDP mandate was broadened to include the donation of Mectizan for the elimination of LF in areas that are coendemic for onchocerciasis and LF, extending the programme to most of Africa.

When it was realized that a combination of Mectizan and albendazole was effective in rapidly reducing microfilariae in the blood of LF infected people,[6] the hypothesis was developed that six years of annual treatment with Mectizan and albendazole could eliminate LF from endemic areas. GlaxoSmithKline (GSK) immediately made a commitment to "donate albendazole to WHO for every country that needs it until LF is eliminated as a public health problem" GSK became a proactive partner with WHO, with country health ministries and with the Global Alliance for the Elimination of Lymphatic Filariasis (GAELF), which included NGO partners. GSK committed to provide funds for alliance building, support centres, monitoring and evaluation, workshops, meetings and communications. They worked through WHO and regional Programme Review Groups, but ensured that programmes are owned and run by the countries. GSK has built employee pride, enhanced the company reputation and with the albendazole donation programme continues to meet societal expectations.[7]

In 1998, Pfizer partnered with the Edna McConnell Clark Foundation to establish the International Trachoma Initiative (ITI), dedicated solely to the elimination of trachoma around the world.[8] Through the ITI, Pfizer provides Zithromax free of charge for approved programmes, and to date has implemented with partners in Egypt, Ghana, Mali, Morocco, Nepal, Niger, Sudan, Tanzania, Viet Nam, and other countries. The ITI expects countries to implement more than just a drug delivery programme, and prior to awarding Zithromax, plans are required for scale–up of drug delivery, and implementation of the ITI 'SAFE' strategy (surgery, antibiotic delivery, face washing and environmental improvements).

There is currently no global praziquantel donation programme, although WHO have been working with Merck to start such a donation. One company, MedPharm, has independently arranged the donation of up to 16 million tablets of praziquantel annually to treat over 5 million children through the Schistosomiasis Control Initiative (SCI).[9] The SCI was established first at the Harvard School of Public Health in 2001 with seed funding from the Bill and Melinda Gates Foundation (BMGF). In 2002 SCI moved to Imperial College, London, and was awarded almost US$ 30 million by the BMGF to prove the principle of country commitment to controlling schistosomiasis and the effectiveness in controlling morbidity of an annual treatment regime. This started the first national programmes in sub-Saharan Africa against schistosomiasis and STH, although earlier successes had been demonstrated in Brazil, China and Egypt.[10] It should be noted that although albendazole is the drug of choice for STH, GSK has no donation programme for areas where there is no LF, because of the scale of the need. However, in 2006, Johnson and Johnson launched a donation programme for mebendazole and this is expected to expand with time.

For some of the diseases in Table 1, however, there is currently no possibility of MDA, thus for trypanosomiasis, leprosy, leishmania and guinea-worm disease, alternative strategies are needed. Human African trypanosomiasis (HAT), and the related American Chagas disease can only be treated with expensive and painful therapy after diagnosis,[11] and so vector control, better diagnostic tools and better medication are urgently needed.[12] The same is true of leishmaniasis. OneWorld Health, a US based NGO, and the Drugs for Neglected Diseases Initiative (DNDi) are both striving to find tools against leishmaniasis.[13] For guinea-worm disease the eradication programme is close to success,[14, 15] with only southern Sudan and Ghana harbouring significant numbers of infected people. This disease, which has been eradicated from so many countries by the efforts of WHO and the Carter Center needs only health education, water filtration and improved sanitation.

Progress and results

WHO is guided by a 2001 World Health Assembly resolution (WHA–54.19), which required every country to offer deworming and schistosomiasis treatment to children in endemic areas and to treat 75% of children by 2010. To date several countries are close to this target (Burkina Faso, Cambodia, Nepal and Uganda), but there is a long way to go.

Onchocerciasis has been controlled in 11 countries, known as the OCP countries because they were the first countries to be treated by

the Onchocerciasis Control Programme (OCP), which initially (1974 –1988) used vector control alone until Mectizan became available through the donation by Merck in 1988, when control combined the two approaches. Surveillance, and treatment with Mectizan where necessary, continues in these countries. The successor of OCP, the African Programme for Onchocerciasis Control (APOC) now delivers approximately 60 million Mectizan treatments annually to a further 19 countries through community-directed treatment (CDT). GAELF has expanded its programme exponentially from 3 million treatments in 1999 to over 45 million in Africa in 2006, and a total of over 381 million treatments were delivered to 43 countries in 2005. However, there is a need for further expansion of coverage in Africa, especially in countries in conflict. SCI has reached 20 million individuals in six countries in 2006, but has expanded coverage to two more countries in 2007. This is just 10% of the cases in Africa, and so much more praziquantel and funds for delivery are needed.

The International Trachoma Initiative has reached 10 million people in 11 countries to date and is expanding coverage annually. The programme has proved to be successful and one of the intiative's flagship countries, Morocco, is very close to elimination of the disease.[8]

The way forward

WHO, with partners, APOC, ITI, GAELF and SCI, and with like-minded individuals from the BMGF, Sabin Institute, the Earth Institute (Columbia University) and others, have been considering for several years the possibility of integration of efforts against NTDs, brought on by the realization that with expansion, mostly funded by the BMGF, an overlap of activities was emerging. They determined that in the future, efforts against some co-endemic neglected diseases should be integrated, and a drug package designed that would have a 'rapid impact' on health, especially among young children, pregnant women and adolescents. Accordingly, these NTD partnerships are working together in an alliance known as the Global Network for NTD Control. In collaboration with the Global Network,[16] new donors are required to provide the funds needed for delivery of the donated drugs – perhaps a total of US$ 200 million per year for five years. The United States Agency for International Development (USAID) and Geneva Global Inc. have already come forward with donations, and so the prospects for the future are positive.[1]

The partners recognize that there are potential benefits to integrating control activities against these diseases, but there are also challenges and risks.

They recommend that there is a need for research to evaluate integrated programmes, and to evaluate the perceived benefits, which might include:

- greater impact and cost effectiveness of multiple interventions;
- shared expertise and greater reach into communities;
- strengthened health systems.

They recognize that there are challenges for international groups:

- Could there be more adequate collaboration between alliances and industry (PDCI, WHO NTD department)?
- Could there be an alignment of goals and intervention strategies?
- Could WHO develop guidelines and collect experiences on the use of multiple medicines?

Challenges also exist for country programmes because:

- Country-specific solutions will be required.
- Collaboration between country disease programmes will need to be encouraged and developed.
- Drug distributors will need training for multiple interventions.
- Monitoring and safety will be vital.

Finally, there will be risks, which have been identified as:

- the potential loss of focus on achieving individual programme goals (e.g. LF elimination vs. other control programmes);
- the loss of identity for individual programmes;
- additional complexity of managing multiple interventions;
- managing adverse experiences;
- possible public resistance to multiple interventions.

Thus, research studies are needed to ensure that mathematical models predicting post-treatment infection rates are accurate, so that frequency of treatment can be determined on epidemiological evidence. Monitoring for possible emergence of drug resistance will be needed, because reports already exist suggesting possible resistance to benzimidazols[17] and ivermectin.[18] New possibilities for control such as the use of therapies targeting *Wolbachia* for both filarial and onchocerciasis control should be vigorously explored.[19–21] In general though the authors firmly believe that the present is a time for action, and a window of opportunity exists to offer better health to the poorest of the poor and give children in Africa a healthier start to life by using pharmaceutical industry donations in the most appropriate way.[22]

Table 1.
The major neglected tropical diseases

Protozoan infections	Helminth infections	Bacterial infections
Leishmaniasis (VL + CL + MCL) African trypanosomiasis (sleeping sickness) Chagas disease	Soil-transmitted helminth (STH) infections: Ascariasis-trichuriasis-hookworm Lymphatic filariasis (LF) (elephantiasis) Onchocerciasis (river blindness) Schistosomiasis Dracunculiasis (guinea-worm disease) Cysticercosis	Leprosy Trachoma Buruli ulcer

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Biographies

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Peter J Hotez *is the Walter G Ross Professor and Chair of the Department of Microbiology, Immunology and Tropical Medicine at the George Washington University, where his major research and academic interest is in vaccine development for neglected tropical diseases and their control. He is the President of the Sabin Vaccine Institute, a non-profit medical research and advocacy organization through which he founded the Human Hookworm Vaccine Initiative, supported by the Bill and Melinda Gates Foundation. He is the Founding Editor-in-Chief of the Public Library of Science (PLoS) Tropical Neglected Diseases, the recipient of several major awards, and the author of over 250 technical and scientific articles.*

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The story of ASAQ: the first antimalarial product development partnership success

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Introduction

ASAQ, the new fixed-dose combination of artesunate (AS) and amodiaquine (AQ), is now available to treat malaria throughout sub-Saharan Africa. The first drug developed by the FACT (fixed-dose, artemisinin-based combination therapy) partners, ASAQ is being made available by the non-profit product development partnership, Drugs for Neglected Diseases initiative (DNDi), in partnership with pharmaceutical company, sanofi-aventis.

ASAQ is an innovative product to treat malaria that is: adapted to the needs of patients of all ages and is a fixed combination of two well-known drugs. Following World Health Organization (WHO) recommendations it uses a simple once-a-day regimen; is easy to manage for the clinician and the patient; is accessible at an affordable price (as a non-patented drug); and is of high quality, in terms of production, packaging and stability.

The development of ASAQ can serve as a model for future drug development to treat neglected diseases. It is important therefore to understand the rationale and the process behind the development; the partners involved in the development, production and promoting availability; and the steps taken in the registration and post-registration phases to ensure that ASAQ reaches the populations who can most benefit from it.

Public health need for improved antimalarial treatments

Globally, approximately 3.6 billion people are at risk of malaria,[1] with 60% of an estimated 350 to 500 million clinical disease episodes occurring annually in sub-Saharan Africa.[2] In Africa, malaria remains the single largest cause of death for children under the age of five years, where it kills one child every 30 seconds; or approximately 3000 children every day.[3] Efficacy studies have shown evidence of rising resistance of *Plasmodium falciparum* to the antimalarial drugs chloroquine and sulphadoxine/pyrimethamine (SP); both widely used for the treatment of uncomplicated malaria.[4, 5]

In response to increasing inefficacy of chloroquine and with the aim of slowing the spread of drug resistance in malaria-endemic regions,[6] WHO in 2001 recommended the worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated falciparum malaria. The combination of artesunate (AS) plus amodiaquine (AQ) was recommended specifically for Africa, based on clinical evidence that had been compiled by the United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) starting in 1998. Figure 1 shows the countries where ASAQ could be of potential benefit.

In 2006, WHO developed guidelines for the use of ACTs as first-line treatment for falciparum malaria everywhere, and in fixed-dose combinations (FDCs) when possible.[7] FDCs, which are user-friendly drug regimens,[8–11] have the potential advantages of improving patient compliance and dosing accuracy;[12] eliminating the risks associated with monotherapy;[13, 14] improving drug safety, effectiveness and acceptability[12]; thereby slowing down the development of resistance to ACTs;[15] and being less expensive than the sum of the individual products as separate tablets or blister packs.[16]

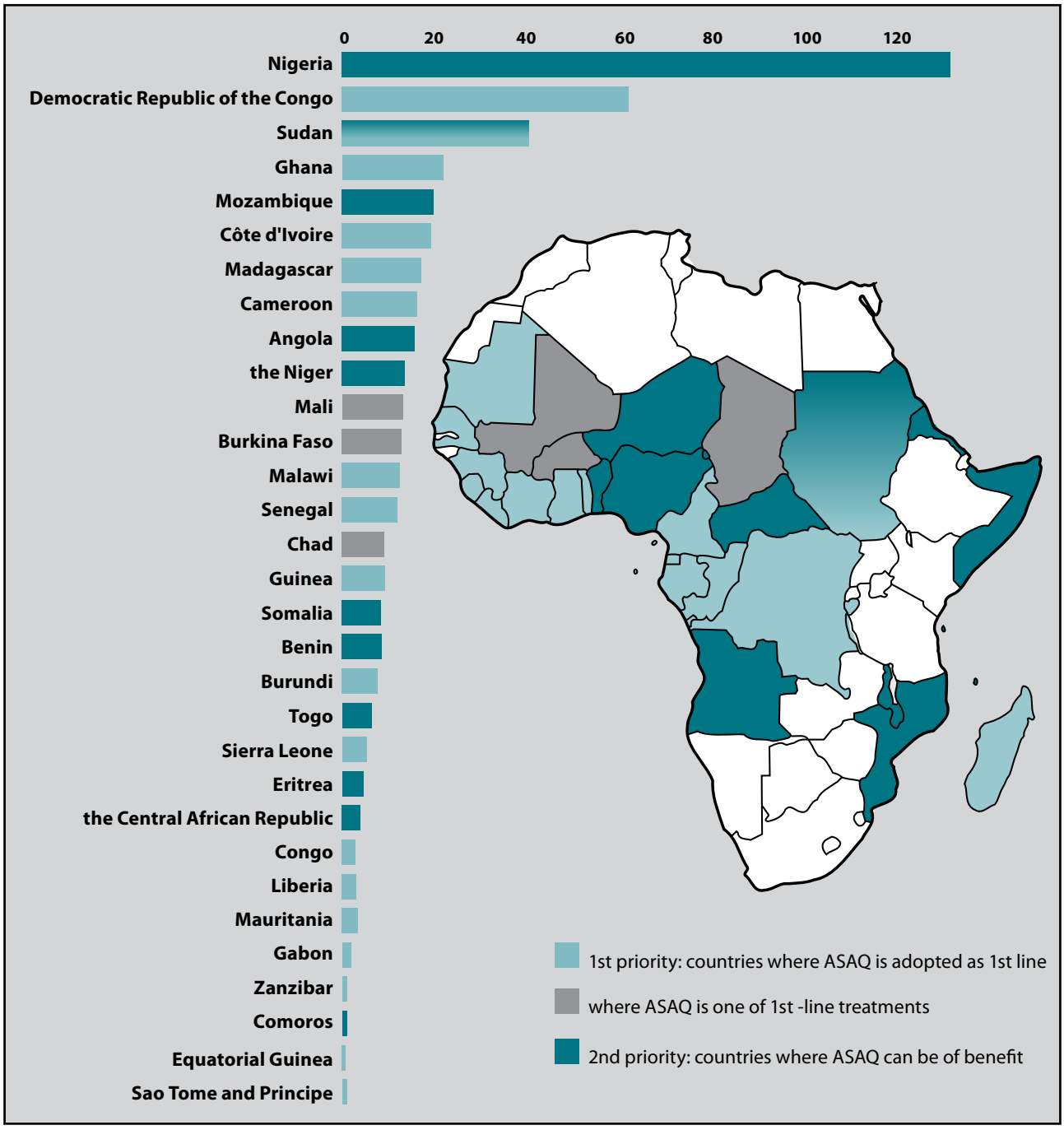
In view of the immediate need to secure changes in antimalarial treatment policy,[17] the FACT project commenced in 2002 to develop two fixed-dose ACTs, including a fixed-dose combination of AS+AQ for international registration that would improve compliance and would be available to all countries where resistance to amodiaquine was low (mainly African countries, but also some Asian countries such as India and Indonesia). Efforts were coordinated by TDR and the Drugs for Neglected Diseases Working Group (DND-WG), which evolved into DNDi in 2003. The development of a fixed-dose combination of AS and AQ was completed by the FACT partners in collaboration with the world's fourth-largest pharmaceutical company, sanofi-aventis, following an agreement signed in December 2004.

Scientific evidence in support of ASAQ

AS and AQ are well-known drugs. Scientific evidence supporting the use of the combination of AS and AQ can be divided into two groups: studies supporting the use of non-fixed-dose combinations of AS plus AQ; and studies supporting the use of fixed-dose combinations (FDC) of ASAQ. Multiple studies have cumulatively included approximately 10 000 patients taking the combination of AS and AQ.

In two separate field studies, which have cumulatively studied ~1500 patients in five sub-Saharan African countries, the documented efficacy of fixed-dose ASAQ has been >95% comparable with both the non-fixed dose combination[18] as well as with Coartem, the only other available fixed-dose ACT. Table 1 outlines the major studies supporting the use of ASAQ.

Figure 1.
Potential public health impact of artesunate + amodiaquine in Africa



The partnership to produce ASAQ

The FACT-ASAQ project, modeled with core and support partners, is considered an innovative partnership because ASAQ has been produced as a "non-exclusive, not-patented, not-for-profit public good" and because developing and developed countries have shared assets and capabilities to produce ASAQ.

The FACT-ASAQ project was facilitated by the extensive research networks built primarily by the two coordinators (MSF, later DNDi; and TDR) with a number of critical partners: Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Mahidol University, Université Victor Segalen Bordeaux II (TROPIVAL), University of Oxford, and University Sains Malaysia (Table 2). All partners contributed their technology, experience, relevant assets, and in some cases finances, to various aspects of the project. When necessary, protocols, scientific methods and other information were discussed and disseminated as part of the training and technology transfer among the partners. In addition to these partners, other organizations, including contract research organizations (CROs) and some smaller pharmaceutical companies, also contributed to the project.

Figure 2.
Simplified dosing regimen with fixed-dose ASAQ. The bi-layer formulation of ASAQ allows for AS and AQ to be taken together, in correct proportions, and with less tablets as compared with non-fixed dose options

	Fixed-dose ASAQ artesunate/amodiaquine 3 dosage strengths available	Co-blistered, non-fixed AS+AQ artesunate/amodiaquine AS: 50mg; AQ: 13mg
Infants (<8 kg)	AS: 25 mg AQ: 67.5 mg	
Young children (8–17 kg)	AS: 50 mg AQ: 135 mg	
Children (17–35 kg)	AS: 100 mg AQ: 270 mg	
Adults (>35 kg)	AS: 100 mg AQ: 270 mg	

Since the end of 2004, DNDi and the FACT partners have collaborated with sanofi-aventis. Existing data – including the stable ASAQ formulation developed by the FACT partnership – was exchanged with sanofi-aventis, who then carried out additional pre-clinical and clinical studies, which were used to compile the marketing authorization application and/or registration file.

As with most product development partnerships (PDPs), funding for the development and production of ASAQ came from both public (original public donors, EU INCO DEV FP5,[22] and TDR have been joined by the following governments: Dutch DGIS,[23] French AFD,[24] Swiss SDC,[25] and UK DFID[26]) and private sources (MSF and sanofi-aventis). In the unprecedented agreement signed between DNDi and sanofi-aventis, no patent protection was sought, and a non-exclusivity agreement was signed between the two parties. Non-exclusivity implies that a marketing authorization will enable third parties to submit simplified applications for a generic version of the drug. ASAQ is being provided for the benefit of underprivileged patients, and both DNDi and sanofi-aventis intend wide distribution across malaria-endemic regions.

Getting ASAQ to the patients who need it

Without compromising drug quality, efficacy, or safety, sanofi-aventis, with the support of DNDi, chose to register ASAQ in Morocco and in malaria-endemic countries as well as to apply for WHO prequalification, in order to allow internationally recognized experts to assess the quality, safety and efficacy of ASAQ. sanofi-aventis manufactures ASAQ and has followed the customary approach to first register a drug in the country of manufacture and to register the brand (in this case, Coarsucam®). The registration process started in December 2005, with marketing authorization granted on 1 February 2007. As of July 2007, ASAQ has also been registered in 17 African countries (Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Gabon, Ghana, Guinea, Ivory Coast, Kenya, Madagascar, Mali, Mauritania, Tanzania (Zanzibar) and Togo). The WHO prequalification process has been chosen based on WHO's regulatory documentation on artesunate and on amodiaquine: Arsumax® (sanofi-aventis artesunate) is already WHO prequalified. The prequalification dossier was submitted to WHO on 23 February 2007.

ASAQ is packaged as Artesunate-Amodiaquine Winthrop® (ASAQ) in boxes of 25 individual blisters at cost price (<US$ 0.50 for children less than 5 years of age and <US$ 1 for older children and adults – constituting a 'no profit, no loss' price) to the public market (national health services and nongovernmental organizations) in malaria-endemic countries. The drug is also available as Coarsucam™ in individual boxes to the private market at prices adapted to local markets, and Coarsucam™ Impact Malaria (boxes of 25 blisters) for the sanofi-aventis Access Card Program (CAP)[27] pharmacies. This tiered form of pricing is aimed at protecting the different antimalarial markets, while offering uniform quality of the same drug. It can be described as a 'one drug, two prices, three packaging' arrangement.

In working to facilitate the implementation and availability of ASAQ, DNDi is engaging a number of partners, including individual experts, countries and regions, WHO and other international organizations, national malaria programmes, research institutes, contract research organizations, funding agencies, and nongovernmental

Table 1.
Studies examining ASAQ

Study name	Study location & duration	Patient population	Primary objective	Major findings
Artesunate and amodiaquine for the treatment of uncomplicated falciparum malaria: a systematic review of safety and efficacy data.[19]	19 countries (18 African). Relevant studies took place from 1999–2006.	Meta-analysis reviewed 27 comparative studies: 4173 patients on AS+AQ and 6477 on a comparator drug.	A systematic review of all documented studies evaluating the efficacy and safety of AS+AQ for uncomplicated falciparum malaria.	For relevant studies (not all had 28-day PCR-corrected data nor robust safety data): AS+AQ more effective than single agent treatment or non-artemisinin-based combinations. AS+AQ day 28 cure rates after PCR correction similar to other ACTs. AS+AQ "well tolerated".
Use of weight-for-age-data to optimize tablet strength and dosing regimens for ASAQ for treating falciparum malaria.[20]	Sub-Saharan Africa. March 2006.	Weight-for-age reference database of 88 054 individuals from sub-Saharan Africa. Data taken from demographic health surveys, observational and intervention studies, and standardized for sex, age and malaria risk.	To design a practical age-based dosing regimen that provides the smallest risks of over- and under-dosage by minimizing the number of age categories and maximizing the proportions of patients predicted to receive doses of AQ and AS within newly defined therapeutic ranges.	Optimal paediatric strength (p): 25/67.5 mg AS/AQ. Optimal adult strength (a): 100/270 mg AS/AQ. Overall dosing accuracy of 83.4% and 99.9% for amodiaquine and artesunate, respectively, was seen with regimen of five age categories: 0–1 months: ½ p 2–11 months: 1 p 1–5 years: 2 p 6–13 years: 1 a > 14 years: 2 a
A comparative clinical assessment of fixed-dose artesunate/amodiaquine (ASAQ), versus loose formulation of artesunate + amodiaquine.[18]	Burkina Faso. October 2004–February 2006.	750 children with acute uncomplicated falciparum malaria. Aged 6 to 59 months, ≥5kg.	To evaluate the efficacy of ASAQ as compared with the non-fixed combination (AS+AQ) in terms of PCR-corrected parasitological cure rate on day 28. Safety also assessed.	**Efficacy** Fixed-dose ASAQ cure rate: 95.7%. Non-fixed-dose AS+AQ cure rate: 96%. **Safety** No unexpected adverse events occurred during this study, with the FDC easier to use and well tolerated.
Comparison of fixed-dose combinations, artesunate/amodiaquine (ASAQ) versus artemether-lumefantrine (AL), in the treatment of uncomplicated falciparum malaria.[21]	4 countries: Cameroon, Madagascar, Mali, Senegal. March–December 2006.	941 patients including 437 children infected with *P. falciparum*. Adults or children weighing ≥10kg.	To evaluate the efficacy (clinical and PCR-corrected parasitological cure rate on day 28 of ASAQ compared with AL (Coartem®)).	Preliminary results show >95% PCR-corrected cure rate at day 28 for both fixed-dose ASAQ and ARLUM, with good clinical and biological safety seen.

Table 2.
Key partners responsible for the development of ASAQ

Development step	Institutions involved
Vital to the efforts of the FACT Project throughout the entire period of development has been the contribution and expert advice of academics.	University of Oxford (United Kingdom) / Mahidol University (Thailand).
Pharmaceutical and preclinical development	**Pharmaceutical and preclinical development**
Preformulation of fixed-dose combinations of ASAQ by developing fixed-ratio oral forms, coordination and local support with partners in the Bordeaux region.	Tropival of Université Victor Segalen Bordeaux II (France).
Formulation of combination product adapted with appropriate stability and biopharmaceutical characteristics and with a viable manufacturing process. Development and validation of analytical methods. First scale-up coordinated with Rottendorf Pharma.	Ellipse Pharma (France).
Set of good laboratory practice-based toxicology studies on single drugs and combinations.	Unitox and Genotox (Brazil).
Development and utilization of toxico-kinetic protocols, bioanalytical methods.	University Sains Malaysia (USM) (Malaysia).
First industrial scale up and good manufacturing practice-based production of the FDC for clinical and stability studies.	Rottendorf Pharma (Germany); Créapharm (France).
Innovative partnership signed with industrial partner.	sanofi-aventis: Contract signed, Dec 2004.
Clinical development	**Clinical development**
Phase I for pharmacokinetic data, biopharmaceutical quality and bioavailability.	USM (Malaysia).
Field-based Phase III to examine efficacy and tolerability of fixed-dose ASAQ vs. non-fixed AS+AQ in children <5 years of age.	CNRFP (Burkina Faso). Cardinal Systems (France).
Support of 10-year survey of efficacy, tolerability, and pharmacovigilance in Senegal.	Institut de Recherche pour le Développement (IRD) (Sénégal), Ministère Français des Affaires Etrangères (FAC 2000 programme), Ministère Français de la Recherche (PAL+), TDR. As of 2007: Ongoing in year 7.
Support of meta-analysis of 31 clinical studies examining AS+AQ vs. other antimalarials.	TDR with FACT partners, MSF/Epicentre.

organizations. Such activities include for instance: the coordination of a study by its founding partner, the Indian Council of Medical Research, to facilitate the adoption of a new antimalarial policy in India; a regional workshop convened with another founding partner, the Kenya Medical Research Institute, to engage national malaria control programme managers and international and regional organizations; and the sponsorship of a tolerability study to be coordinated by MSF/Epicentre. DNDi has convened an independent panel of experts, the FACT Implementation Advisory Group, to provide independent advice and critical guidance about issues related to ASAQ implementation and rational use and towards ensuring equitable access. Also, DNDi will use the sanofi-aventis payment (3% of the net private sector earnings over a period of seven years) to further lower the drug's public sector sale price.

Implications of ASAQ for development of other needs-driven drugs

DNDi was founded in 2003 as an independent, not-for-profit product development partnership (PDP) by five publicly-funded research organizations: Malaysian Ministry of Health, Kenya Medical Research Institute, Indian Council of Medical Research, Oswaldo Cruz Foundation in Brazil, and the Institut Pasteur in France, along with MSF and TDR (as permanent observer). DNDi is the first

initiative of its kind committed to fighting against the most neglected diseases (such as human African trypanosomiasis, leishmaniasis, and Chagas disease) which burden the developing world. As a patient-needs-driven, 'virtual' R&D organization, DNDi does not conduct research but instead capitalizes on existing fragmented R&D capacity, complementing it with additional expertise as needed. DNDi's project portfolio in June 2007 includes 22 projects at different stages of development.

DNDi anticipates the launch of the second product of the FACT partnership: an FDC of AS and mefloquine (MQ) targeted for South-East Asia and Latin America. Having developed ASMQ in collaboration with Farmanguinhos (a state-owned pharmaceutical company in Brazil), DNDi will manufacture, register, and market the drug in collaboration with Cipla, a major pharmaceutical company in India, for South-East Asia. A major impetus to undertake this project was that the loose combination of AS and MQ has been widely used in Thailand for the past 13 years, and has been proven to be effective and safe for the treatment of uncomplicated falciparum malaria in South-East Asia and Latin America.[28–31]

The successful launch of ASAQ is clear evidence of DNDi's progress as a PDP, whose strength lies with its focused management of private and public partners. By virtue of the success of the FACT project, PDPs have been clearly demonstrated as being capable of producing public goods.

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Biographies

Bernard Pécoul, *Executive Director of the Drugs for Neglected Diseases initiative (DNDi), has served as a physician with Médecins Sans Frontières (MSF) and has managed public health projects in Honduras, Malaysia and Thailand. Co-founder and Director of Research and Training at Epicentre, he also served as Executive Director of the French section of MSF, overseeing 100 field projects in 40 countries. From 1998 to 2003, he was Executive Director of the MSF Campaign for Access to Essential Medicines, where he advocated for policies to lower drug prices, increase research into neglected diseases, and re-produce unprofitable but medically necessary drugs.*

Ann-Marie Sevcsik*, Scientific Communications Manager at the Drugs for Neglected Diseases initiative (DNDi), has worked in medical communications for the past three years after doing medical, molecular research on hepatitis and HIV during graduate work at the University of California, San Francisco, and undergraduate studies at Harvard University.*

John Amuasi, *a frequent consultant with the Drugs for Neglected Diseases initiative (DNDi), trained as a physician in Ghana and recently graduated from the University of Minnesota in the USA with a masters in health policy.*

Graciela Diap *is Medical Coordinator for the new fixed-dose combination of artesunate and amodiaquine (ASAQ) in the new Fixed-dose Artesunate-based Combination Therapies to treat falciparum malaria (FACT) project and facilitated and accelerated the optimal implementation of ASAQ in Africa. Trained in internal medicine, she has spent 15 years working with MSF.*

Jean-René Kiechel, *Manager of the new Fixed-dose Artesunate-based Combination Therapies to treat falciparum malaria (FACT) project, has gained over 30 years experience in pharmaceutical research and development (R&D) since earning a PhD in Chemistry (minor in Pharmacology) from the University of Basel in Switzerland. He has worked in various industry-based scientific management positions in France, Switzerland and the USA with Sandoz, Bristol-Myers Squibb, Rhone-Poulenc Rorer, and sanofi-aventis, and has contributed to the successful registration of half a dozen drugs and several investigational new drug (IND) applications.*

Managing intellectual property for global health outcomes: the example of product development partnerships

Robert Eiss

Introduction

As first demonstrated by the Commission on Health Research for Development, the distribution of research resources across the spectrum of health problems reflects a stark imbalance, with some of the most important determinants of disease burden, such as enteric and acute respiratory infections, relatively neglected. Narrowing the resource gap requires strategic commitments both from public agencies in high-income countries, which represent the significant majority of global public expenditure on health research, and counterparts in developing nations. Moreover, the pharmaceutical and biotechnology industries are deterred from investing in products to reduce disease burdens in low-income countries due to concerns with recouping investment and lack of adequate delivery infrastructure, among other considerations. A well-cited seminal review by Médecins Sans Frontières (MSF) demonstrated that, among therapeutic interventions licensed from 1975–1997, only 1% were specific to tropical diseases.

"PDPs are charting new territory. They must make deals that extend well beyond the scope of conventional commercial agreements, stipulating access conditions to ensure the product reaches the target population."

Rectifying these imbalances will require coordinated efforts among the diverse systems of donors and institutions that engage in the global health research enterprise, as well as novel incentive structures to reduce upstream and downstream constraints on the ability of the research community to deliver global health products. These include the ownership and allocation of intellectual property, data sharing, issues related to manufacturing capacity and regulatory requirements.

One of the most progressive developments in addressing neglected diseases is the establishment of public–private partnerships (PPPs) to catalyse research and development. Numerous precedents now exist, such as the Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development and the International AIDS Vaccine Initiative (IAVI). The emergence of product development partnerships (PDPs) over the past decade has provided a unique mechanism – a hybrid public/private approach – by which to generate new products for the neglected diseases of poverty. PDPs employ a variety of strategies to achieve their goals, from creating new technologies to ensuring that the technology developed is available and affordable to as many beneficiaries as possible in the developing world. The challenge lies in providing access to needed technologies and bargaining how the technology is to be distributed or marketed, while simultaneously offering appropriate incentives to partners that enable the commitment of research, development and manufacturing resources. PDPs are charting new territory in that they are based on operational and intellectual property (IP) management models that borrow from both the public and private sectors.

Unlike traditional research and development (R&D) agreements, PDPs must make deals that extend well beyond the scope of conventional commercial agreements, stipulating access conditions to ensure the product reaches the target population. These terms and conditions frequently focus on strategic use of intellectual property, and often have to address such issues as market segmentation, pricing and distribution.

Several PDPs are reaching maturity, with products in clinical development for poverty-related diseases, having reached workable solutions to ensure access and affordability, from planning production, to meet the size of demand, to end-user acceptability of the new product. And although many PDPs are still in early development and face significant challenges as more projects progress to the clinical stage, they may be pioneering a new form of social contract related to international public goods and the transfer of technology, with broad ramifications for the development of needed medical products for non-viable markets.

There is no single business model being pursued. PDPs vary from 'virtual organizations', that contract all aspects of product development to universities and private companies, to those that have developed considerable international capacities and expertise in product management and regulatory affairs. They employ a diverse range of negotiated agreements, including licensing agreements, know-how and distributor agreements, sponsored research contracts and other arrangements. Although their business models vary, PDPs employ a common set of strategies in managing IP for global health outcomes, usefully summarized by A Taubman. These include:

- defining territorial markets: separating industrialized markets from developing countries, or focusing on target markets;
- enabling earnings from high-income markets to subsidize product availability in developing countries;

- often establishing distinct pricing structures for the public sector, social marketing, and private markets;
- balancing more open licensing for the public sector with exclusivity over lucrative markets, as an investment incentive for partners;
- enabling a covered technology or product to extend to applications relevant to 'western' markets when feasible, as a negotiating tool and investment incentive;
- establishing royalty rights in a manner that benefits the party requiring the greatest incentive;
- providing for access to the developed technology in the event that the research/industry partner abandons the project or does not pursue developing country access requirements.

To cite one representative example, as part of its synthetic biology work the University of California at Berkeley has developed a new method of microbial drug production for the anti-malarial drug artemisinin. The technology was licensed royalty-free to the Institute for OneWorld Health (iOWH) and to a spin off company, Amyris, to scale-up this low-cost production process. The process could potentially reduce the cost of artemisin-based therapy to 10% of the current price. Through an integrated and shared enterprise the University of California at Berkeley will engineer the drug precursor-producing microbe; Amyris will develop the large scale fermentation process needed to produce the product at commercial scale; and iOWH will perform the needed regulatory work to demonstrate bioequivalence of the microbial-produced product and pursue current supply-chain and distribution models. Once the production process is in operation, Amyris will transfer it royalty-free to iOWH, which is expected to license the drug to a developing country company to manufacture and distribute at cost.

"An effective and efficient drug development pipeline requires the continued development of an international clinical trials system that engages local investigators, communities and ethical review committees."

Ensuring product availability and access

As PDPs plan for access, they now face a series of practical and conceptual challenges to ensure supply, affordable price and effective delivery once the product is successfully developed. An early elaboration of requirements and approaches for access is critical so that plans are not developed incrementally or after the product is developed. Indeed, experience demonstrates that even where certain products were developed for distribution in developing countries, uptake has been sluggish or stalled due to a variety of downstream considerations; for example, the combination anti-malarial Coartem, praziquantel for the treatment of schistosomiasis, or the slow uptake of hepatitis B vaccines.

Pricing issues

A key consideration in access negotiations is target pricing. PDPs typically require the product to be made available at affordable or reasonable prices, which may lead to complex negotiations on how to calculate price or consideration of available price-discriminating models. Setting price is contingent on both parties knowing in advance the technical details of production, marketing and distributions costs. A clear framework to compute manufacturing cost is required. Since many PDPs enter negotiations based on early-stage discoveries, stipulating price in a contractual arrangement can be an impractical prospect. In most instances, the cost of the final product is the cost of production plus a reasonably negotiated mark-up (e.g. cost-plus).

Market segmentation

Market segmentation has emerged as a common issue in negotiation. Although there are common sources for differentiating between countries (e.g. World Bank income data) challenges emerge with the division of rights in so-called 'mixed payer' markets such as Brazil and India. As more agreements are pursued, it may be useful to generate descriptive case studies on tiered pricing and its effectiveness at segmenting domestic markets. A correlative need is to establish methods to limit or prevent arbitrage or leakage between public to private markets, or between targeted sectors.

Early-stage licensing

Research universities remain a primary source of early stage discovery, core technologies and often of lead compounds. They are the source that will drive the global health pipeline through basic discoveries of molecular and cellular mechanisms in health and disease. Through licensing schemes with both PDPs and conventional industrial partners, universities are adopting several approaches to transfer technologies in a manner that offers the broadest benefit to populations in need. These include commitments to humanitarian licensing as an extension of the university's public mission. Their role in PDPs will likely become even more pronounced as these partnerships seek new and innovative drug leads and exploit advances in functional genomics and proteonomics.

There are several constructive actions that could assist PDPs in their interactions with academic institutions, including the establishment of inventories of the IP rights held, and licensing status in key global health fields. A prototype database is in development at the US National Institutes of Health, based on the US Federal Interagency Edison database of invention reports. At the institutional level, there is growing interest among technology transfer offices to operate against metrics aligned with both economic and social goals. Moreover, the Association of University Technology Managers (AUTM) – a leading professional society of global scope – is considering new initiatives in performance metrics, which potentially could facilitate academic licensing to PDPs if measurements incorporate global health or global access considerations.

A second crucial source of early-stage discovery and new drug targets are small biotechnology firms. These firms offer an exceptionally diverse set of high-technology platforms. However, small firms are often concerned about weakening their commercial positions by sharing platform technologies for use in the development of non-commercial products. The types of outreach initiatives that have been undertaken with universities, through organizations such as Intellectual Property in Health Research and Development (MIHR) and the AUTM, may equally benefit small biotechnology companies (e.g. dissemination of case studies). A key challenge

is to demonstrate creditable demand to encourage risk-taking by corporate partners. In several areas, such as HIV, pneumococcal and rotavirus vaccines, useful modelling work is being pursued to assess demand and its implications for financing mechanisms.

Negotiating the IP landscape

Each of the PDPs practice due diligence and where needed engage in IP mapping exercises to ensure 'freedom to operate' and avoid prospects of being blocked or unduly stalled. The IP assembly issues are becoming more challenging due to the increasing need for proprietary tools. This is a particular challenge with regard to broad umbrella or vaccine component patents, where a variety of technologies may be required to express or purify an antigen, bolster immunity or devise a delivery system. Related problems include royalty stacking and lack of ownership of IP to cross license.

Responses to patent thickets include mapping of licenses, as well as exploration of creative licensing schemes. There is an emerging range of IP management tools that can be applied depending on the particular needs of the scientific challenge. However, more systematic efforts are needed to identify where and when current or emerging IP management strategies might best be considered, and to facilitate their application. The challenge may be to identify the specific technology platforms around which the alignment of public–private interests are ripe and the key institutions to bring together in such a consortium-based approach. Negotiating the patent landscape and access to research tools is a general challenge for the scientific community. But creative models in the health sciences may find the most fertile ground in the context of global health products, since they represent non-commercial or 'low margin' R&D.

Systemic challenges

Intellectual property management is one of a set of necessary skills or requirements that may reduce the time-lag between development and implementation. PDPs are helping to frame innovative solutions to manage IP to advance global health R&D and engage needed partners. Most importantly, an effective and efficient drug development pipeline will require the continued development of an international clinical trials system that engages local investigators, communities and ethical review committees. It will require robust local systems for quality control and regulatory approval, and legal systems within manufacturing countries that enable the supplier to effectively support and protect its patent rights. Another key need is greater engagement of the scientific community and funding agencies in operational and health services research, including methods to adapt interventions to local conditions and integrate them into existing services.

Conclusion

A number of actions could both contribute to a wider understanding of issues surrounding IP and product access, and strengthen the capacities of public–private partnerships in health product development to manage IP for global health outcomes:

- developing best practice guidelines and disseminating these widely;
- developing and disseminating case studies on different IP approaches related to market segmentation, tiered pricing, and royalties, among other topics;
- organizing inventories of IP rights held, and licensing status in key global health fields;
- encouraging academic licensing practices that make products more accessible to impoverished populations, and provisions within research sponsorship agreements that are responsive to the special requirements of PDPs;
- supporting IP mapping and/or IP landscape analysis for products of particular priority, or disseminating such landscapes where available;
- instituting training programmes and personnel exchanges to build research and technology management competencies and partnerships in low- and middle-income countries;
- encouraging needed market analysis, such as estimates of demand, to engage corporate interest.

PDPs have matured and progressed along the continuum from R&D to dissemination. Many have secured funding and negotiated successful deals with now numerous partners. Deals are highly contextual, and although best practices will continue to emerge and be refined, a set of best principles or working tenets is clearly established to ensure product access and availability. In all cases, however, the role of IP in PDP agreements is to provide incentives for private investment in public health and to structure and define the nature of the relationship among the partners, with regard to how rights will be shared or exercised. There is nothing particularly novel about the terms of agreement reached by PDPs; rather it is their totality as a public–private hybrid that sets them apart. Collectively, PDPs are broadening our creative understanding of practical ways to resolve the public policy dilemma of balancing private incentive to generate needed R&D investment against the goal of access guarantees to those in need.

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Biography

Robert Eiss, *a graduate of the University of Maryland at College Park and Oxford University, has held senior management positions at the United States National Institutes of Health (NIH), where he presently serves, and the White House Office of National Drug Control Policy. He helped to initiate the Multilateral Initiative on Malaria, started a cooperative venture between NIH and the World Bank to assess the effects of health on productivity at the household and macroeconomic level and conceived the 'Global Forum on Bioethics'. He also served as Chief Executive Officer of an international nongovernmental organization to promote the innovative management of intellectual property.*

Regulatory strategies of product development partnerships: some perspectives

Chris Hentschel
Jörg Möhrle
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Product development partnerships (PDPs) first appeared on the health scene in 1999. Bringing together partners from both public and private sectors, PDPs were created to fill an urgent need for new health tools to diagnose, cure, and prevent diseases that kill millions of people every year but are not profitable enough to drive the commercial research and development (R&D) that normally delivers product innovation. They promised an innovative way out of the 'market failure' that had practically brought R&D for neglected diseases to a halt.

Despite their broadly common objectives, well-established PDPs have differing points of view on regulatory strategies and the concomitant safety and quality validation that these strategies sustain. Some, like the Medicines for Malaria Venture (MMV), rely on established regulatory pathways that historically have been synonymous with the highest international quality validation. Others believe time is of the essence because we are catching up after years of inaction and, therefore, are exploring newer pathways, including approval in the country of manufacture, and then of use, so as to reach patients as quickly as possible. Yet others hold that it is not international validation but rather supporting and strengthening the growing expertise in developing countries that provides the best option. All understand that they are acting on behalf of the most vulnerable patients in developing countries and seek to ensure that the medicines whose development they support are safe and of high quality.

It is noteworthy however that most PDPs do not explicitly endorse a particular registration strategy. Here we examine MMV's regulatory strategy and compare it to other PDPs.

Standards are a critical element of the ICH drug development process

An international or International Conference on Harmonisation (ICH) drug goes through many stages in its life cycle before it reaches the patient. Each stage must be conducted according to codified standards of good clinical practice (GCP), good laboratory practice (GLP) and good manufacturing practice (GMP).

The drug R&D process starts with the identification of a molecular target in the pathogen/parasite. Libraries of compounds are screened to find those that selectively inhibit the target. These 'hit' compounds are then tested for drug-like qualities and a 'lead' compound selected, which is then re-engineered and optimized until it can be considered a 'drug candidate' ready for preclinical testing in animals. This entire discovery process takes between 3 and 5 years.

Once a drug candidate enters preclinical development, the cost of goods, compound scalability, stability and safety are assessed. The candidate compound also undergoes preclinical animal safety studies. If no significant toxicities are detected in animals, the compound is tested for the first time in healthy human volunteers (Phase I). In Phase II clinical trials the activity of the compound against the disease, and its optimal dosing, is determined. In pivotal Phase III clinical studies the drug's efficacy is confirmed against a comparator product in large populations.

The whole process can take up to 10 years and costs can be as high as US$ 800 million[1,2] (for a comprehensive review see Nwaka and Ridley).[3]

After completion of clinical development, the sponsor will submit a comprehensive drug dossier, containing the results of all the above tests, to a regulatory authority to obtain authorization to market the drug. Regulatory authorities are the final stumbling block in this journey, and they have the final say on whether the drug gets to market. As a new drug has to be registered in each country of use, registration dossiers are typically submitted to several countries simultaneously.

When safety and efficacy data quality is paramount

MMV was created to discover, develop and deliver safe, effective and affordable antimalarial drugs through effective public–private partnerships. Its goal is to bring drugs of the highest validated quality to the underprivileged at the lowest possible cost – a mission aligned with World Health Organization (WHO) former Director-General, Gro Harlem Brundtland's aspirational pledge "The era of poor drugs for poor people is over".

Drug regulation and the origins of ICH

The challenge of providing safe and effective medicines has grown with the 'chemotherapeutic revolution' of the 20th century. While this revolution has unquestionably enhanced

public health, it has had its share of serious setbacks. Indeed, changes in the way drugs are regulated have been typically "borne out of adversity, out of events that have killed and injured thousands.[4]"

A concern for drug quality led to the publication of the United States Pharmacopoeia in the late 1820s. Over the following decades regulations were instituted to guard populations against the sale of inferior, adulterated, or often downright dangerous food and drugs. In 1862 a single chemist was appointed to the Department of Agriculture, marking the birth of the US Food and Drug Administration (FDA), the oldest federal agency dedicated to consumer protection.

After numerous tragedies (such as the well-known thalidomide case in the 1960s) caused by medicinal products that had not been evaluated to rigorous standards, regulations were tightened in the name of safety. Drug manufacturers had to prove to the FDA that their products were safe and effective before they could go on the market. Many countries followed the US example and implemented laws and regulations for the evaluation of new medications. However, these regulations were often inconsistent with each other and created a very complex and non-transparent environment for the development and approval of new medications.

In 1989, a WHO conference of Drug Regulatory Authorities (ICDRA) initiated the first step towards harmonization of these various regulations. In April 1990, the representatives of the regulatory agencies and industry associations of Europe, Japan, and the USA met to plan the International Conference on Harmonization (ICH) and discuss terms of reference. The ICH also includes three observers, WHO, the EFTA (European Free Trade Area represented by SwissMedic) and Health Canada, as well as the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).[5]

The regulatory authorities of countries adhering to ICH and those that participate in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme [6] (e.g. Malaysia, Singapore and South Africa) are often referred to as 'stringent regulatory authorities'.[7] The ICH's achievements include producing guidelines for evaluation and approval of new medicines that are consistent between countries and scientifically sound.

To validate the quality of products from its pipeline MMV usually requires their initial evaluation by a stringent regulatory authority (SRA) that possesses adequate resources, expertise and track record to assure the highest validation of drug quality, safety and efficacy (see box above). Naturally, to market or distribute a drug in a country requires the additional approval of the National Regulatory Authority (NRA) of that country. However, MMV recognizes that while some regulatory authorities in developing countries have, or aim to have, the resources and expertise to review complex new drug applications[8] and assess adherence to GCP and GMP, most do not. Thus if quality is paramount and not just a phrase with little operational basis, a thorough review by an SRA is needed to assure compliance to internationally recognized quality and safety guidelines and importantly assist endemic country NRA in assessing drugs for local conditions.

MMV is thus committed to ICH standards not only during the conduct, analysis and reporting of individual clinical trials, but also by submitting its products for registration to an ICH-conforming regulatory authority for marketing approval or opinion. To date MMV and partners have submitted two full regulatory filings, to the European Agency for the Evaluation of Medical Products (EMEA) and to SwissMedic respectively. This approach is not only part of its guiding principles, but is also critical to MMV's close collaboration with the pharmaceutical industry partners, which by and large are "firmly committed to ensuring that all their medicines meet the high standards needed to ensure patient safety.[9]"

Other PDPs such as the TB Alliance and the International Partnership for Microbicides[10] have regulatory philosophies similar to MMV's. "Our goal is to gain approval for any product we develop from stringent regulatory authorities as well as from others [NRAs]," stated M Spiegelman, director, Research and Development, Global Alliance for TB Drug Development. Mr Spiegelman further noted that besides its strong commitment to reach a universal standard of quality, the TB Alliance feels that stringent regulatory approval might in some instances offer a quicker approach to drug availability in high-burden countries whose NRAs trust the quality determined by these agencies. In addition, and in view of TB-related variables, new and better drugs are urgently needed in all countries not just the least developed.

Quality validation alternatives

WHO prequalification. Arguably, stringent regulatory authorities such as the FDA, EMEA or SwissMedic are not really the most appropriate bodies to evaluate drugs for diseases that are not endemic to these regions. Yet the countries most in need of such regulatory competence often do not have the capacity to ensure the safety and quality of medicines from different suppliers around the world or, for reasons of national sovereignty, do not wish to rely on the currently small number of SRAs.

To address this problem, as well to help guide procurement decisions by international bodies, WHO initiated its **prequalification project** in 2001. It is important to stress that WHO prequalification is not intended as an alternative to NRA marketing approval but to support and complement it.

The prequalification process can take from six months to several years depending on the complexity of the case under review. Companies wishing to have a product prequalified voluntarily submit a dossier to WHO, to allow qualified assessment teams to evaluate its quality, safety and efficacy. The manufacturer must also open its manufacturing sites to an inspection, using regulatory experts from among 28 of the world's leading national regulatory agencies, including experts from Europe, Canada and Australia. These are typically the very same experts who work for the stringent regulatory authorities.

EMEA's Article 58. Another validation method allowing new drugs for neglected diseases to be assessed by an SRA is EMEA's Article 58. This article, the result of a consultation and collaboration between EMEA and WHO, establishes a mechanism whereby the EMEA may give a 'scientific opinion' for the evaluation of certain medicinal products for human use intended exclusively for markets *outside* the EU.[11] An analogous option of this type is not yet offered by the US FDA. RTS,S, the malaria vaccine candidate under development by GlaxoSmithKline Biologicals in partnership with the PATH Malaria Vaccine Initiative, will be one of the first vaccines to follow that route.

When saving time is paramount

The Drugs for Neglected Diseases Initiative (DNDi) was established in 2003 funded by, and as an initiative of, Médicins Sans Frontières (MSF). Speed was of the essence, and one of DNDi's concerns centred on the delays caused by the time required to obtain sufficient data to satisfy the criteria of stringent regulatory authorities.

To mitigate delays and costs, DNDi with its partner, sanofi-aventis, is employing a regulatory strategy adapted to its priorities. It obtained initial registration of its new antimalarial ASAQ in the country of manufacture, Morocco, and has subsequently submitted the dossier to a number of malaria-endemic countries and to WHO for prequalification.[12] As Morocco is not part of ICH[13] nor is it usually considered a reference regulatory authority for antimalarial drugs, the organization subsequently emphasized that it was not attempting to bypass internationally recognized quality standards but was relying primarily on the WHO prequalification process to validate the safety and efficacy of its product. "In making that choice, we reaffirmed our compliance with internationally recognised quality standards. Morocco is where this drug is manufactured, and it is customary to register a drug first in the country of manufacture.[14]" The prequalification process is currently ongoing. The speed advantage is yet to be proven, what is already clear, however, is that this strategy can attract controversy and thus requires additional time and resources to communicate its benefits to stakeholders. In this context, DNDi also states, "We reject the argument that 'Western regulatory authorities' are the only ones that are qualified to address public health issues in the developing world."

WHO prequalification and procurement through international organizations

Prequalification by the WHO is one of the criteria stipulated by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), GAVI (Global Alliance for Vaccines and Immunisation) and the United Nations Children's Fund (UNICEF), for the medications they purchase. The prequalification procedure is accelerated if the newly developed drugs, aiming for procurement via these funding agencies, have prior approval from an SRA ("Abridged procedure if approved by stringent authorities like EMEA and USFDA"[15]). However, the capacity of the prequalification project assessors is already quite stretched, as a result only five antimalarial products have been prequalified of the 20 submitted.[16]

At the PATH Malaria Vaccine Initiative (MVI), too, a desire to accelerate the development process, while maintaining quality, is an ongoing challenge – but chiefly for the product manufacture phase. MVI values speed, but with a clear caveat: "Safety is our first priority throughout the development process; we are also on the lookout for regulatory pathways that would speed up availability of a vaccine," stated Christian Loucq, director, MVI. "That's why we are looking at India and China, where manufacturing standards are able to fulfil WHO requirements. It must be remembered that the bulk of vaccines being used in most countries today are produced in India at WHO prequalified facilities."

Indeed, MVI does not compromise on the safety and quality of its clinical trials – research is always conducted to ICH GCP standards. In due course, MVI might consider collaboration with manufacturers in developing countries such as India and, subsequently seek registration in the country of manufacture and WHO prequalification, in order to produce a vaccine at a lower cost. As international procurement agencies will only buy WHO-prequalified products (see box above) the latter step is considered essential and could bring the product to market 18 months sooner, saving lives.

MVI thus chooses a regulatory strategy both suited to vaccines and pragmatism, without compromising on quality. The final marketing decision, of course, lies with the NRAs.

Conclusion

Whatever the ultimate criteria are regarding regulatory strategies, be it quality, speed, or suitability of the initial regulatory agency, it is clear that PDPs are researching and developing innovative new drugs for neglected diseases, and providing safe, effective and accessible products for vulnerable populations in the developing world. They also share an underlying belief that the mother who buys a new medicine for her child in a developing country deserves similar assurances of safety and efficacy for her child as one seeking treatment at the best clinic in the developed world.

When evaluating different potential regulatory strategies, it is important to recognize, however, that the relative importance assigned to quality, speed, cost and the perceived suitability of the initial regulatory agency, are all organizational preferences that may be radically affected by the disease and technology in question. Regardless of the approach taken, however, the end goal for each PDP is a high-quality, safe and effective product that meets the needs of its users – whoever and wherever they may be.

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Biographies

Chris Hentschel *graduated in biochemistry from King's College, London, United Kingdom. His early career focused on basic biomedical research at Imperial Cancer Research Fund, London; as lecturer at the Swiss Federal Institute of Technology (ETH), Zurich; and as a Fogarty Fellow with the National Institutes of Health, USA. He has been Chief Executive Officer/Scientific Director at the Medical Research Council's Collaborative Centre in the United Kingdom and Department Head at Molecular Genetics, Celltech from 1983 to 1987. In 1999, he became a senior research fellow at the Emerging Technology Program of Wharton Business School. He is also advisor to a European venture capital fund and a member of the Supervisory Board of the Global Medical Forum, Zurich.*

Jörg Möhrle *is Director of Clinical Development at the Medicines for Malaria Venture (MMV). He has extensive experience in basic malaria research and more than 10 years of drug development experience in the pharmaceutical and biotech industries. He holds a PhD and recently obtained an MBA focusing on aspects of the strategic planning of MMV.*

Jaya Banerji *manages communications for MMV. She was instrumental in setting up the communications department for the Drugs for Neglected Diseases Initiative (DNDi) and has worked for over 15 years in both the non-profit and commercial sectors in India, the Middle East, Switzerland and the United Kingdom.*

Acronyms

AAVP	African AIDS Vaccine Programme
ABC	abstinence, being faithful, using condoms
ACT	artemisinin-based combination therapy
AFD	Agence Française de Développement
AMC	advance market commitment
APOC	African Programme for Onchocerciasis Control
ARV	anti-retroviral
ASAQ	artesunate and amodiaquine
AUTM	Association of University Technology Managers
BMGF	Bill and Melinda Gates Foundation
BMP	Blantyre Malaria Project
BOO	build, operate, own
BOOT	build, operate, own, transfer
BOT	build, operate, transfer
CAB	community advisory board
CAP	Access Card Program
CDC	Centers for Disease Control
CDT	community-directed treatment
CIPIH	WHO Commission on Intellectual Property, Innovation and Public Health
CISM	Manhiça Health Research Centre
CME	Continuing Medical Education
CNRFP	Centre National de Recherche et de Formation sur le Paludisme
CRO	Contract Research Organizations
CS	cellulose sulfate
DALY	disability-adjusted life year
DFID	Department for International Development (United Kingdom)
DGIS	Dutch Ministry of Foreign Affairs
DNDi	Drugs for Neglected Diseases Initiative
DND-WG	Drugs for Neglected Diseases Working Group (MSF)
DPT	diphtheria-pertussis-tetanus
DST	Drug Susceptibility Testing
EDCTP	European and Developing Countries Clinical Trials Partnership
EFTA	European Free Trade Area
EMEA	European Agency for the Evaluation of Medicinal Products (European Medicines Agency)
EU INCO	
DEV FP5	European Union International Cooperation with Developing Countries Funding Programme, Round 5
FACT	fixed-dose artemisinin-based combination therapy
FDA	Food and Drug Administration (United States)
FDC	fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
GAELF	Global Alliance for Elimination of Lymphatic Filariasis
GAIN	Global Alliance for Improved Nutrition
GCP	good clinical practice
GDP	gross domestic product
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLP	good laboratory practice
GMP	good manufacturing process
GSK	GlaxoSmithKline
HAT	Human African trypanosomiasis
HPRU	HIV Prevention Research Unit (South Africa)
IAVI	International AIDS Vaccine Initiative
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research

IDC	innovative developing country
IFFim	International Finance Facility for Immunization
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IND	investigational new drug
iOWH	Institute for One World Health
IP	intellectual property
IPM	International Partnership for Microbicides
IRD	Institut de Recherche pour le Développement
ITI	International Trachoma Initiative
IVD	in vitro device
KEMRI	Kenya Medical Research Institute
KCCR	Kumasi Centre for Collaborative Research
LF	lymphatic filariasis
MDA	mass drug administration
MDGs	Millennium Development Goals
MDP	Mectizan Donation Programme
MDP	Microbicide Development Programme
MIHR	Centre for the Management of Intellectual Property in Health Research and Development
MMV	Medicines for Malaria Venture
MQ	mefloquine
MRC	Medical Research Council (South Africa)
MSF	Médecins Sans Frontières
NACO	National AIDS Control Organization (India)
NGO	nongovernmental organization
NIH	National Institutes of Health
NIMR	National Institute of Malaria Research
NTD	neglected tropical diseases
NRA	National Regulatory Authority
OCP	Onchocerciasis Control Programme
OECD	Organisation for Economic Co-operation and Development
PDP	product development partnership
PEPFAR	President's Emergency Plan for AIDS Relief
PIH	Partners in Health
PMI	President's Malaria Initiative
POC	point-of-care
PPP	public–private partnership
QA/QC	quality control/quality assurance
R&D	research and development
RBM	Roll Back Malaria Partnership
SCI	Schistomiasis Control Initiative
SDC	Swiss Agency for Development and Cooperation
SIGN	Safe Injection Global Network Alliance
SOP	standard operating procedure
SP	sulphadoxine/pyrimethamine
SRA	stringent regulatory authorities
STH	soil-transmitted helminth
TB	tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
TPP	target product profile
UNAIDS	United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USM	University Sains Malaysia
WHO	World Health Organization

Key publications of the Global Forum for Health Research

DATA ON R&D FOR HEALTH INVESTMENTS

The Global Forum for Health Research is the only organization that regularly tracks and reports on the world's research and development (R&D) investments for health. It advocates for evidence-informed, efficient and effective investments in research to improve the health of poor and otherwise marginalized populations and reduce health inequities.

Monitoring Financial Flows for Health Research 2007: Behind the global numbers

Mary Anne Burke, Andrés de Francisco, Stephen Matlin (eds.)
2008 (English). ISBN 978-2-940401-04-8

This 2007 collection of studies looks behind the global totals, analysing R&D for health expenditures in Argentina, China, Mexico and the United States. It also looks at investments in the research of cancer and 20 historically high-burden infectious diseases. For many low- and middle-income countries affected by the double burden of both noncommunicable and communicable diseases, matching investments with research priorities is of paramount importance.

Monitoring Financial Flows for Health Research 2006: The changing landscape of health research for development

Andrés de Francisco and Stephen Matlin (eds.)
2006, 95 pages (English). ISBN 2-940286-42-6

This 2006 report describes recent global funding trends and initiatives for research for health, providing estimates of resources spent on R&D for health. It also presents WHO 2003 burden of disease estimates and projections to 2030. The report highlights the vital role of the public sector in all countries to support research for health, to create an enabling research environment and to strengthen research capacity to meet present and future health challenges.

EVIDENCE ON NEGLECTED RESEARCH PRIORITIES

Equity, defined as equality of opportunities among people, is a central component of human rights and stimulates sustained human development. One of the most important ways to achieve health equity is to make sure R&D investments are put towards research that addresses the needs of the least well-off groups. The Global Forum collates information, commissions literature reviews and stimulates debate on research priorities and gaps for the benefit of people in low- and middle-income countries (LMICs).

Research Issues in Sexual and Reproductive Health for Low- and Middle-income Countries

Andrés de Francisco, Ruth Dixon-Mueller, Catherine d'Arcangues
2008, 68 pages (English). ISBN 2-940286-50-7

This joint report (Global Forum for Health Research and World Health Organization) identifies gaps, priorities and multi-disciplinary approaches in sexual and reproductive health (SRH) research, an area identified as the 'missing Millennium Development Goal'. Looking specifically at currently underserved populations in LMICs, this report is a solid contribution to efforts to develop an evidence base for improving the quality, availability and use of sexual and reproductive health information, products and services. It uses a rights-based, life-course framework for analysing and filling gaps in current knowledge of SRH problems as they are experienced by women, men and adolescent girls and boys. The report also raises essential research questions for policy-makers and programme managers to consider to create a favourable policy environment for advancements in SRH.

Research Capacity for Mental Health in Low- and Middle-income Countries: Results of a mapping project

Pratap Sharan, Itzhak Levav, Sylvie Olifson, Andrés de Francisco and Shekhar Saxena (eds.)
2007,156 pages (English). ISBN2-940286-54-X

Although mental and neurological disorders comprise 13% of the global burden of disease and are a leading cause of disability worldwide, mental health remains among the most neglected, poorly resourced and underresearched areas in public health. This joint report (Global Forum for Health Research and World Health Organization) can be used to facilitate evidence-based decision-making in funding and priority setting for mental health research in LMICs. The report, based on a three-year study that mapped mental health research capacity in 114 LMICs in Africa, Asia and Latin America, is the first systematic research study of this scale. Its findings confirm the pressing need to improve research capacity in mental health in LMICs and fill research gaps that obstruct equity in health research. It also makes recommendations to review and strengthen mental health research management.

TOOLS FOR ENHANCING HEALTH EQUITY

Learning from Experience: Health care financing in low- and middle-income countries

Diane McIntyre
2007, 76 pages (English). ISBN 2-940286-53-1

This report offers a framework to assess the performance of health care financing systems and improve their equitability, efficiency and sustainability. By reviewing health care financing in LMICs, this report presents possibilities for optimizing the three main functions of health care financing: revenue collection, pooling of funds and purchasing. The report presents a range of country case studies that highlight factors that have contributed to the successful set-up and implementation of these functions. A user-friendly fold-out table summarizes international experience in the performance of these functions in terms of feasibility, equity, efficiency and sustainability.

The *BIAS FREE* Framework: A practical tool for identifying and eliminating social biases in health research

Mary Anne Burke y Margrit Eichler
2006, 64 pages (English). ISBN 2-940286-43-4

The *BIAS FREE* Framework is an integrative tool that can be used to identify and remove biases in health research that derive from any social hierarchy. This makes the *BIAS FREE* Framework an essential tool for getting at the roots of health-related social inequalities and producing clear and objective research reports, articles and funding proposals for decision-makers. While the *BIAS FREE* Framework is applicable not just to research but also to legislation, policies, programmes and practices, this publication focuses on its application to health research in particular. The Framework's strength lies in its ability to adapt its lens to hierarchy-rooted biases of all types, including gender, race, ability, class, age, geographical location and sexuality.

Application of Burden of Disease Analyses in Developing Countries: Implication for policy, planning and management of health systems

Adnan A. Hyder, Li Liu, Richard H. Morrow, Abdul Ghaffar
2006, 64 pages (English). ISBN 2-940286-41-8

To date, there has been rather scant literature on the application of burden of disease (BoD) measures in LMICs. This publication demonstrates the practical value of

evidence-based decision-making through the collection and application of measures of BoD, such as DALY, QALY and HEALY in 11 LMICs. Reviewing a series of seven case studies supported by the Global Forum for Health Research over a period of several years, this publication shows how BoD measures may be used to highlight inequities and set priorities. The review demonstrates the continuing need for an internationally agreed summary measure that adequately addresses equity issues.

The Combined Approach Matrix: A priority-setting tool for health research

Abdul Ghaffar, Andrés de Francisco, Stephen Matlin (eds.)

2004, 68 pages (English). ISBN 2-940286-26-4

A systematic, evidence-based and inclusive process is critical to identifying and setting the research priorities that will make the greatest contribution to people's health. The Combined Approach Matrix is a tool developed by the Global Forum for Health Research that enables the collection, organization and analysis of the information necessary to set research priorities based on a scientific process involving all stakeholders in health and research for health. The tool facilitates comparisons between the likely cost-effectiveness of different types of interventions. It also helps institutions at the national, regional and global levels ensure that more health research is conducted on the most important and often most neglected areas of diseases and the multi-faceted determinants of health.

No Development without Research
A challenge for research capacity strengthening

Yvo Nuyens

2005, 44 pages (English). ISBN 2-940286-37-X

Research capacity strengthening (RCS) has a strong potential to contribute to health, development and equity. This publication reviews the literature and surveys the successes and failures of RCS in the health field. It also proposes a comprehensive framework for RCS in various functions of the health research system (stewardship, financing, resource generation, production and utilization of research) and in various phases of an iterative research process, from managing the research agenda to producing, promoting and utilizing evidence in policy and practice.

POLICY BRIEFINGS

Why research for health?
Research for Health: Policy briefings (series) vol. 1

2006, 12 pages (English). ISBN 2-940286-47-7

Countries that have invested consistently in the broad spectrum of health research are now advancing rapidly in health and in economic development. In many countries, however, the benefits of health research are not optimized due to low investments, absence of a culture of evidence-based policy-making or lack of capacity. This joint publication (Global Forum for Health Research and Council on Health Research for Development) briefly provides unfinished and new research agendas, new trends in health research, components of favourable national health research systems (NHRS) and suggestions for countries and research sponsors to make research for health work.

VOICES FROM STAKEHOLDERS

A Report on Forum 11
Equitable access: Research challenges for health in developing countries

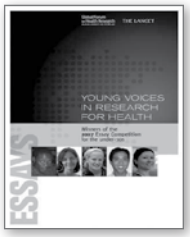
2008, 76 pages (English). ISBN 978-2-940401-03-1

Global Forum for Health Research annual forums are a premier international event in health research for development. In 2007, Forum 11 took place in Beijing, People's Republic of China, bringing together some 600 key stakeholders to discuss research issues, best practices and gaps in securing equitable access. This Forum 11 report provides an overview of the key issues discussed, detailing ideas on the use of evidence in policy- and decision-making, encouraging innovation in research and promoting equity and human rights approaches to health research. Other central themes include: research priority setting, research capacity strengthening, possibilities with inter-sectoral collaboration, advocacy for more research and resources and communication of research results. The publication includes a user-friendly CD-ROM that features the final meeting documents.

Global Forum Update on Research for Health Volume 4
Equitable access: Research challenges for health in developing countries

2007, Pro-Brook Publishing. 180 pages (English).
ISBN 978-2-940401-01-7

In the fourth volume of Global Forum Update on Research for Health, thirty leading institutions and professionals from across the world consider the current state of research in ensuring equitable access to achieve better health in LMICs. This publication provides insights into how research is, or could be, playing a role in identifying and overcoming economic, geographical, institutional, political, socio-cultural and technological barriers to equitable access.



Young Voices in Research for Health 2007: Winners of the 2007 essay competition for the under-30s

2007, 144 pages (English). ISBN 978-2-940401-00-0

«There needs to be more support for research done by researchers and research networks of developing countries themselves under their own leadership and control.»

«Let each one of us be the access. First and foremost, let us be the solution.»

This sample of young people's perspectives on 'Equitable access: Research challenges for health in developing countries' can be found in the anthology 'Young Voices in Research for Health 2007,' which features the complete collection of winning essays. The 2007 Young Voices in Research for Health competition has been jointly sponsored by the Global Forum for Health Research and *The Lancet*.

ABOUT THE GLOBAL FORUM

2006 Review: Innovating for better health

2007, 28 pages (English). ISBN 2-940286-52-3

This review of the Global Forum's activities in 2006 highlights its innovative and comprehensive approaches to health research, recognizing the complex and multi-sectoral origins of factors that determine people's health. It presents a synopsis of the Global Forum's work to make a difference in global health, including initiatives, networks, partnerships, collaborations, studies commissioned, publications and workshops in which the Global Forum has taken a leadership or supportive role.

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The ethical imperative of reducing health inequities, of closing the gap between the health of the poorest and those who are better off, demands the utmost collective effort.

In the last few years, public–private partnerships (PPPs) and product development partnerships (PDPs) have gained growing popularity as mechanisms for increasing access to essential drugs. An expanded pipeline of candidate drugs and vaccines for clinical trials has been established.

***Health Partnerships Review,* a collection of articles by experts and practitioners in the field, aims to contribute to the debate about the future role of PPPs and provide pointers to key areas for urgent attention: greater and more sustainable financing over the longer term and better mechanisms for coordination; strengthening of organizational capacities; creation of legislative, regulatory and service infrastructures and assessment frameworks that will ensure that the new products are effective, safe, affordable and accessible to those in need and that they are taken up and used.**

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