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Innovative Finance for Health

– Exploring Incentives for Neglected Disease R&D

Sida

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Jonas Ahlén, Development Finance Advisor
Peter Lundström, World Infection Fund
Josephine Rudebeck, World Infection Fund

Innovative Finance for Health – Exploring Incentives for Neglected Disease R&D

Department: Development Partnerships

Author: Jonas Ahlén, Peter Lundström, Josephine Rudebeck

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1. Introduction

1.1 Background

In low-income countries infectious diseases account for a large portion of the burden on the health care systems and cause the highest numbers of deaths as well as of lost healthy years[1], even if a shift towards increasing importance of some chronic diseases has occurred[2]resulting in the so called double burden. Based on other publications and health statistics[3] six important communicable diseases (or groups of diseases) in poor countries can be identified: acute respiratory infection, HIV/AIDS, diarrhoea, vaccine-preventable childhood diseases, malaria and tuberculosis. These diseases cause a vast majority of the infectious disease 15 million annual death toll, of which nearly half are children under the age of five.

Considering the above facts, there is an imminent need for research, development and production of new medicines and vaccines targeting diseases that, exclusively or predominantly, affect poor people in developing countries. There is a lack of incentives for the pharmaceutical and biotechnology sector to invest in products and services for developing countries. Estimates put the funding backlog at USD 50 billion per year for global public goods in health.[4]

1 DALYs, Disability Adjusted Life Years, as defined by the World Health Organization (http://www.who.int/healthinfo/boddaly/en/)

2 Olle Edqvist rapport 2007: The potential for Swedish contributions to health research of relevance for poor countries

3 Ann Lindstrand, Staffan Bergström, Hans Rosling, Birgitta Rubenson, Bo Stenson, Thorkild Tylleskär, Global Health: An introductory textbook (Stockholm: Studentlitteratur, 2006), and Dean T. Jamison, 'Investing in Health' in Dean T. Jamison, Joel G. Breman, Anthony R. Measham, George Alleyne, Mariam Claeson, David B. Evans, Prabhat Jha, Anne Mills, Philip Musgrove (eds.), Disease Control Priorities in Developing Countries (: Oxford University Press, World Bank, 2nd edition, 2006)

4 Charles Griffin, Innovative Finance for Global Helath, Brookings Institute 2008

Although traditional donor funding for drugs and vaccines has increased in recent years[5], there is a real need to develop innovative financing mechanisms that can help mobilise additional capital, helping the development of drugs and vaccines for poor people. Creating incentives for the pharmaceutical industry to develop new drugs and vaccines is essential, as well as catalysing private investments that address the diseases of the developing world. The public sector can increase its effectiveness as a R&D funder by actively seeking to promote additional private sector investment. Sida already funds research projects in the health sector, but more can be done to utilise available financing mechanisms, including credits and guarantees.

Official development aid works to distribute funding and technical knowledge to poor countries, but is ill equipped to handle problem oriented initiatives that can mobilise support for innovation and create solutions to poor peoples needs. In sectors that rely on heavy research and technological investments, the global development community has an opportunity to play a catalytic role in product development, with the potential to leverage limited official funds by multiples of private sector investment.

There are several historical cases where development aid has managed to achieve reduced poverty levels and bring about radical change on a global scale by using problem oriented initiatives to support innovation. Examples include the eradication of infectious diseases such as smallpox, decreased child mortality and the development of high yielding agricultural crops. However, many structural constraints exist for industry to allocate resources towards neglected sectors in developing countries – political and legal framework is often opaque, markets are perceived as insecure, purchase power is low etc. Therefore the overwhelming majority of research and development for product development is focused on the needs of the industrialised world. Poor countries are at best peripheral markets with a negligible impact to large corporation's profitability. The developing world only becomes interesting to the private sector as potential markets when the most obvious market risks are removed, and when purchasing power is sufficiently high. A central challenge for the development aid community is to create better incentives for private sector to channel innovation and product development for the needs of poor people.

5 Ewert, Global Health Research Funding Summaries, 2007

Private market funding for the research-heavy biotechnology sector has traditionally come from cash infusions by specialist investors or from multinational pharmaceutical companies through buyouts or licensing deals for the innovations that have been initiated in smaller innovation-focused companies. Bankruptcies in the biotechnology have historically been comparatively few, but the current financial crisis has cut funding for the sector to the lowest level in a decade. Companies that cannot find funding or a strategic partner are likely to face bankruptcy or will simply go into hibernation, doing just enough to keep the company alive and wait for better times. The amount raised by the sector fell by 54% year to date. In the United States, biotechnology companies are raising less cash than they have in a decade with financing falling to $8.2 billion through September, down from $17.9 billion last year.[6] The current funding shortfall is seriously threatening the development of drugs based on biomedical breakthroughs.

1.2 Goal and Purpose of Study

The overall purpose of the pre-feasibility study is to enable an increased cooperation between aid organisations and private business. Specifically, the purpose of this study is to investigate the feasibility of creating a mechanism for the development and manufacturing of affordable drugs and vaccines to address the most important communicable diseases in poor countries.

The main task is to support the development of a mechanism for financing. Importantly, the study should seek to identify the prerequisites for making such a mechanism successful, including potential organisational and budget constraints at Sida as well as its interaction with the pharmaceutical industry. The report should seek to answer the following two questions:

Is there a need for new and innovative systems for the development of drugs and vaccines and diagnostics for poverty related diseases? And if so, is there scope for a potential cooperation between Sida, industry and research community to foster this development?

Although the target sector is drugs and vaccines and primarily will be evaluated within the Swedish research community, this financing mechanism is envisaged to be utilised in other sectors as well.

6 Olmos/Waters, Bloomberg News, 21st November, 2008

1.3 Methodology

The study was initiated by Sida following the study by Claes Lindahl "Att ta itu med fattigdomen", where one of the main recommendations was to investigate new areas to utilise credits and guarantees. The project was commissioned by Johan Åkerblom as a cooperation between Sida and the World Infection Fund (VIF). Methods will include desk studies, interviews with researchers and financiers, as well as surveys targeting key industry representatives. The team-leader for the study will be Jonas Ahlén, independent financial advisor, with co-authors Peter Lundström and Josephine Rudebeck of VIF. A steering group at Sida consisted of Johan Åkerblom, Lars Liljeson, Ulrika Hessling-Sjöström, Viveka Persson, Anders Molin, and Olle Terenius. A reference group assembled by VIF consisted of Anders Björkman, Professor, Karolinska Institute; Vinod Diwan, Professor, Karolinska Institute; Håkan Mandahl, former Deputy Managing Director, Swedish Association of the Pharmaceutical Industry (LIF); Anders Molin, Head of Health Division, Sida; Olle Terenius, Research Secretary, Sida; Göran Tomson, Professor, Karolinska Institute; Claes Ånstrand, Secretary General, World Infection Fund (VIF); Bo Öberg, President Medivir HIV Franchise AB.

1.4 Limitations

For the purpose of the study, the sector limitations will include affordable drugs and vaccines that address diseases in least developed countries, though not limited to infectious diseases. Traditional funding for neglected disease research will be briefly discussed, but the emphasis will be on recent developments in financing mechanisms aimed at engaging with the private sector in the fight against poverty.

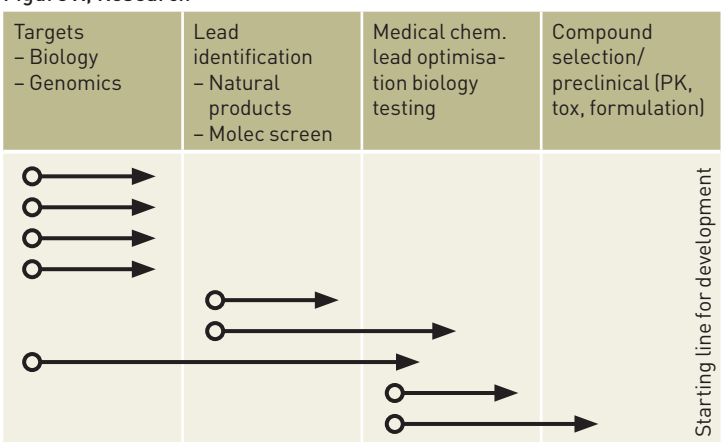
1.5 The Specific Conditions for Health Sector R&D

First and foremost, it is important to establish that health sector R&D is high-cost and high-risk. High-cost since it is time consuming and requires extensive amounts of highly qualified manpower; high-risk since the majority of initiated projects never make it all the way to the market. This is essentially true for all health sector R&D and explains the cautiousness with which more or less all medical projects are considered before they are actually initiated. When it comes to R&D aimed at products that specifically or predominantly target the health issues of poor peoples and societies, the hurdles are even bigger since potential return on investment is significantly lower than for products targeting strong markets.

From idea to product – step by step[7]

One of the central goals of many early-stage research endeavours is to generate knowledge (manifested as scientific publications) rather than to obtain actual medicines or other products. As illustrated in Figure X below many projects never make it as far as the second step. On the other hand new projects may be initiated along the drug discovery path, but generally very few proceed to the end, i.e. the starting line for *development* (see below, Figure Y for next steps). This line typically also represents the end of *public sector* funding.

Figure X, Research



The Industrial Drug R&D Process

The industrial R&D process for drugs can basically be divided into four components (of which the first three have been covered in Figure X above):

1. Identification of a biological system, or target, the inhibition of which will result in a desired therapeutic effect.
2. Discovery of classes of molecules that inhibit this system and the undertaking medicinal chemistry to optimise the efficacy of compounds while limiting their toxicity (5 to 7 years).
3. Selection of compounds as potential drugs and non-clinical testing and evaluation to assess whether they have the characteristics suitable for clinical development (1 to 2 years).
4. Clinical testing, development and registration (5 to 8 years).

7 This chapter is based on, and adapted from material from Medicines for Malaria Venture (http://www.mmv.org/).

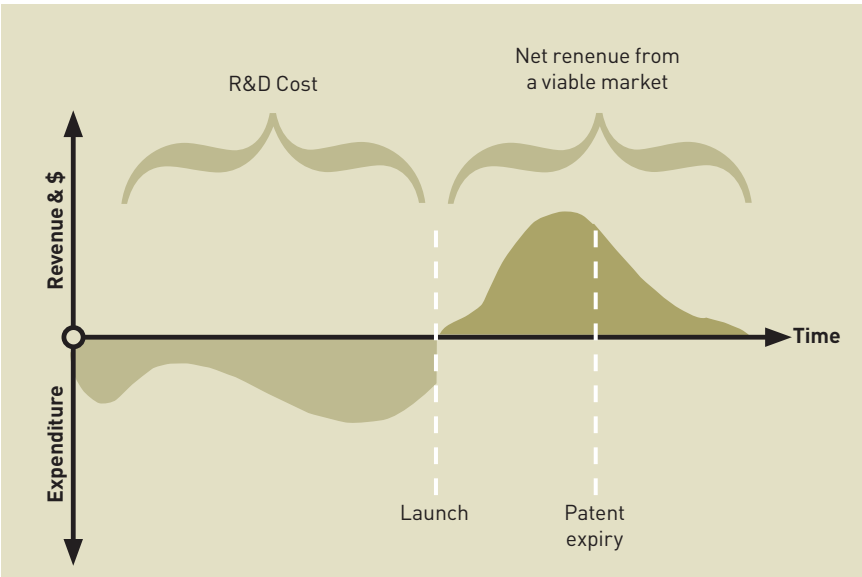
Figure Y, The industrial R&D process

Discovery			Development				Registration	Clinical use
Explore. Biology	Chemical Lead Discovery	Optimizn. of activity	Pre-Clinical	Clinical phase I	Clinical phase II	Clinical phase III		Post-marketing Surevilliance
			Non-clinical: Process Chemistry, Formulation, Pharmacokinetics, Toxicology					
Target(s)	Screening Traditional medicines	Chemistry SAR	Synthesis PK Safty in animals	PK Safety in humans	Proof DRF More safety	Efficacy More safty	Satisfying regulatory agencies of efficacity and safety	Safety efficacy Effectivness
			Non-clinical assessment continue throughout process					

The economics of industrial drug R&D

The economics of the drug R&D process are illustrated in Figure Z. In this figure the pink section corresponds to costs over time and the blue section corresponds to income generated from selling products. Obviously for a company the blue 'return' needs to outweigh the pink 'costs of investment'. Four additional features of pharmaceutical R&D need to be added to this equation.

Figure Z, Costs and return from industrial drug R&D



1. The process of drug R&D is high risk. Many projects are initiated in industry but only a small number succeed. A large amount of the costs associated with a serious R&D effort are therefore the costs of failed projects.
2. The process of drug R&D requires a long-term engagement and investment. It may take anywhere from three to seven years to convert a research concept into a chemical compound that can be taken into the clinic for trial. It may then take from five to eight years to register it as a drug and commercialise it in a way that generates a return on the original investment.
3. The earnings for any product are limited by its patent life. Once a drug is no longer 'on patent' in a particular country, other companies are free to manufacture 'generic' versions of the drug. As the costs for these generic products do not need to take into account the cost of the R&D that produced the drug, they are usually less expensive. This results in both a lower price and a reduction in the original company's market share, significantly affecting its income. Thus, companies investing in drug R&D must aim to recover the costs of that investment before its patents expire. Patents normally run for 20 years from the date of filing, which needs to be in place before the beginning of the development stage.

The size of the costs of R&D varies from indication to indication and also from country to country, but they are large and require a high level of funds and long-term commitment. A single project, supported from discovery through to development and registration will probably require 10s of millions of dollars. Given that most projects fail over the 15 year period it takes to produce a drug, the total research costs for a portfolio of projects to produce drugs usually amount to 100s of millions of dollars per drug.

Addressing the Specific Financing Shortfalls of R&D for Poverty Related Diseases

The 10/90 gap[8]

It has been said that less than 10% of the worldwide expenditure on health research and development is devoted to the major health problems of 90% of the population. Thus, it is the diseases of the rich that drive health research primarily, despite the fact that R&D on infectious diseases in low-income countries would be substantially more cost-effective, from a health point of view, than it is on welfare diseases.

In recent years the 10/90 gap has been questioned since the landscape of health research for development has changed in important ways. As a result of these changes, the total global expenditure applied to research relevant to all the health problems of developing countries cannot be estimated with any meaningful degree of accuracy. There is however no doubt that the imbalance in health R&D expenditure is still enormous.

A more nuanced picture is provided in "The New Landscape of Neglected Disease Drug Development"[9], a report prepared by the London School of Economics and published by the Wellcome Trust in September 2005.

The report implies that some dismal 'old truths' about R&D on poverty related diseases have to be revised:

- *Current perceptions of neglected disease drug development are missing the mark*
- *Current policy thinking around neglected disease drug development is rooted in a set of shared understandings based on the pre-2000 R&D landscape for these diseases :*
  - *One of these understandings is that only 13 new drugs have been developed for neglected tropical diseases since 1975, with the main problem being that these diseases are simply noncommercial for companies to invest in.*

8 In 1990, the Commission on Health Research for Development estimated that only about 5% of the world's resources for health research (which totaled US$ 30 billion in 1986) were being applied to the health problems of developing countries, where 93% of the world's burden of 'preventable mortality' occurred. Some years later, the term '10/90 gap' was coined to capture this major imbalance between the magnitude of the problem and the resources devoted to addressing it. Since then, the landscape of health research for development has changed in important ways: global expenditure on health research has more than quadrupled to over US$ 125 billion in 2003; there are many more actors engaged in funding or conducting health research relevant to the needs of developing countries; but the epidemiology of diseases has shifted substantially, so that many developing countries are now experiencing high burdens of non-communicable diseases such as cancer, diabetes, heart disease and stroke, as well as continuing high burdens of infectious diseases and injuries. (Global Forum for Health Research webpage)

9 www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtx026592.pdf

– *Another is that, although Public-Private Partnerships (PPPs) for drug development have started, they are inexperienced and it is too early to judge their viability.*
– *A third common view is that the real experience and capability in drug development lies with multinational pharmaceutical companies, who must therefore be brought back into the neglected disease field if we are to achieve success.*
– *The logical outcome would then be to focus on new policies to commercialize neglected disease markets on a scale to match large company needs (billions not millions).*

It is interesting to note that the findings of the Report differ (from the perceptions stated above) on a number of important issues:

- *The landscape of neglected disease drug development has changed dramatically over the past five years.(At the end of 2004, over 60 neglected disease drug development projects were in progress, including two new drugs in registration stage and 18 new products in clinical trials, half of which are already at Phase III. Assuming there were sufficient funding, at standard attrition rates this would be expected to deliver eight to nine drugs within the next five years)*
- *This renewed activity – at a level unheard of in the past two decades – has occurred in the absence of significant new government incentives and largely without public intervention; and is not explained by our current understanding of why companies do or do not conduct neglected disease R&D.*
- *Failure to recognize and understand these changes, and what* motivates them, *may lead to misdirected and wasteful public policies or, at worst, to the collapse of a valuable and active source of new neglected disease drugs.*

(Italic text extracted from "The New Landscape of Neglected Disease Drug Development")

These relatively new findings must of course be taken into account when assessing the situation in global health/neglected disease R&D, i.e. in order to avoid unnecessary duplication of efforts it is crucial to canvas current R&D projects on a global basis before deciding where to allocate resources.

1.6 Scale of the Problem

When it comes to the burden of infectious diseases, the scale of the problem can be expressed in (rough) figures:

HIV/AIDS: 40 million cases. 3 million dead per year
Tuberculosis: 60 million cases. 1 million dead per year
Malaria: (up to) 500 million episodes. 2 million dead per year, mainly children

Pneumonia: 1 billion cases. 4 million dead per year, mainly children
Diarrhoeal diseases: 4 billion cases. 2 million dead per year, mainly children
Measles: 30 million cases. Half a million dead per year, mainly children

Infectious disease is one of the main obstacles for advancing health and development in the developing world. In low-income countries, infectious diseases account for well over half of all sickness and mortality. Young children and pregnant women are the groups most affected, but the diseases have grave consequences in all stages of life; for school attendance, education and employment.

For many infectious diseases there are satisfactory vaccines and treatments, but these do far from always reach those in the greatest need of them. In the developing countries, particularly in the countryside, even getting a diagnosis can be difficult. And those who do may not afford the medications.

Another problem to be dealt with is resistance development; the old drugs are no longer effective. And in other cases there is no medication available whatsoever.

1.6.1 Medical Research Today

Not very long ago, the developed world faced a similar situation, with infectious disease as the main cause of poor health, but thanks to economic growth, successful development of medications and vaccines (antibiotics for bacterial infections and vaccines for measles and polio, for example) and the bringing about of well functioning public health systems and medical services, improved housing, water, sanitation etc. these medical conditions mean less today. Along with this positive trend, the R&D focus has been shifted towards so called welfare diseases, or at any rate, away from the diseases that exclusively or predominantly affect the poor.

Medical R&D today is principally, and at an increasing rate, driven by the powers of the market. Drug development is motivated by a possible, marginal health improvement in wealthy groups of patients in countries where medical security systems are generous. But infectious agents do not recognize national boundaries: Globalization has led to infections with for example HIV/AIDS, SARS and avian influenza also in the developed countries.

1.7 Priority Areas for Research

1.7.1 Demand for drugs, vaccines and diagnostics for neglected diseases

The demand for drugs, vaccines and diagnostics for neglected diseases is a complex matter; it is enormous and it is negligible at the same time. The demand for a cure or prevention of a potentially deadly disease is of course unquestionable to anyone who is sick or at risk of becoming sick (the same could be said for diagnostics since a proper diagnosis is required in order to move on to treatment), but when actual purchasing power is taken into account this demand is of no economic significance. Demand must therefore be measured in terms of medical urgency, and this should guide the priority setting.

However it would hardly be meaningful in this study to write down a wish list which does not consider the limitations on the supply side, i.e. the Swedish resource base. This must set the frames of what can be discussed, and hopefully the Swedish scientific supply can meet one or more of the medical demands of developing countries.

It is also crucial that medicines, vaccines and diagnostic tools are both affordable and well suited to function in the kind of environment where the diseases are present, i.e. hi-tech solutions that require unbroken cold-chains, complicated regimens, specially trained staff etc. is of lesser value in low-income settings with weak infrastructures.

2. Innovative Finance for the Health Sector

2.1 Background

This chapter sets out to identify relevant examples of innovative financing for the health sector in developing countries. The purpose is to identify new ways to mobilise funds for health research by leveraging private sector participation and ways to better meet the challenges facing the sector. It is not the purpose of this chapter to describe or quantify traditional channels of donor funding to health research, but to discuss how new ways of finance may complement traditional donor funding to the sector. For the past several years, with the establishment of the Millennium Development Goals, Global Alliance for Vaccines and Immunisations (GAVI), The Gates Foundation and other initiatives, there has been a strong emphasis towards building momentum for what is often referred to as innovative financing mechanisms in the health sector. There has been a general realisation that financing arrangements can create incentives for the development of new products and technologies fill market gaps and encourage behavioural change to combat major communicable diseases.

Donors have expressed three fundamental aims with developing innovative financing solutions for health:[10]

1. Generate new revenue to address global health problems
2. Change characteristics of existing funds through financial engineering
3. Increase private sector contributions to health

During this time disbursements of development cooperation assistance for health increased from USD 4.6 billion in 2002 to USD

10 OECD Background Note, Lessons for Development Finance from Innovative Financing in Health. 2008

8.5 billion in 2005, with the largest increase coming from bilateral donors. Between 2002 and 2005 contributions from bilateral donors increased from USD 3.5 billion to USD 7.2 billion.[11] It is likely that this increase in funding has largely been influenced by the global leadership shown by the likes of Gates Foundation and the British government, having chosen health as a major priority area for development cooperation.

2.1.1. Public vs. Private Research Funding

The relative cost efficiency associated with funding health research with public or private means is the subject of much debate. While some studies conclude that private research funding is comparatively more expensive, these studies often fail to account for the opportunity cost of capital for allocating public funds for this purpose. In other words, an accurate analysis must take into account not only the private sector cost of capital but also the social cost associated with allocating public funds to the sector rather than employing it elsewhere in the economy.

Table 1: Who funds what in the combat against neglected diseases

	Government Money	Donation Money	Investment Money	Combinations
Service Delivery	ODA/IDA	Philanthropy	Private Funds/ MNCs	Co-financing
Product Delivery	Global Fund/ GAVI	Philanthropy	Private Funds/ MNCs	Co-financing
Product Develoment	Push/Pull mechanisms	Donations to Push/Pull	Pharma/Biotech industry	PDPs

Source: Brookings Institute

Economic benefits to creating public private partnerships to combat neglected diseases may include the opportunity for pharmaceutical companies to access knowledge and experience from developing countries, as well as access to facilities that may otherwise not be available to private corporations. Studies show that public private partnerships show similar overall failure rates as pharmaceutical industry averages. However, projects with public funding were superior in terms of time needed to bring a vaccine or drug to market, as well as superior in terms of product innovation levels.[12]

11 ibid.

12 DFID Health Resource Centre, Developing New Technologies to Address Neglected Diseases, 2006.

Among critics of public/private partnerships, some believe that research for neglected disease could be done more efficiently and cheaper by the public sector whereby public funds would enable the private sector to deliver vaccines and consequently forego the patent system offered by market incentives.[13]

The working group led by the Center for Global Development which was assembled to analyse the feasibility of a market guarantee to incentivise industry, in the form of a Advance Market Commitment (AMC), concluded that the combination of competitive private sector involvement and public funding would lead to faster and better vaccines, an approach that is also supported by earlier examples of public private partnerships such as the Malaria Vaccine Initiative and the International Aids Vaccine Initiative.[14]

2.1.2. Push vs. Pull Mechanisms

When analysing ways to incentivise industry behaviour, it helps to distinguish between mechanisms that are aimed to *push* private sector involvement in a certain direction, and mechanisms that set out to *pull* industry in a certain direction. Push mechanisms include traditional donor funding for research and other types of public/private partnerships for product development that can cover initial costs and help catalyse private sector interest in a prioritised sector from a development perspective. Pull mechanisms on the other handset out to create an incentive in the form of a certainty of market demand, or guaranteed market, for said product, thereby influencing private sector participants to allocate resources in that prioritised field, knowing that there will be a demand for their products or services.

Push and pull mechanisms have been used in isolation as well as combined. It is widely believed that push and pull initiatives are complementary and can be used in different combinations to obtain an optimal funding mix. These types of incentive mechanisms for health research should be analysed on a needs basis and case by case to determine what type of incentive and how much funding is required to mobilise research to maximum effect. Early examples of simultaneous push and pull financing from the pharmaceutical sector include the US Orphan Drug Act of 1983 and the Meningitis C vaccine in the UK in 1994.

13 Donald Light, Making Practical Markets for Vaccices, PLoS Med 2(10), 2005.

14 Centre for Global Development, Global Health Policy, 2006.

2.1.3. Effect on Industry behaviour

It is reasonable to expect that different types of firms respond differently to various types of incentives. Push financing will probably be more effective with small to medium sized research and biotech/biopharma companies, whereas pull mechanisms would primarily be targeting big multinational pharmaceutical companies. Biotech research firms typically target smaller markets and products in the range of a few hundred million USD, where big pharma needs to go for products with a market potential of around one billion USD for the economics to work.

Small research companies and biotechs have been responsible for much of the product innovation in the pharmaceutical industry, and it is likely that these companies could greatly contribute to the development of drugs and vaccines for neglected diseases. There is evidence that these firms respond well to push financing, since this incentive best corresponds with their organisational setup and product development strategy. It is less likely that a small or medium sized company could fully engage in a large pull strategy, such as an AMC, at least in the absence of an accompanying push component.[15]

Pull mechanisms are more likely to attract primarily large multinational corporations that have the ability to bring drugs and vaccines through the development phase to finished commercialised product. There is evidence to show that pull financing such as an AMC can affect industry behaviour, especially if there is already some market potential to incentivise research. It is not likely, however, that a pull mechanism alone will initiate an R&D interest at a major pharmaceutical company if this is not already a prioritised sector in the organisation.[16]

2.1.4 Response by different stages in the R&D pipeline

The best position within the R&D pipeline for push and pull will again depend to some degree on the specific technology and firms involved. It is usually assumed that push can have its greatest impact where there is high scientific risk involved. It follows that push strategies are more suitable for early stages where financing options available are scarce and development risks are perceived greater than potential future monetary payoffs. Conversely, the strongest

15 DFID Health Resource Centre, Developing New Technologies to Address Neglected Diseases, 2006.

16 Mary Moran, Impact of Product Development Partnerships on R&D, 2008.

response to pull mechanisms would come at a point in time where the developing company has a clear vision on how to bring a product from the discovery/research stage through to commercialisation, generally at the stage of animal/human/clinical tests.

2.1.5 Cost efficiency

It is difficult to make an accurate assumption on relative cost efficiency of push vs. pull financing. In general, the components to consider are actual monetary costs incurred, comparative failure rates and comparative costs of capital. However, these components leave some room for interpretation and have been the subject of some debate. Studies show that failure rates for publicly funded push projects are similar to overall industry levels, but that public private partnerships are better at reducing risk and costs. In terms of R&D effectiveness, push financed projects were superior in terms of time to market, health value and innovative nature of products when compared to industry levels of neglected disease development.

When analysing the cost efficiency of pull mechanisms much consideration needs to go into the consequences of overpaying. For the recently developed pilot AMC for pneumococcal vaccine, the size was calculated using a model estimating the risk-adjusted returns for firms based on the specifics of that market, demand forecast, product pipeline and the amount of incremental private sector investments required to serve the developing world. The size of the market guarantee for pneumococcal vaccine development was recommended to be USD 1.5 billion, assuming that this would provide a sufficient financial return to the company for the incremental investment they will have made towards use of these products in developing countries.[17] One concern with this type of calculation is that accurate market prices are extremely difficult to model and predict, and there is a risk for the AMC size to be set too high, thereby creating a windfall profit for the pharmaceutical industry which would result in inefficient use of public money.

Overall, it can be expected that some level of push financing will be needed to incentivise industry even in sectors where an AMC style pull strategy is in place. These financing strategies will in most cases be complimentary and could combined increase the speed and effectiveness of developing drugs and vaccines for neglected diseases.

17 DFID Health Resource Centre, Developing New Technologies to Address Neglected Diseases, 2006.

2.2 Innovative Financing for Health

This section sets out to describe a few relevant and recent examples of innovative financing mechanisms and pilot projects that have been developed to mobilise funds to the health sector in poor countries. Although there is not an agreed definition of innovative financing for development, this term has come to be used to describe the fairly recent mechanisms presented as alternative ways to mobilize a combination of public and private funds to help reach the millennium development goals. These initiatives that use public funds to bridge the gap between science and product are also often referred to as Product Development Partnerships (PDPs).

The new funding models have been developed to complement Official Development Assistance (ODA) funding for development. Both global health partnerships and the financing mechanisms that channel funds to them have seen a high degree of public-private collaboration. A key component of innovative financing is its presumed ability to engage the private sector in a way that traditional ODA has not previously managed. There is considerable scope for innovative financing tools in the health sector, not least in the transition period from laboratory to market. This section seeks to identify the different innovative funding modalities currently being tested for neglected diseases. It does not present an exhaustive list of health finance initiatives, and it does not include traditional donor funding of health research.

2.2.1 Frontloaded Funding Model: IFFIm

The International Financing Mechanism for Immunization (IFFIm) was initialized in 2005 by the UK government as a way of bringing forward, or *frontloading*, donor financing and helping governments make good on their commitments of increased aid volumes, without further straining their national budgets. The funds are generated by issuing bonds in the capital markets backed by the donor countries full faith and security as collateral. Although there are considerable costs associated with issuing bonds, IFFIm is thought to be one of the most viable examples to quickly increase aid volumes.

IFFIm was launched with the financial backing of France, Italy, Norway, Spain, Sweden and the UK, with later additional commitments from South Africa and Brazil. Its financial base is made up of legally binding obligations of future donor contributions from the participating countries, which is then used as a base to borrow additional money in the capital markets. The ability to borrow

against future commitments of sovereign entities enables IFFIM to leverage the funds at a relatively low cost, and to receive funds as a frontloaded lump sum. IFFIm is administered by the World Bank which also acts as treasury manager.

The goal for IFFIm is to raise 4 billion USD to be used for immunization projects within the Global Alliance for Vaccines and Immunizations. It is expected that by frontloading these funds 10 million lives could be saved in diseases that can be prevented or limited by vaccines over a ten year period.[18] In 2006 the Swedish government mandated a contribution to IFFIm of 276 million SEK through the foreign ministry and finance ministry, to be paid out over fifteen annual installments. It was argued that although a relatively limited contribution, it was an important initiative that Sweden wished to support and thereby to create an incentive for other donors to join.[19] The inaugural bonds were issued in November 2006 and were priced at a competitive rate to a wide range of investors. A second bond targeting the Japanese retail market was launched in March 2008. The scale and predictability of funding that this type of frontloading of donor contributions brings has allowed GAVI to successfully expand their distribution of pentavalent vaccines, as well as other efforts targeting tetanus, measles and yellow fever.

2.2.2 Market Guarantee Model: AMC

The Advance Market Commitment (AMC) is an initiative launched by the finance ministers of Italy Canada and the UK with the ambition to support research, development and production of vaccines for neglected diseases. Under the arrangement, donors create a viable market for vaccines in the developing world by committing money to guarantee the price of vaccines upon delivery. This creates an incentive for pharmaceutical companies to make the substantial investments associated with developing vaccines for neglected diseases. Industry participants commit to supply vaccines at sustainable prices even after the initial fixed price donor funding under the AMC has been exhausted, which also enables governments in poor countries to better budget and plan for long term health programmes.

The AMC responds to one specific market failure; the pharmaceutical sector's inability to develop drugs and vaccines for neglected diseases – because of perceived costs and market risks

18 www.iff-immunisation.org

19 UD2006/28057/MU

associated with doing business in developing countries. The purpose of the arrangement is to create a results based and marked driven mechanism that will incentivise producers to develop more and better vaccines at prices that can open the markets of the developing world. The vaccine producer can only receive AMC funds if a new quality assured vaccine is ready for production, and one or more developing countries have documented demand for this product. All interested pharmaceutical research companies can apply for AMC funding subject to a) delivery of a vaccine with certain minimum requirements formulated by an independent panel of experts, and b) guaranteed delivery of a specific quantity of vaccines at a preagreed price.

A pilot AMC was launched for pneumococcal vaccines with the aim to demonstrate the feasibility and proof of concept. The purpose of the pilot is twofold. First, it will save lives quickly, possibly preventing up to 7 million deaths by 2030. Second, it will enable the participating parties to assess the impact of the mechanism to determine if it is possible to replicate the AMC model for other health sector priorities, such as malaria vaccines.[20] In late 2006 a potential Swedish participation in AMC was ruled out in a joint decision between the foreign and finance ministries. The decision makers expressed a reluctance to support the initiative with aid budget until further analysis of the concept had been conducted. Specifically, the DAC-ability of AMC needs to be better understood, as well as the comparative advantages for Sweden to support a market based mechanism vis-à-vis the already substantial support to traditional research funding through institutions such as GAVI, WHO, UNICEF, The Global Fund and others.[21] Having been fairly recently launched there has not yet been a mid-term review carried out or other useful evaluation of the AMC that could help determine its effectiveness.

2.2.3 Targeted Debt Relief Model: Debt2Health

In September 2007 the German government launched a new model to channel financing to the Global Fund for the purpose of fighting infectious diseases. In an initial agreement, the German and Indonesian governments agreed to cancel 50 million EUR of Indonesia's debt on the condition that Indonesia invests half of

20 www.vaccineamc.org

21 UD, Beslut: Svar till brev om svenskt stöd till initiativ om stöd till forskning, utvecklilng och produktion av vaccin för utvecklingsländernas behov, Advanced Market Commitments, AMC, 2006-11-27.

the freed up money in health programs through the Global Fund. Germany is the first donor country to support global initiatives through debt forgiveness and have a conversion target of 200 million EUR over a four year period. The funds will be used for health programs in Germany's partner countries and will be additional to existing development cooperation funding.

"Debt2Health is a win-win situation for all: It increases predictability for the Global Fund to do its important work, Indonesia strengthens the health system in the country and Germany lives up to its responsibility in the fight against AIDS, tuberculosis and malaria."[22]

By applying the proven instrument of debt swaps to public health financing through the performance based system of the Global Fund, the Debt2Health initiative will make it possible for developing countries to receive economic relief while its citizens benefit from health services. The Global Fund has approved a two year pilot phase for Debt2Health in four countries – Indonesia, Pakistan, Kenya and Peru. Benefits to the Global Fund include increased and predictable funding sources, as well as increased national ownership in health programs.[23]

2.2.4 Venture Capital Model: Great Challenges Exploration Fund

In a new and interesting initiative launched to introduce some entrepreneurial thinking to the health research sector and to combat neglected diseases, the Bill & Melinda Gates Foundation will donate 100 million USD over a five year period to small and novel medical research. In October 2008, the foundation announced it had paid out 104 grants of 100,000 USD each to scientists and experimenters in 22 countries. The programs ambition is to be additional and complementary to the foundations already substantial support to health research, and to operate more like a Silicon Valley type of venture capital fund, spreading risk capital to a large number of projects in small installments. It is acknowledged that this is a high risk strategy and that many projects will fail to deliver meaningful results. However, enabling researchers to try new and novel ideas has a good potential to reach new paths in health research. Examples of challenges posed to researchers to come up with new innovations include; creating new vaccines for diarrhoea, HIV, malaria and tuberculosis, as well as creating drugs or delivery systems that limit the emergence of resistance.

22 Heidemarie Wieczorek-Zeul, German Development Minister.

23 www.theglobalfund.org/en/files/publications/debt2health/D2HMechanisms.pdf

"Most of the approaches that have been tried to date and that are in the pipeline have been from a sort of orthodox way of looking at vaccine. Some novel approaches need to be tried".[24]

In a selection process the foundation together with a committee of sixty professionals awarded the 104 grantees from 4000 applicants who were encouraged to present "out of the box" research ideas. The committee will review and evaluate each grantee in one year's time, with the possibility for a select few promising projects to apply for a second round of funding of up to 1 million US dollar.[25]

2.2.5 Price Subsidy Model: GPOBA and AMFM

The Global Program for Output Based Aid (GPOBA) is an interesting initiative within the Private Infrastructure Development Group, a multi donor entity set up to channel funds to infrastructure projects predominantly in Africa. Output-based aid is a strategy of using explicit performance based subsidies to support the delivery of basic services. These services are usually contracted out to private sector entities, with the public sector committing to payments complementing or replacing user fees upon actual delivery of services. GPOBA's mandate is to fund, design, demonstrate and document output-based aid approaches to improve delivery of basic infrastructure and social services to the poor in developing countries. Sida already supports GPOBA with 45 million SEK.

Although predominately engaged in basic infrastructure projects such as water and electricity, GPOBA has supported health projects on a few occasions. One example is a maternal health services program in Yemen, which provides a "mother-baby package" of services as defined by the WHO. The GPOBA subsidy will help poor women access the health package. In Uganda, a government run program to improve health service provision has received technical assistance funds to study the feasibility of an OBA scheme to create more efficient delivery of health services.[26]

The Affordable Medicines Facility for Malaria (AMFM) was initiated to increase access to effective malaria treatment in developing countries by subsidising the delivery of antimalarial drugs such as artemisinin-based combination therapies, thereby making them available to more people. A 2004 study by the US Institute of Medicine concluded that a global high-level subsidy was the most

24 Dr. Yamada, President of Global Health, Bill & Melinda Gates Foundation.

25 www.gcgh.org

26 www.gpoba.org

efficient way of making antimalarial drugs widely available at affordable prices.[27] The subsidy would be available to all manufacturers of the specified drugs meeting predetermined criteria of efficiency, safety and quality. The high quality drugs would reach buyers at prices comparable to cheaper and less effective alternatives, and allow drugs to flow through existing channels.

The goal is to make these new, expensive drugs as cheap as old drugs for the vast majority of developing country consumers, driving the old inefficient drugs out of the market. Although promising and widely supported, the challenge has been in taking this concept from theory to practice, and the board of the Global Fund is currently debating on how they can move forward with this initiative.

The subsidy or "cash on delivery" model shows great potential, and donors such as DFID are trying similar approaches in other sectors. In order to bring the concept to work on a broader scale, recipient countries need more education on how to manage the process. The GPOBA program management have realised this and are putting much emphasis on developing local knowledge centres in their cooperation countries.

2.2.6 Solidarity Tax Model: Product Red and UnitAid

Product Red is a model based on taxes on consumer goods and charitable auctions and was launched in 2006 to tap into private funds as a way of complementing donor funding to the Global Fund. Through successful cooperation with companies such as Apple, American Express, Converse and Gap, Product Red has managed to channel over 110 million USD to Africa in two years. The concept relies on the companies' willingness to forego a portion of their profit for charitable causes on a select range of products. Every time a consumer buys a "Red" product, the company who makes that product will give up to 50% of its profit to the Global Fund to be spent on health projects in four African countries.[28]

Product Red has proved a valuable additional contributor to the Global Fund alongside traditional donors. Although simple and effective, the model has been drawing some scepticism due to its heavy reliance on celebrity drawing power to mobilise partner corporations. The Irish rock star and global health advocate Bono has been a high profile champion of Product Red but it is not clear

27 Institute of Medicine, Saving Lives, Buying Time – Economics of Malaria Drugs in an Age of Resistance, 2004

28 www.joinred.com

that this type of model can easily be institutionalised without the involvement of these key people. Also, much of the revenue to date has been generated through charitable auctions, leaving the consumer goods solidarity tax model unproven as a stand alone effort.

In 2006, the French government launched the Solidarity Tax on Aircraft Tickets, for the purpose of contributing to the funding of global public goods. The revenue will be channelled to support the health sector in developing countries through UnitAid and other sectors may follow if the concept is proven successful. In 2007 alone UnitAid received USD 368 million in revenue from the solidarity tax. The initiative is also supported by a number of developing countries, who levy the airport tax and thereby make financial contributions themselves. One of the benefits to this initiative is the relatively low administrative costs associated with collecting the tax revenue since it is structured as an earmarked rate increase on an already existing tax.[29]

Both the consumer and air traffic models for solidarity taxes have made significant financial contributions to the health sector. The major challenges to achieving an optimal scale and sustainability will be how to expand the revenue base without increasing administrative costs. If successful there is great potential for this model to be replicated for recipient organisations outside the health sector.

2.2.7 Learning from Experiences

The Children's Vaccine Initiative (CVI) was a predecessor to GAVI that failed in its mission to develop vaccines for neglected diseases primarily due to political issues and failure to convince industry of its intentions. The initiative was launched in 1990 by UNICEF, WHO, the World Bank, the Rockefeller Foundation and the UNDP in an attempt to create a coalition dedicated to saving million of lives by closing some major gaps in global vaccine development and delivery. The idea behind the CVI was to work with all the players in immunisation, including industry, to find a new approach to vaccine development that could be sustained in developing countries.[30] The project never took off due to lack of funding, and perhaps more importantly unforeseen political aspects because the WHO and UNICEF could not agree on which organisation should be the leader in immunisation efforts. Neither was eager to give up any prestige on this upstart initiative. In 1998 the involved parties

29 http://unitaid.eu/index.php/en/The-air-ticket-levy.html

30 IOM, The Childrens Vaccine Initiative – Achieveing the Vision, 1993.

were met with the goal to come up with a plan to deal with the decline of childhood immunisations worldwide. The Gates Foundation had just entered the picture and eventually convinced all interested party that a new effort was needed to rejuvenate immunizations. Gates would put up USD 750 million in seed money for a new Global Alliance for Vaccines and Immunization, (GAVI).

Estimates put the total funds raised since 2000 under the innovative financing mechanisms at over USD 2 billion. Some critics point out that although successful in raising funds from both public and private sources, the majority of funds to date are provided by one donor – The Gates Foundation. Nevertheless, it appears that the concept of innovative finance mechanisms or PDPs has stuck, and that many donors have high hopes for this type of funding tool for health research as well as other sectors in the future. Unfortunately there is little evidence from these recent initiatives to support any certain direction for future work, simply because they have not had time to build a track record. Most efforts are still in their pilot phase, and some have only just been launched. It will probably take another couple of years before mid-term reviews will yield significant results, and these initiatives can start to show proof of concept. The early indications from initiatives such as IFFIm show promising signs, however, having recently completed a second round of financing. Perhaps as important, these efforts show clear examples of problem based approaches to development aid rooted in an entrepreneurial mindset, and they have a strong potential to achieve the goals of a complementary funding source for development aid that can substantially leverage private sector funding and expertise.

2.3 Sida's Potential Role in Innovative Health Finance

2.3.1 Swedish Government Support to the Research Sector

Sweden spends a relatively high proportion on R&D at around 4% of GDP, with the private sector providing about 75%. Public sector research funding is primarily paid out through grants to universities and through research councils and agencies.

The largest provider of public research funding is the Swedish Research Council (VR). Their focus is supporting basic research at academic institutions and dedicated research institutes, with an annual disbursement of around SEK 2.5 billion per annum. The budget for research support is likely to increase drastically as a part

of the October 2008 Research and Innovation bill. The Swedish Governmental Agency for Innovation Systems (Vinnova) acts to promote economic growth in Sweden by supporting innovations linked to R&D. A strong focus is on needs-driven research in close cooperation with private sector as well as promoting networks between industry and civil society. In pharmaceutical and diagnostics research, Vinnova is focused on generic technologies, to complement government agencies supporting other parts of the research process.

Once the R&D process continues moves on to a corporate format, there are several government institutions with a mandate to provide risk capital to foster economic growth. Industrifonden has some 20 investments in life sciences in pharmaceutical, technical and diagnostics sector, primarily focused on small research driven biotechnology companies. Swedfund invests in companies with a clear development and poverty reduction agenda, most of their portfolio companies have some link to Sweden.

2.3.2 Bilateral Aid Support to Health Research

In its Policies for Global Development in 2003, the Swedish government makes a commitment to help achieve the Millennium Development Goals by providing global public goods to least developed countries. A further commitment was made towards an increased focus on cooperation with private sector and the Swedish resource base in general.

There is a strong connection between health and development, and Sida aims is to assist poor countries in building inclusive, equal and high quality health services. The department for research cooperation gives grants to health research in universities and other institutions, regional networks and international research programs. They also support the Swedish research community in their work that is of interest to developing countries. One prominent area of traditional research support is HIV/AIDS, where Sida since 1989 has been an active contributor with an increasing focus of sexually transmitted diseases in developing countries. In a joint Sweden/Tanzania project, Sida funded research has developed a vaccine to strengthen the human immune system to combat the HIV virus. The vaccine is currently being tested in Sweden and will then be tested in Tanzania.[31]

The official position of the Swedish government is that increases in foreign aid should first and foremost be achieved by

31 www.sida.se/sida/jsp/sida.jsp?d=422

more countries adopting the UN goal of 0,7% of GDP for development cooperation. But in the spring 2006 budget proposition decision to support GAVI financing through IFFIm, it was concluded that drastic efforts are needed to achieve the MDGs, and that innovative financing mechanisms should receive broad support.[32] Although fairly limited in scale, the Swedish support to IFFIm is believed to have a catalytic effect on other donors joining the initiative, and is seen as a way to mobilise private sector funds for prioritised sectors in development cooperation.

2.3.3 The Future Role of Development Loans and Guarantees

In the 2006 Lindahl report on the future of Sida's credit and guarantee system,[33] it was concluded that there are strong incentives to continue using credits and guarantees as a financing forms for Swedish development cooperation. The report recommends a reformed system that could be more efficiently managed and better contribute to reducing poverty in a sustainable manner. One of the key aspects will be to focus on additionality and catalytic effects which could contribute to greater development returns than traditional aid. This will among other things mean an increased focus on providing local currency financing in cooperation with partners in local markets. A central theme will be to use a problem based approach in addressing distribution of global public goods. Furthermore, Sida should use the credit and guarantee system to better leverage the Swedish resource base to mobilise resources outside the official aid organisations for development purposes. The report recommends that Sida should use the reformed system to develop two new instruments that can contribute to a problem based approach to sustainable development. The specific objectives of these new instruments will be to stimulate cooperation with the private sector to develop new technologies in areas such as energy, environment, climate change, health, urban transport and water.

2.3.4 Market Guarantees

In an effort to broaden the utilisation of credits and guarantees, a pilot project has been proposed with the aim of encouraging innovation in difficult sectors through a market guarantee product, similar in structure to the AMC, where Sida would initiate new technological developments by paying a third party for the success-

32 Regeringens proposition 2005/06:100.

33 Lindahl, Att ta itu med fattigdomen, 2006.

ful delivery of this technology. The purpose of the market guarantee is to cover some of the risks associated with innovative business that has a direct bearing on sustainable development and that addresses specific problems for poor people.[34] The overall goal is to make innovations and new technologies available on global markets at prices that make them accessible to the neediest. In effect, the guarantee will enable product development that would otherwise not happen because of perceived risks.

Much like the AMC, the proposed market guarantee would mean that Sida makes available a guarantee to the company that successfully develops a specific predefined product or service with substantial poverty reduction potential. An example could be affordable vaccines or clean energy technology. Sida commits to purchase the product or service at an agreed price and quantity for a specified period of time, thereby creating a secure initial market to the producer. This market will only be guaranteed if the product or service meets the preagreed minimum requirements. Sida then transfers the product or service to the recipient country for distribution to its population. The successful provider will have full ownership of its innovation except from an obligation to deliver the product or service below a certain price for a period of time to prevent market abuse. This hurdle price must be acceptable to industry participants while at the same time being affordable to poor people. Evidence from the AMC process shows that product pricing is a difficult and timely exercise and one that must be rigorously evaluated to ensure its affordability and to prevent windfall gains to industry participants.[35] Examples of innovations where a market guarantee is believed to be useful could be as diverse as preventive health and vaccines for neglected diseases, micro hydroplants for small scale energy generation, water purification services, and high yielding agricultural produce.

2.3.5 Innovation Loans

A new type of loan product is proposed based on similar principals as Sida's conditional loans that are now managed by Swedfund, but with the specific purpose to stimulate innovation in difficult sectors that are of interest for poor people. The new innovation loans would be given to research institutions or private companies to

34 ibid.

35 DFID, Health Resource Centre, Developing New Technologies to Address Neglected Diseases, 2006.

develop products or services with clear relevance for development. The loan can be subsidised by offering grace periods and low interest rates for a specified period. If the industry participant is successful in developing a new product and thereby can find a market on commercial terms, they are required to repay the loan at market interest rates. If, however, the innovation does not find a market then all or part of the loan can be written off. It is believed that offering this type attractive financing with risk mitigants will influence industry participants to develop products and services for difficult markets. It is likely that that innovation loans will be complimentary to market guarantees, probably attracting small to medium sized research organisations rather than the large multinational companies that would be more interested in market guarantees. At present, the law of capital ordinance prevents Sida from investing in private enterprise. [36] Although exemptions have been possible, most of the private sector activities are channelled through Swedfund who also took over the conditional loan stock in 2007. Sida's role should be to assume excess risk where this can be motivated by clear development gains, but the interaction with private markets should be handled by Swedfund. Several cooperation projects between Swedfund and Sida have been launched in recent years, including framework credit agreements and risk sharing arrangements. Innovation loans could be greatly benefited by combining the private sector expertise of Swedfund with Sida's credit enhancement capabilities and this joint effort should be explored further.

2.3.6 Organisational Constraints

The Lindahl report stresses the issues of internal capacity and incentives to promote an active utilisation of credits and guarantees. A central credit and guarantee unit should handle all non-grant financing forms; this would create a knowledge center and allow for streamlining of processes. Furthermore, the report suggested a credit council to include representatives from Sida, SEK, EKN Swedfund and private enterprise that could support the internal decision making process. Although this suggestion has been abandoned in subsequent deliberations, it is clear that Sida will have to draw on substantial external resources to make the reformed credit and guarantee system successful. Internally, separate decision making processes from the traditional grant based

36 Kapitalförsörjningsförordning (1996:1188)

funding need to be worked out create faster, market based decision making. Also, internal incentive mechanisms will need to be reviewed. Today program officers are measured on *amounts disbursed* which does little to create incentives to work with alternative financing forms. A more accurate yardstick would be *amounts mobilised* which would create a stronger focus on credits and even more so on guarantees. Finally, Sida may need to increase its dedicated financing staff to deal with these new instruments and to increase the understanding of these produ9cts within the organisation, not least the embassy staff, in order to achieve critical mass of deal flow. Management will be required to make some upfront human resource investments in order to build the financing mechanisms that can at the same time be additional to traditional ODA and also catalytic to the private sector.

3. The Swedish Resource Base

3.1 The Swedish Pharmaceutical Sector

3.1.1 Swedish companies and products with relevance for global health issues – background

Sweden has a strong tradition as manufacturers of medical products. With the acquisition of MedImmune AstraZeneca has confirmed its interest in the area. In MedImmune, AstraZeneca has a strong technological base in the area of monoclonal antibodies and vaccines, which can contribute to new solutions to prevent and treat infectious diseases. AstraZeneca also has operations in Bangalore, India, for TB Drug Development.

Several small- and medium sized biotechnology companies, some spin-offs from universities have emerged. About 150 of these are members of SwedenBIO. Some of these companies are working with, for instance, antimicrobial agents (Medivir), diagnostics (Vironova) or vaccines (SBL vaccines) also among the spin-offs from the universities are focused on infectious diseases (such as Innate Pharmaceuticals in Umeå).

Of 169 biotech products moving into or in clinical trials in 2007, 19 were within the field of infection, including 9 in the area of HIV/AIDS[37].

One example of a product developed by Swedish researchers is the first oral cholera vaccine which was developed by Jan Holmgren and Ann-Marie Svennerholm, Gothenburg. In cooperation with Vietnamese scientists production of a Vietnamese cholera vaccine has been developed. Several adjuvants (adjuvants are added to many vaccines to increase their immunogenicity and efficacy) have been developed and patented, by Jan Holmgren and Nils Lycke, Gothenburg, and Eurocine Vaccine AB.

37 An analysis of the Swedish Biotech Pipeline, SwedenBIO/Invest in Sweden Agency/Vinnova, April 2007.

Hans Rosling, professor of Public Health at the Karolinska Institutet, has with the foundation Gapminder managed to bring knowledge of global health by combining expertise in public health with existing statistics and technical visualization opportunities. In a vivid, educational manner and with the help of computer animation he describes developments in health and welfare in an international perspective. Gapminder's software Trendalyzer is now bought by Google.

Professor Ulf Landegren at the Rudbeck Laboratory in Uppsala has invented, and Olink AB, has developed and commercialized the Padlock technology as well as the Proximity Ligation Technology, which enable detecting and analyzing microorganisms with great sensitivity and specificity. The Padlock technology analyzes nucleic acids while Proximity Ligation Technology detects antigens on the surface of microorganisms. Olink AB has signed agreements with Affymetrix and Applied Biosystems regarding commercialization of these technologies.

An entirely new type of medicine for bacterial infections is being developed by Innate Pharmaceuticals Ltd, founded by Professor Hans Wolf-Watz, together with other researchers at Umeå University and the Karolinska Institute. By disarming the pathogenic bacteria – not killing them like today's antibiotics do – the risk of emergence of resistance to the drug is reduced. Innate Pharmaceuticals has signed a cooperation agreement to develop drugs for diarrheal diseases with Syngene Ltd., Bangalore, India.

At the Royal Institute of Technology the so-called Pyrosequencing technology was developed. This technology has been used for studies of how small differences in the human genome (called SNPs) affect the risk of developing complex diseases such as multiple sclerosis, atherosclerosis and have serious symptoms of common infectious diseases. Pyrosequencing technology is the base of the listed company Biotage and is the basis for the new massively parallel DNA analysis method (Massively-parallel DNA Pyrosequencing) which was appointed method of the year by Nature in 2007. The method allows analysis of the entire genome of a bacterium in one day, something that previously took months to implement.

3.2 Survey of Selected Swedish Companies

With reference to the findings described in Chapter 2.3.1 (Effect on Industry behavior) whereby it is shown that the response to incentives created will differ in relation to the size of the company, a sur-

vey was created targeted towards small/medium sized research and biotech companies in Sweden as well as the regional offices of some of the multinational pharmaceutical companies.

3.2.1 Objective of Survey

The overall objective with the survey was to map the number of ongoing research projects by Swedish pharmaceutical and biotech companies within infectious diseases and to summarize the main obstacles as seen by the sector to increase the development and manufacturing of affordable drugs and vaccines for the most important communicable diseases in poor countries.

3.2.2 Data behind Survey

A total number of 23 pharmaceutical and biotech/biopharma companies in Sweden were selected[38] [39] as recipients of the survey. The purpose of the survey was to find out whether the creation of a financial mechanism/incentive would encourage pharmaceutical and biotech companies to develop new drugs, diagnostic tools and vaccines aimed at infectious diseases of low income countries.

The survey consisted of two questions set against the background of the aim and purpose of the Pre-Feasibility Study initiated by Sida[40].

Question 1

Would your company be able to develop drugs, diagnostics and vaccines aimed at poverty related infectious diseases? If "yes", please exemplify*.

*If possible, describe the product/s in short; current prerequisites, budgeted cost and time-line until launch and calculated use of the product

38 the selection of pharmaceutical companies to contact was based on relevance in terms of ongoing research in the field of infectious diseases

39 In addition to the questionnaire, an interview with representatives from Pfizer's Swedish branch was conducted (Johan Brun, Medical Director; Lars Nyman, Medical Adviser; Bengt Mattson, Manager, CSR and Environmental Affairs; Sven-Eric Söder, Director Government Affairs). Several issues regarding infectious diseases and the problems associated with R&D were touched upon, but the main message was that new drugs will be developed as soon as there is a viable and stable market (including stable systems for distribution, functioning health systems and sufficient political stability et cetera) and that attempts to incentivise big pharma industry hardly would be cost-effective before these prerequisites are met

40 "The overall purpose is to enable an increased cooperation between aid organisations and private business. Specifically, the purpose of this study is to create a mechanism for the development and manufacturing of affordable drugs and vaccines for the most important communicable diseases in poor countries".

Question 2
What kind of incentive would be necessary to initiate such a process?

3.2.3 Response from companies

A total of 11 out of 23 companies submitted written answers to the questions above out of which 7 companies gave concrete examples of product development, thus providing a snapshot of products already in the pipeline of the companies or waiting to be further developed if funding was provided.

The rate of response by the companies selected is just below 50% and in most cases response was submitted after a written reminder was sent to the companies to do so. All the questionnaires were addressed to the CEO of each company.

The quality of response varied to a certain degree. Some responses referred to company products that were already on the market and targeted towards the identified segment. Others stated that they did not conduct R&D in Sweden.

It became apparent that the most informative and detailed answers were provided by companies with promising products in the pipe-line or products waiting to be developed if partly externally funded. The products described were diagnostic tools for management of HIV, Virulence blocking agents, development of vaccines for malaria, TB and Sleeping Sickness, new therapies and preventive measures against malaria, TB, HIV and HIV transmission.

In all cases a *lack of financial resources* was mentioned as the main reason for not being able to continue to develop a product. As one company put it "The projects are shortly running out of financial support, progressing very slowly or hibernating due to a lower priority than projects with better market prospects"

Another company stated:

"It is quite clear that we could speed up the development of these projects with increased financial resources. All three projects have left the pre-clinical stage…"

There was an awareness that scientifically sound and promising projects from a medical point of view were held back due to inability to compete with projects with better economical prospects from a company/market point of view.

3.2.4 Submitted suggestions on incentives

Several suggestions were given; the most extensive were from companies with projects in the pipe-line or "shelved" projects. Excerpts are quoted below:

"A financial support from SIDA (or any other non-profit organisation) to run the projects efficiently, but without profit, to registration will be necessary. After registration SIDA should have the unrestricted right to freely use the drugs in developing countries. If there should be a market in other countries the profit there should be split between SIDA and the pharmaceutical company. This might pay for Sida's costs related to production and distribution of the drugs to developing countries and be the carrot which the pharmaceutical company will need to give the projects the attention they deserve."

"What is needed is Commercial markets/established business model, international funding and procurement or corporate social responsibility".

"With increased financial resources our platform could be easily developed to incorporate exciting products for HIV management in the developing world. Possible applications for the technology are Paediatric diagnosis, HIV drug resistance testing and Viral load monitoring"

"Our company has many ideas, functional prototypes and products that are needed by people who cannot afford them. We think that support with development, like converting research prototypes into medical products, including clinical trials, cost for certification and registration etc. would make a substantial difference in taking these ideas to market. In many instances it appears difficult for governments to realize that by spending now on proper monitoring they will reap vast financial and social savings in the near future. The funding of national pilot projects would go a long way in showing that proper monitoring of e.g. HIV patients is beneficial to all stakeholders"

3.2.5 Follow-up

In order to follow up on the original survey and gain a deeper insight of the prevailing view of how and if incentives could serve to refuel interest in increased R&D within this sector, a second set of questions were formulated and distributed. Four (4) companies representing both Big Pharma and Small and Medium Business were willing to respond.

Out of these, the two Big Pharma companies have as yet not come back with their views – the reason for the delay is most likely that the process to get an approved "official" view in these questions requires a consolidated statement by the Head Office.

The response from the other two small/medium sized businesses reflected their present situation – products in the pipe-line with a vision on how to bring the product from a scientific stage to commercialization or to a larger market.

One company stated that "if a financial incentive would be available today, it would help to speed up and de-risk the process of increasing the volume of a product which in turn would result in a decrease in price which in turn would give patients in developing country easier access to the product".

As a response to our question "what is the next hurdle or threshold" to get over in connection with the product development of your company the following situation was described by a diagnostic company:

We (the company) have a portfolio of prototypes, near products and potential improvements of already marketed products in the pipeline with possible future applications that would drastically improve the wellbeing of many patients in the developing world, but we currently lack the economical resources to bring all of these to market in the short term. Due to financial constraints we must focus on projects that bring short term revenue and are therefore forced to leave interesting R&D projects to the future. Our immediate short term goal is to reach break even. This would then allow us to use resources to expand both our R&D and marketing efforts. In order to achieve this we are in need of further funding.

When asked about the level of economic incentive needed to overcome major "hurdles" the variation of R&D cost was mentioned depending on the nature of project:

A rough estimate of the cost for different projects varied from 1–5 MSEK for minor modifications to existing products to the development of for example a diagnostic test including clinical trials and documentation which was roughly calculated to 9–15 MSEK.

Regional presence was also mentioned as a way of increasing the companies' capabilities to build on collaborations with local partners resulting in an increased ability to provide technology transfer and technical support. The cost for this was estimated to around 3–6 MSEK.

What would you state as the main reason for lack of investment in a product development by e.g. Venture Capitalist?

Swedish investors appear to be reluctant to invest in a company that deals with the developing world. A comment often heard is that they do not have knowledge of these markets and are therefore skeptical; there is concern over political instability and potential payment issues.

If a financial mechanism was in place, would that increase your company's interest in absorbing ongoing external research projects?

It seems that an interest is already there from companies, but funding is needed to be able to take a larger part in these kinds of studies. A possibility to at least cover expenses for providing material for external cooperation would make a large difference. Often companies are part of some cooperation projects with Swedish research groups but due to economical reasons these are usually limited to sharing ideas and some materials.

Would economic Incentives be a plausible way to engage pharmaceutical companies?

Yes, diagnostic and pharmaceutical companies may already be interested in developing products for resource-limited settings, but find it hard to find investors for their projects.

3.3 Swedish Research

3.3.1 The Big Picture – Sweden's comparative advantages

In the following some of the factors supporting the assumption that Sweden has a strong potential within the field of global health research have been listed.

Sweden has:

- A long tradition of high quality research on infectious disease.
- High, partly unique, class equipment and laboratories (for example one of very few biosafety level 4 laboratories in the world)
- A unique health care system which enables long term patient follow-up
- A very well-developed organization for prevention and control of infectious diseases
- Well-developed infrastructure for pharmaceutical trials, and with solid documented experience

- World-leading research/understanding of infectious disease mechanisms, new strategies for diagnosis, prevention (vaccines) and treatment
- World-leading research on the mechanisms of antibiotic resistance development and strategies to reduce antibiotic use
- A pharmaceutical and biotechnology industry with small, medium and large companies that are focused on infectious diseases

All this has contributed to Sweden being entrusted with hosting the EU's infectious disease control agency, European Center for Disease Prevention and Control, ECDC. Continued and increased research efforts are most likely, the best way to also maintain this institution in Sweden in the future.

An absolute and politically important advantage is the fact that Sweden does not have a colonial history, which is crucial to our ability to smooth functioning of cooperative research with disease-affected countries. Also our long history of international peace efforts, aid, assistance and international research contributes to this position.

Sweden's global contacts have also given us a pool of experts with considerable experience of "tropical diseases" which also constitute the main diseases of poverty, but also of so-called emerging infectious diseases such as avian flu, Ebola, and more.

3.3.2 Swedish Research Environments

In Sweden, there are a large number of research settings with interest and opportunities for research in fields related to global infectious diseases, and Sweden is already in the top class in many research fields.

These research fields include:

- Microbiology
- Immunology
- Biotechnology
- Epidemiology and Biostatistics
- Public Health Research

Immunology / Microbiology / Biotechnology

Research in the areas of immunology, microbiology and biotechnology is mainly performed at the following institutions:

- University of Gothenburg[1]

- Karolinska Institute, Department of Microbiology, Tumor and Cell Biology[2]
- Centrum för Infektionsmedicin (CIM), Infektionskliniken, Karolinska Universitetssjukhuset, Huddinge[3]
- The Royal Institute of Technology, Stockholm (Kungliga Tekniska Högskolan, KTH)[4]
- The Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet, SMI)[5]
- Stockholm University (SU)[6]
- Umeå Centre for Microbial Research (UCMR)[7]
- Uppsala University[8]

For a more detailed description of the institution's specialities, see endnotes.

Public Health/Medical Epidemiology/Biostatistics
Research in the areas of public health, medical epidemiology and biostatistics is mainly performed at the following institutions:

- Karolinska Institute[9]
- Nordiska högskolan för folkhälsovetenskap, Nordic School of Public Health[10]
- The Swedish Institute for Infectious Disease Control[11]
- Umeå University[12]

For a more detailed description of the institution's specialities, see endnotes.

Some 80 research groups at the institutions mentioned above are working on poverty related infectious diseases or issues associated to the field.

3.3.3 Getting into Details – Current Research Status

Swedish global health research projects – an updated inventory
In order to secure an updated inventory of ongoing Swedish global health research projects a survey was conducted in which the (heads of) the aforementioned research groups were asked whether they:

- currently are working on projects with the potential of resulting in actual products, i.e. diagnostic tools/medicines or vaccines, had there been interest and financing from the pharmaceutical industry (and if so, to describe the projects/products briefly)
- have feasible ideas for such products that they have not yet pursued due to lack of interest from funders/industry (and if so, to describe the projects/products briefly)

A total of 80 questionnaires were sent out and 45 replies were submitted out of which 36 were positive. There is however an overlap, i.e. some of the projects have been reported by more than one researcher.

Altogether there appears to be 26 unique projects of which six (6) were categorized as diagnostic tools, five (5) as medicines, fourteen (14) as prevention/vaccines and one (1) as other.

Diagnostics	Medicines	Prevention/vaccines	Other
6	5	14	1
2 TB 1 malaria 1 borreliosis 1 resistant bacteria 1 detection of DNA/RNA/ proteins	1 HIV/AIDS 2 malaria 2 African sleeping sickness	7 HIV/AIDS 2 malaria 2 TB 1 pneumonia 1 trachoma 1 diarrhoea (possibly expandable to H. Pylori)	A software for data handling in relation to research on and treatment of HIV infected patients

The recipients of the questionnaire were also presented with an additional (optional) question for which the answer frequency – not surprisingly – was significantly lower: *We would also like you to share with us your thoughts on how academia and industry better could support and draw advantage from each other.*

The replies cannot be squeezed into a matrix or table; however they were so few that they can be rendered in full:

- This initiative is a very good one.
- It is absolutely of greatest importance that academic institutions can develop cooperation with the industry/enterprises. Considering the dismal history of the Swedish research society with insufficient and short-term funding, industrial cooperation would be a significant and important support for many researchers. This must definitely increase and be developed further in all forms.
- This is one of the major difficulties. Ideally, IAVI would serve as an 'honest broker' but they have turned into one of those stakeholders who pursue their own agenda. It is difficult to find out which companies might be interested – where is the point of intersection?
- Experience from industry and innovations should get higher impact when applying for academic positions. If this would be

the case more researcher would dare to test their ideas and try to develop them further instead of putting their papers on the academic bookshelf.

- For development of vaccines and medicines, close contacts with the industry is a basic condition if you are working in the academia. It is important to transfer knowledge of suitable partners between the two, for example through the financing of start-up projects.
- It is of course crucial to come up with new medicines and vaccines against the diseases of poverty. I personally have a long experience of interacting with Big Pharma as well as with smaller biotech enterprises. During all these years ideas from Swedish research groups strikingly rarely (practically never) result in useful products.

  Also, in my experience it is just as important to develop methods for ensuring correct use of new products. If we look at the example of HIV/AIDS every patient who comes under treatment generates a vast quantity of data – data on treatment, dosing, outcome, resistance development etc. These data must then be easily accessed in order to enable doctors and nurses to give the optimal treatment, at the administrative level to assess which regimens are adequate and to enable continuous research on how different medicines are actually used and what functions in real life.

  Treatment for the diseases of poverty requires translational research, i.e. rapid transfer of research results to patients as well as rapid transfer of patient observations back to the researchers. Working in this manner research results can more effectively lead to better diagnostic end treatment methods than today for the individual patient.

  In the present paradigm we work in a cycle which looks like this: Usage --> Data collection --> Analysis --> Publishing --> Communication of results --> Training staff in new methods --> new type of usage --> Data collection, et cetera.

  This Cycle might take years to go through, and this time we don't have – especially in the areas Sida work in.
- The industry must be closer to the academia and must have the courage to put stakes into basic research projects – unlike how it is today when 100% success must be expected for the industry to become interested.

The survey conducted for this study is by no means exhaustive; it merely reflects what the researchers answered upon being asked which of their projects they perceived as most relevant for collaboration with the industry. The total number of current Swedish research projects is thus far greater.

4. Conclusions and Recommendations for Sida

4.1 Conclusions

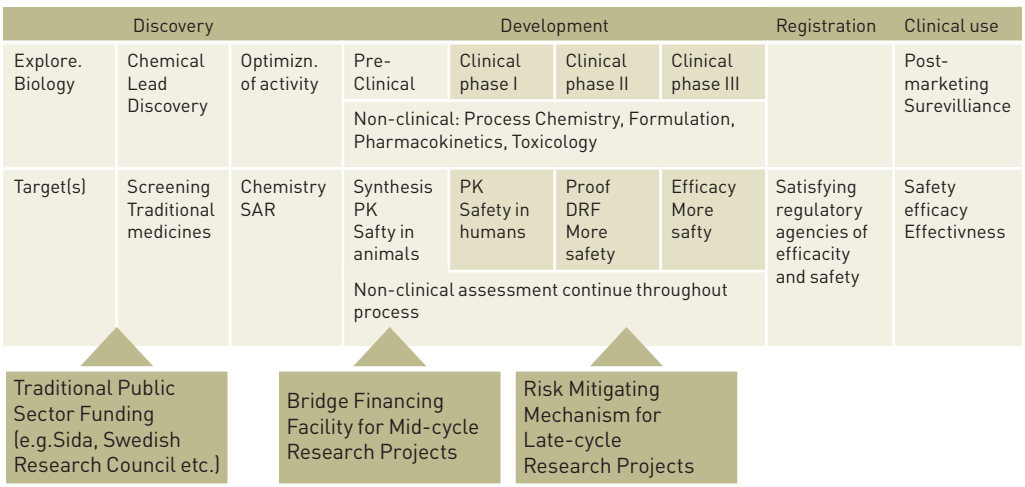
The initial conclusions from reviewing existing health finance initiatives, and canvassing the Swedish industry and research communities, are encouraging. It is clear that more funding is needed for R&D on poverty related diseases, and there is a potential to use existing modalities to address the specific financing gaps in this sector. However, this does not necessarily imply that current mechanisms are sufficient, but rather that there is scope to expand some of the ideas currently being explored to increase funding for neglected diseases. Moreover, it is highly likely that such financial support would be a cost-effective allocation of resources in respect not only to the expected positive effects on R&D per se, but also to increase the involvement of private enterprises and ultimately to ease the burden of disease in poor populations. It appears that the Swedish health research community is well positioned and that reinforced incentives to focus their efforts in the field of poverty related diseases would yield significant production of required knowledge. The same can be said for Swedish SMEs. Though too small a number of respondents to draw specific conclusions from, the survey conducted for this study points in a promising direction. According to the reference group economic incentives are likely to have the biggest impact if applied to this sector and the stages of the R&D pathway that SMEs typically represent.

The central question of this study as outlined in the introduction was whether there is a need for new and innovative systems for financing R&D for poverty related diseases, and if there is a role for Sida to play alongside industry and research community in this field. The desk study and interviews with financing professionals have shown that there is great potential in the many modalities that are currently being tested by several multilateral development part-

nerships. It is our conclusion that there is still need for additional funding, and that there is potential to replicate and expand some of the modalities already tested, rather than reinvent a whole new system. It is also our conclusion that Sida has an important role to play in fostering R&D for neglected diseases, and has the potential to assist the pharmaceutical and biotechnology industry by designing a financing mechanism that can help mobilise the Swedish resource base.

To better understand the financial prerequisites for bringing new products to market, it is useful to consider the full development cycle. The figure below illustrates the different phases of drug development, and what the likely financing sources can be for each individual phase.

We have highlighted three areas of the R&D process where Sida could play a catalytic role in supporting product development.



4.2 Recommendations for Sida

4.2.1 Swedish Academia and Research Institutions

Swedish research on global health issues and, more specifically, poverty related diseases is of high international standard. As shown in the figure above, the first stages of the R&D pathway typically rely on funding from the public sector. Economic incentives aimed at early-stage research would indeed be beneficial from a know-

ledge-generation point of view (which in turn, constitutes the foundation for all successful product development). Such financing is however, already in place, at least technically, through the Swedish Research Council and Sida, though to an insufficient extent. The Swedish Research Council has historically had its focus on basic research and its priority setting has been guided by scientific quality, rather than medical urgency. This may change in the near future as the Swedish Research Council in its research strategy for 2009–2012 opens for a more need driven approach: *Basic research in areas of high priority should receive an annual increment of SEK 200 million, i.e. a total of SEK 800 million over the planning period. Initially, two programmes are to start: 'Globally Changing Societies' and 'Energy, Climate and Environment'. Additional high-priority areas will be identified, after which the Board will decide which programmes to start in the latter part of the period.*[41]

The other important funder of Swedish research in this field, Sida, on the other hand has very small funds that can be allocated to domestic research (in part due to DAC restrictions).

A common view in the research community is that there actually is a financing gap within the Swedish public sector. So called innovative financing mechanisms which attract additional funding from private sources are however very unlikely to generate the desired catalytic effects when applied to stages prior to commercialisation.

In order to optimise the outcome of Swedish R&D efforts in the field of third world health it would most probably be beneficial to strengthen the coordination between Sida on the one hand and other actors in public sector research funding on the other hand. A possible first step could therefore be to gather relevant stakeholders to a consultative meeting.

4.2.2 Bridge Financing Facility

It appears that many research driven companies have trouble attracting capital at various points in the mid-cycle product development process, as briefly discussed in chapter 3. While there are some well-established sources of public funding for early stage basic research, companies often experience a gap in available financing at some point before their innovation has reached a stage that is interesting for private financiers.

The exact point at which financing dries up may vary from one company to another, but initial evidence suggests that around the

41 http://www.vr.se/responsibilities/researchpolicy/thecouncilsresearchstrategy20092012.4.76ac7139118ccc2078b80003530.html

pre-clinical/tox test stage many research projects run into financing difficulty. At this stage a cash infusion in the order of SEK 2–3 million could be sufficient to "bridge" the project to the next stage, at which point it may have a significantly better chance of attracting commercial funding. The bridge financing facility could therefore be both additional and catalytic, since it will help bring a research project with relevance for neglected disease development forward to a stage where it attracts private money.

In practice, this type of facility could be structured along the lines of the Innovation Loans as outlined in the Lindahl report and briefly discussed in chapter 2. However, close attention needs to be given to the optimal setup of such a facility. Experience from Sida's work with Conditional Loans show that they are very cumbersome to administrate. A framework agreement setup could be envisaged that would make for a more manageable facility, where a lump sum is allocated for periodical call offs according to a predetermined set of criteria. It should also be possible for a company to apply for additional funding if they are unable to attract commercial funds after the first injection is depleted, and their research still shows real prospects for poverty reduction. Furthermore, it is not clear that the loan model will yield the most efficient results. In reality, contributions to this stage of the research cycle must be considered very risky, and it is likely that very few projects will make it commercialisation. It is possible that an equity contribution along the lines of a venture capital model would yield similar results in terms of risk and return, but with significantly lower administrative costs.

Whether in the form of an innovation loan or some variation on that theme, a bridge financing facility to this stage of the research cycle could make a significant impact to bringing products with clear relevance to poverty reduction forward. It could also bridge mid-stage R&D projects forward to other types of funding at a later stage, such as commercial equity financing or an AMC type subsidy. Crucial to its success, however, will be for Sida to draw on expertise in innovation management and private sector support from other institutions that already have that infrastructure and knowledge, such as Vinnova and Swedfund. One possible model for this facility could be an innovation fund managed by Swedfund with technical and product related support from Vinnova and with a financial backing from Sida in the form of a guarantee to attract cheap financing, possibly with some form of subsidy mechanism attached if needed. A first step could be for Sida to

call relevant parties to a consultative meeting to further discuss possible modalities for cooperation. We conclude that the bridge financing facility is an interesting area for further study.

4.2.3 Risk Mitigating Mechanism

In the late stages of product development, incentives can be needed to encourage research firms and large pharmaceutical companies to prioritise products with relevance for poverty related diseases. As discussed in chapter 2, perceived risks associated with developing markets, such as unstable political and financial environment or weak purchasing power, often deter private firms to enter these markets alone.

The market guarantee model as pioneered in the AMC pilot for pneumococcal vaccines provides a targeted risk mitigation effort addressed at a specific market failure – developing countries weak purchasing power for products they strongly demand. The AMC model has huge potential, and could provide a blueprint for incentives to late-stage product development if it proves to be successful. However, it is too early to determine the relative effectiveness of this model, since it is only just launched. Furthermore, market guarantees require a commitment of larges sums of money to be effective, and also require considerable investment in administration and infrastructure. It is probably wise to share the risks in this type of endeavour with other donors, as is the case with the AMC in the framework of the GAVI Alliance. Nevertheless, if the objective is to support the commercialisation of drugs and vaccines in the late-stage R&D cycle, an AMC-style subsidy appears to be the most interesting model for public/private cooperation.

The Lindahl report outlined market guarantees as a potential future financing tool for Sida, and recent political discussions seem to favour new ways of using development aid to incentivise private sector involvement in the development of drugs and vaccines for neglected diseases. The preferred modality of such support would certainly need to be evaluated further and in more detail, but one possibility could be for Sida to identify one prioritised research area and look into the possibility of setting up a second AMC within one of the existing multilateral channels. The alternative would be to set up a standalone market guarantee structure, which could probably draw on experiences made elsewhere and could incorporate the knowhow of existing organisations such as Vinnova and VIF. It should be noted that this is likely to be a substantial task,

and that GAVI spent several years and substantial resources to set up the initial AMC. It should not be ruled out, however, that other types of risk mitigation initiatives could provide better risk and return characteristics, such as partial guarantees for credit, currency or commercial risk. Historically, Sida's development loan and guarantee portfolio has not targeted the health sector. An effort to direct these existing instruments towards this area could help mitigate some of the risks facing the late-stage development process for drugs and vaccines for neglected diseases. For example, credit risk coverage in the form of a bank guarantee could help industry attract more financing for projects with relevance for poor countries, although it is perhaps not likely that a credit guarantee alone would be sufficient to bring about a change in behaviour among large multinational corporations. A first step could be for Sida to assemble relevant industry stakeholders to better understand their specific risk coverage needs. We conclude that market guarantees could be an interesting area for further study once more evidence of its effectiveness is available, and that other types of risk mitigation initiatives could be of equal interest.

Appendix 1.

Summary of Financing Mechanisms

The recently developed innovative financing tools are promising initiatives that show potential to catalyse increased private sector involvement in developing vaccines for neglected diseases. So far, however, it is a bit premature to draw any real conclusions on their relative effectiveness, since most are too young to have yielded any meaningful track record. It is too early to talk of "proof of concept", and this probably won't be possible until thorough midterm reviews have been conducted on the initiatives. It is clear though that the different initiatives have been effective in various ways to attract additional funding to the complement official development assistance. This positive momentum should be encouraged and be expanded to include other sectors as well.

The *frontloaded funding model* has been a success, but one that is heavily dependant on financial markets for financing. Recent volatility in stock markets may affect the risk willingness of investors to participate in this type of activity. On the other hand, the strong backing of the underlying donor countries should provide a safe haven for investors, and it could turn out that this type of pooled financing will be benefited in times of financial stress. High transaction costs further emphasise the rationale for carrying out this funding activity in a multilateral fashion going forward.

The *market guarantee model* shows great potential in mobilising large multinational corporations to the neglected disease arena, but requires a vast infrastructure of expertise reference groups, as well as substantial upfront investment in terms of market and pricing analysis. Other donors, such as DFID who have been strong advocates of the AMC model, have expressed a willingness to continue this type of activity and to expand it into other sectors, once they see real evidence that the model is working. They stress, however, that since it is a new approach with substantial costs and risks

attached, they will likely continue working with market guarantees in a multilateral format, sharing costs and risks with other donors.

The *venture capital model* pioneered by the Gates Foundation shows perhaps the most innovation friendly way of fostering product development, with a particular emphasis on promoting young and novel ideas away from the traditional research path. In doing so they accept that the vast majority of investments will not pay off, but by supporting many small initiatives they can make a real difference by capturing a small handful of ideas that have the potential of changing the course of neglected disease research. This model could also be considered as a loan model, which would limit the financial risk somewhat, but would also require more administrative work.

The *price subsidy model* appears to be working well in the infrastructure sectors with successful delivery examples in rural electrification and water connectivity. These efforts should be continued and used to try new things as well. The health sector has benefited from price subsidies schemes as well, but the nature of this type of instrument means it has centred on product delivery rather than product development. As such it can be a meaningful complement to product development initiatives.

Finally, the *solidarity tax model* and *debt relief model* have shown promising examples of how to channel additional funds to the Global Fund and UnitAid. Some initiatives such as the French Airline Tax have been surprisingly effective; others like Product Red have been questioned in terms of sustainability. Clearly a national tax levy can have a significant contribution, even for a relatively small country like Sweden. This is will be a political consideration and will probably not be Sida's decision.

Appendix 2.

TOR: Framework for Pre-Feasibility Study

Purpose and Goal of Study:
The overall purpose is to enable an increased cooperation between aid organisations and private business. Specifically, the purpose of this study is to create a mechanism for the development and manufacturing of affordable drugs and vaccines for the most important communicable diseases in poor countries.

The main task is to develop a mechanism for financing. Importantly, the study should seek to identify the prerequisites for making such a mechanism successful, including potential organisational and budget constraints at Sida as well as its interaction with the pharmaceutical industry. Although the target sector is drugs and vaccines and primarily will be evaluated within the Swedish research community, this financing mechanismis envisaged to be utilised in other sectors as well.

For the purpose of the study, the sector limitations will include affordable drugs and vaccines that address diseases in least developed countries, though not limited to infectious diseases.

Suggested Report Structure

Chapter 1: Introduction (VIF/JA)
In low-income countries infectious diseases account for a large portion of the burden on the health care systems and cause the highest numbers of deaths as well as of lost healthy years[1], even if a shift towards increasing importance of some chronic diseases has occurred[2]resulting in the so called double burden. Based on other publications and health statistics[3]six important communicable diseases (or groups of diseases) in poor countries can be identified: acute respiratory infection, HIV/AIDS, diarrhoea, vaccine-preventable childhood diseases, malaria and tuberculosis. These diseases cause

a vast majority of the infectious disease 15 million annual death toll, of which nearly half are children under the age of five.

Considering the above facts, there is an imminent need for research, development and production of new medicines and vaccines targeting diseases that, exclusively or predominantly, affect poor people in developing countries.

There is a lack of incentives for the pharmaceutical and biotechnology sector to invest in products and services for developing countries.

Although donor funding for drugs and vaccines has increased in recent years, there is a real need to develop innovative financing mechanisms that can help mobilize additional capital, helping the development of drugs and vaccines for poor people. Creating incentives for the pharmaceutical industry to develop new drugs and vaccines is essential, as well as catalyzing private investments for pharmaceuticals that address the diseases of the developing world.

The public sector can increase its effectiveness as a R&D funder by actively seeking to promote additional private sector investment. Although Sida already funds research projects in the health sector, more can be done to utilize available financing mechanisms, including credits and guarantees. Achieving the leverage effect of improving the efficiency of available funding systems, while at the same time catalyzing private sector investment will be essential to reaching Sidas development goals.

Chapter 2: Financing Mechanisms (JA)

The purpose of the chapter is to investigate whether it is meaningful for Sida to develop new financing mechanisms for the health sector in developing countries, and if so how this mechansim should operate for optimal impact. Focus should be on designing an instrument that can adress the specific financing shortfalls of the pharmaceutical sector, taking into account appropriate level of risk coverage, ability to leverage aid money with external funds etc.

1. *Mapping of Sida's Financing Mechanisms*
   - Taking into account the relevant considerations and excerpts from the recent KGU report
   - Analyzing current constraints in Sida's financing mechanisms
   - Introducing Innovation Loans and Market Guarantees to the tool kit
   - Aid budget, Organisation and other considerations

2. *Mapping of External Financing Mechanisms*
   – What are the prioritized areas of funding for the health sector within the donor/DFI community?
   – What are donors and DFIs already doing to successfully mobilize private resources: DFID Challenge Funds, USAid guarantees, IFC etc.
   – What mechanisms currently exist specifically for the health sector: GAVI Alliance AMC/IFFIM, Gates Foundation, WHO
   – What other subsidy mechanisms could be considered: World Bank/PIDG/GPOBA?
   – Potential cooperation with research funds – Vinnova, Vetenskapsrådet?
   – Are there any other interesting initiatives being developed in the DFI community: FMO and other European DFIs
   – What could be applicable solutions for catalyzing health finance, that are currently successful elsewhere in the private financial sector?

3. *Lessons Learned From External Examples*
   – What works and what doesn't?
   – What are the major constraints to raising funds for pharmaceutical reseach and health sector in general?
   – Are there any specific organisational constraints involved?
   – Do existing financing solutions correspond to needs/constraints of pharma sector?
   – Do existing financing solutions correspond to actual demand for specific health services in developing countries?
   – What is missing?

4. *How Can Sida Best Contribute to Financing of the Health Sector*
   – Is a meaningful contribution feasible given Swedish aid budget?
   – What is needed from Sida's internal process and organisation?
   – How can the relevant financing mechanisms best be developed?
   – Who are the interesting cooperation partners in this field?

Chapter 3: Medical Issues (VIF)

Overall aim: To investigate whether Swedish aid efforts could create financial incentives for the pharmaceutical industry to increase their actions in the fight against poverty-related infectious disease.

1. *Mapping of the Swedish research sector*

- Delimitations:
  - What are the strong (important) areas of Swedish research within the field of infectious diseases?
  - Inventory:
  - Status today: mapping out relevant research projects in Sweden (current and future).
- External considerations:
  - What is happening on the international level within the defined area including examples of important research projects.
  - What is the current situation in regard to international competition within R&D today and how might this reflect on the future strategy of the pharmaceutical industry.
  - Mapping of the needs in developing countries including an analysis of whether these will/can be met by the commercial sector.

2. *Mapping of the pharmaceutical sector*

- Strong development projects within the medical sector in Sweden
  - Within the pharmaceutical sector
  - Within the Life Science sector (including SMEs)
- External analysis
  - A survey of the global situation within the pharmaceutical sector with regards to development of drugs and vaccines that address communicable diseases in low income countries.

3. *Areas of application and types of therapies*

  - Drugs
  - Vaccines
  - Diagnostics
  - Other products/services
- Planned investments and launches
  - Known (official) commercial launches in the near future
- Commercial prerequisites
  - Need (demand, emerging markets etc.)
  - Underlying factors for lack of investments/lack of funds for research of infectious diseases within the pharmaceutical sector

4. Further considerations

- How could collaboration between researchers and industry improve in regards to R&D for new drugs and vaccines targeting developing countries
- How could the pharmaceutical sector benefit from the ongoing/future important Swedish research within infectious diseases
- How could the existing commercial constraints be overcome:
  – Through the companies/enterprises
  – Through society/including Swedish Aid
  – Through general and/or specific other strong measures

Chapter 4: Recommendations for Further Analysis and/or Implementation (VIF/JA)

Chapter 5: Conclusion (VIF/JA)

Restrictions

- Rules & Regulations of the Swedish society
- Rules & Regulations concerning competition
- Rules & Regulations concerning intellectual property rights
- Other identified restrictions

Endnotes

1. *The University of Gothenburg* has a long tradition of research on mucosal immunology and vaccines for mucosal pathogens/diseases, for example diarrheal diseases such as cholera and ETEC; respiratory infections with a focus on pneumonia and influenza, and genital infections, especially chlamydiae and HSV-2.

   University of Gothenburg also has a strong research project, the mucosal Immunobiology and Vaccine Center (MIVAC), which is a strategic research center with support from the Foundation for Strategic Research. The center has 19 teams, including more than 100 people with a focus on basic immunology, cell biology, protein chemistry, glycobiology, microbiology and vaccinology.

   The University has also in recent years run a large water project in cooperation with Kristineberg Marine Research in Fiskebäckskil focusing on microbial pathogens in water and the influence of environmental factors (climate, etc.).

2. At the *Department of Microbiology, Tumor and Cell Biology* (MTC), Karolinska Institutet, there is a large number of researchers focusing on poverty related infectious diseases such as malaria, tuberculosis, HIV, diarrheal diseases and Pneumococcal infections, including pneumonia, both in basal molecular level and with a focus on products such as new vaccines and diagnostics. By combining modern genetic tools including large-scale sequencing with epidemiology and clinical data, disease mechanisms and the spread of infectious diseases in the world are studied. The interaction between the host (humans) and microbes relevant to the onset of disease and latent infection are investigated

using advanced imaging technology and infection models. Also, the human defence against infections, innate as well as acquired immune response, is studied.

3. Focus on *CIM* is on immuno-pathogenic and therapeutic studies of chronic infectious diseases, particularly HIV, hepatitis and tuberculosis. The Foundation for Strategic Research (SSF) appointed CIM one of six national strategic research centers. These centers will be time limited, scientifically focused and geographically collocated research environments. SSF's intention is that these centers will have sufficient intellectual and technological masses to become world leading.

4. *KTH* were among the first to realize the potential of modern biotechnology and has actively strived to transform its department for biochemistry and bioprocesses to a full-fledged School of Biotechnology. KTH has hosted a couple of Sweden's largest scientific projects, where one of them, the Human Proteome Atlas, is ongoing. Mathias Uhlén, Professor at the Department of Microbiology, has as a scientist and entrepreneur created several new Swedish biotech firms with international development force. He has co-founded six new companies related to his research, Pyrosequencing (now Biotage), Affibody, Magnetic Biosolutions, Creative Peptides, SweTree Visual Genomics and Bioinformatics.

5. *The Swedish Institute for Infectious Disease Control* (SMI) is a governmental expert agency, with the mission to monitor the epidemiological situation for infectious diseases in humans. It is also responsible for promoting protection against such diseases. SMI has for many years been engaged in the fight against infectious diseases in poor countries. SMI assists the Government and other authorities with expert advice and how to combat and control these.

   The Swedish Institute for Infectious Disease Control has built up a large knowledge base and experience of contagious diseases as HIV / AIDS, malaria, tuberculosis, hepatitis, diarrheal diseases, pneumonia (Pneumococcal infections), control of hospital-related infections and biosafety as well as antibiotic resistance. SMI operates several ambitious vaccine development projects, including HIV and tuberculosis, where SMI is active

in the whole process from the design of new vaccine prototypes through animal testing to full-scale field trials on humans in Sweden as well as in Africa.

For a number of years SMI has, on the basis of their expertise, provided assistance to both international organizations and poor countries directly with knowledge to strengthen the ability to fight poverty-related infectious diseases. For example, SMI has participated in efforts to combat HIV / AIDS in many of the world's poorest countries (including Guinea-Bissau, Tanzania and Mozambique) since the disease was discovered in the early 1980s. Tools for diagnosis and monitoring of HIV infection were established early and SMI has ever since played a leading role in the development of these areas, including the Cooperation Center for UNAIDS and WHO. On this basis, the SMI participated in numerous development projects which among other things include local capacity-building, epidemiological surveillance, voluntary testing, blood donor screening and preparation for vaccine trials and prevention of mother to child HIV transmission.

SMI has unique skills for research and identification of infectious diseases worldwide dissemination via so-called molecular epidemiology. These include HIV, tuberculosis, hepatitis and malaria, but also many other important infectious agents. SMI currently has Europe's most modern laboratory of the highest safety class (P4) and has since decades built up a unique knowledge base and experience in domestic and exotic microbes, especially viral and bacterial zoonoses. Through high-quality research and innovation, and through a series of active international networks, SMI's Centre for Microbiological Preparedness (KCB) occupies a leading role in terms of both diagnostic and research for a number of so-called emerging infections.

Astrid Fagraeuslaboratoriet at SMI has laboratories for animal testing of P3-organisms, and is the only laboratory in the Nordic region in which one can work with primates when conducting, for example, HIV research.

SMI has received special support from the government to build a clinical vaccine platform for research and evaluation of vaccines. This platform is of great importance for the new vaccine products to be tested in an adequate manner and enables comparison with previous attempts, or with other products. The

platform is also used internationally in several development projects which secures that Sweden will be a major player in the field.

6. *Stockholm University* (SU) performs research within a wide range of scientific themes including bioinformatics, immunology, microbiology, molecular biology and social anthropology, where about 4 internationally leading groups at the Department of Immunology, Wenner-Gren Institute and the Department of Genetics, Microbiology and Toxicology are working on issues related to the infection biology. The Department of Immunology has a long and internationally well-established tradition of train students from developing countries with assistance from the Multilateral Initiative on Malaria (MIM) and the EDCTP. Since 2006, the Department of Genetics, Microbiology and Toxicology (GMT) has a P3 laboratory in which mosquitoes infected with P. falciparum, the most dangerous malaria parasite, can be worked on. Only a handful such laboratories exist in Europe and the one at SU is the first of its kind in the Nordic region.

7. Since many years, *Umeå University* holds a strong position in microbiology and were pioneers in the country to establish recombinant DNA technology as a tool for molecular genetic research and biotechnological applications. The strong microbial research in Umeå was highlighted in 2007 by the Swedish Research Council with a large appropriation for the establishment of the Laboratory for Molecular Infection Medicine Sweden (MIMS). This new research unit was started by researchers who belong to a multi-faculty center for microbial research, Umeå Center for Microbial Research (UCMR), and who work in the fields of microbiology, molecular biology, structural biology, medical biochemistry, organic chemistry and physics. Research in UCMR focuses on the pathogenic mechanisms of various microorganisms, such as bacteria, viruses and parasites. The projects consist mainly of basic research while the new findings may develop in applied direction, for example, in the creation of new vaccines and anti-microbial agents. Among other things, the so-called virulence blockers were identified and characterized and now constitute a basis for biotechnology development in the region. UCMR has also received support

from the Swedish Research Council to run a research school in 2008–2012. A total of 50–60 graduate students, both from Umeå as national and international partner universities will participate in the program within the first two years.

FOI CBRN protection and security in Umeå has a P3 laboratory that is part of a European network. The network provides access to unique collections of diseasecausing bacteria including pathogens that cause severe diarrhoea in the third world, such as Vibrio cholerae and Burkholderia.

8. *Uppsala University* has its strengths especially in the fields of microbiology, molecular biology, pharmacology and structural biology, where a dozen leading international groups located at the Biomedical Center and Uppsala University Hospital is working with infection biology. These research groups study bacterial, viral and parasitic disease mechanisms, antibiotic resistance, dosing of antimicrobial agents and rational strategies for the development of new drugs against infectious diseases. In addition, several groups at Rudbecklaboratoriet and Ångströmlaboratoriet are world leading in the development of new, cheap and rapid diagnostic methods for different types of micro-organisms. The development of these diagnostic projects takes place in collaboration with the National Veterinary Institute and the Swedish University of Agricultural Sciences.

   At Uppsala University another world leading group work on the subject pharmacometrics and develops pharmacokinetic and pharmacodynamic models of value to make the preclinical and clinical drug development more efficient. An important objective of the models is to predict the relationship between dosing regimens and response to therapy at an early stage.

9. *Karolinska Institute* has the highest concentration of research on global health in northern Europe, with a network of public health and international health researchers.

   Three quarters of the world's maternal mortality and two-thirds of child mortality could be prevented using known interventions, if they only were implemented to scale. The group "Health systems and policy" at IHCAR's goal is to bridge over the Know-Do Gap – so that evidence-based knowledge will come to use in policy and practice. The group's work is based on the belief that research, training and practice are naturally

interrelated in the health care/health systems research. The vision involves long-term work in which capacity-reinforcing and institutional cooperation with selected countries is the foundation and postgraduate students from resource-poor environments comprise a cornerstone. The research is composed both of the ground- work for mapping and understanding of the processes within existing systems, and of intervention research in which different methods and strategies to improve health are studied and evaluated.

At the Department of Medical Epidemiology and Biostatistics (MEB) there is a group working on infection epidemiology, with two adjunct professors funded by the European Center for Disease Prevention and Control (ECDC). The group works among other things with infection modelling and analysis of infection risks in different parts of the world.

10. *Nordiska högskolan för folkhälsovetenskap*, Nordic School of Public Health, based in Gothenburg has started a Nordic network for global health and organizes a series of meetings and courses on this subject.

11. At *The Swedish Institute for Infectious Disease Control* global health research is conducted, both in Sweden and internationally especially in Africa (Uganda, Tanzania, Mozambique, Guinea-Bissau, etc.) SMI also participates in a number of EU projects aiming at a better understanding of the emergence and spread of disease and resistance development with relevance to global infectious diseases such as severe Pneumococcal infections (pneumonia, blood poisoning, meningitis), malaria, HIV and tuberculosis. The linkage between chronic infections to cancer is also studied.

12. *Umeå University* hosts a global health research center on, with Professor Stig Wall as project manager. The research center has its origin in the unit of Epidemiology and Public Health in Portsmouth, but is based on a number of research projects and collaborations, primarily in Ethiopia, Tanzania, Vietnam, Indonesia, Nicaragua and South Africa. Medics, sociologists, statisticians, social workers, physiotherapists and health economists are associated with the center.

Sida works according to directives of the Swedish Parliament and Government to reduce poverty in the world, a task that requires cooperation and persistence. Through development cooperation, Sweden assists countries in Africa, Asia, Europe and Latin America. Each country is responsible for its own development. Sida provides resources and develops knowledge, skills and expertise. This increases the world's prosperity.

Innovative Finance for Health – Exploring Incentives for Neglected Disease R&D

Despite all efforts to stimulate research, development and production of drugs against neglected diseases (malaria, tuberculosis etc) efficient and affordable drugs are still lacking. This study, commissioned by Swedish International Development Cooperation Agency, proposes three different areas of possible action: A research program, a bridge finance facility for mid-cycle R&D and a risk mitigation mechanism for late-cycle R&D.

SWEDISH INTERNATIONAL DEVELOPMENT COOPERATION AGENCY

Address: SE-105 25 Stockholm, Sweden.
Visiting address: Valhallavägen 199.
Phone: +46 (0)8-698 50 00. Fax: +46 (0)8-20 88 64.
www.sida.se sida@sida.se

Sida