Report of EWG (DRAFT)

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ACRONYMS

AMC	Advanced Market Commitment
ARV	Anti-Retroviral Drug
C2F	Cap to Fund
CD	Chronic Disease
CDPP	Chagas Disease Product Prizes
CPMF	Provisional Contribution to Financial Transactions
CPMRD	Committee on Priority Medical Research and Development
CROs	Contract Research Organisations
CTDL	Currency Transaction Development Levy
DALY	Disability-Adjusted Life Year
DCs	Developing Countries
DFID	Department for International Development (United Kingdom)
EC-IMI	European Commission – Innovative Medicines Initiative
EPF	Economic Prize Fund
EDL	Essential Drugs List
EFPIA	European Federation of Pharmaceutical Industry Associations
EMEA	European Medicines Agency
ETS	Emissions Trading Scheme
EU	European Union
EWG	World Health Organization Expert Working Group on R&D Financing
FAPESP	State of São Paulo Research Foundation
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
FRIND	Fund for R&D in Neglected Diseases
FTO	Fast Track Option
GAVI	Global Alliance for Vaccines and Immunisation
GBOs	Grassroots Business Organizations
GDP	Gross Domestic Product
GFATM	Global Fund to Fight AIDS, TB and Malaria

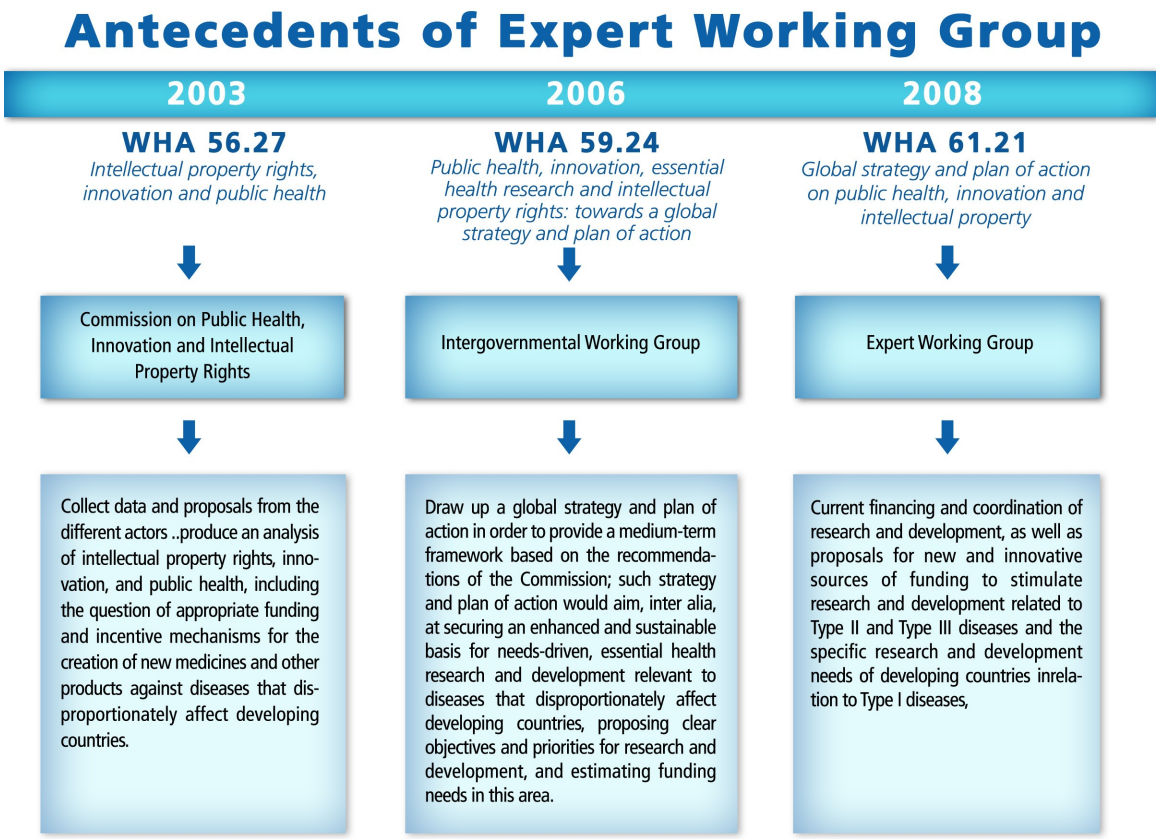
GIP	Green Intellectual Property
GSK	GlaxoSmithKline
HIF	Health Impact Fund
IAVI	International AIDS Vaccine Initative
IDCs	Innovative Developing Countries
IFFnd	International Finance Facility for neglected Diseases
IP	Intellectual Property
IRFF	Industry R&D Facilitation Fund
LDCs	Least Developed Countries
LIDCs	Low Income Developing Countries
LMICs	Low and Middle Income Countries
MMV	Medicines for Malaria Venture
MNC	Multinational Pharmaceutical Company
MVG	Minimum Volume Guarantee
MVI	PATH Malaria Vaccine Initiative
NCDs	Non-communicable Diseases
ND	Neglected Disease
NTD	Neglected Tropical Diseases
ODA	Official Development Assistance
ODL	Orphan Drug Legislation
PAHO	Pan American Health Organisation
PATH	Program for Appropriate Technology in Health
PDP-FF	Product Development Partnership Financing Facility
PDPs	Product Development Partnerships
PIPE	FAPESP's Technological Innovation in Small Businesses program
PMV/pf	Priority Medicines and Vaccines Prize Fund
PRV	Priority Review Voucher
QALYs	Quality-adjusted Life Years
R&D	Research & Development
RH	Reproductive Health
Rol	Return on investment

S&T	Science and Technology
SBIR	Small Business Innovation Research Programme (United States)
SBIRI	Small Business Innovation Research Initiative (India)
SBRI	Small Business Research Initiative (United Kingdom)
SMEs	Small to Medium Enterprise
TDR	WHO-based Special Programme for Research and Training in Tropical Diseases
TIPR	Transferable Intellectual Property Rights
TPP	Target Product Profile
VRR	Vaccine Research Relief
VSC	Voluntary Solidarity Contributions
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme
WT	Wellcome Trust
WT-SDD	Wellcome Trust Seeding Drug Discover

Executive Summary

There is persistent and growing concern that the benefits of the advances in health technology are not reaching the poor. The emphasis of the developed world is naturally on the solution of the problems that affect it predominantly. This is in spite of the evidence of the heavy burden of disease on the poor, which in addition to being one of the more egregious manifestations of inequity, could undoubtedly affect overall global stability. There is convincing evidence of the poor bearing a double burden of disease, but there is still no indication of adequate research and development to address the Type II and III diseases. This growing focus on the diseases of the poor has led to examination of the relationship between intellectual property rights, innovation and public health, and the gap in the innovation cycle with the concern that strict observance of IPRs could be inhibiting the application in public health generally to the benefits of innovations that take place in the developed world.

The Chart below gives a description of the evolution of the Expert Working Group



The following represents a synthesis of the work of the EWG and the conclusions/recommendations in line with its mandate.

Financing of Research and Development

Examination of financing was not limited to the mobilization of resources, but also encompassed the efficiency of allocation of such resources. There are two major considerations with respect to financing of R&D-stability and avoidance or mitigation of market risks. The stability of financing is so critical it cannot be left solely to market mechanisms especially in relation to the needs of the developing countries. The schemes examined included those intended to front-load financing by creating an international financing facility which has been modified to become for the time being the International Financing Facility for immunization to generate funds through bond offerings for the purchase of vaccines. This arrangement may produce stability but does NOT generate additional funding.

In order to mitigate market risk the Advance Market Commitment scheme has been developed whereby group of donors have made a binding commitment to purchase a vaccine, thereby creating a quasi-market that eventually removes or reduces the risk to the agent that develops the vaccine.

Note: These two mechanisms are to be welcomed, but must be followed carefully to determine if indeed they lead to stability of funding and to keep under review their potential to address other technologies besides vaccines which are well established s and have a long history of successful application.

But there is also need for incentive structures to stimulate R&D when there is no market or there is market failure in the production and diffusion of knowledge. The EWG examined this in the context of the nature of knowledge as a public good and pointed out the two main incentive structures available. These basically are the IPRs and public support. The relevance of the integrity of IPRs is well documented with respect to the need to foster and favor R&D. However, attention was paid more specifically to the role of the public and the need to reinforce this role in both developed and developing countries in the provision of knowledge leading to appropriate technologies of particular interest to the developing countries. Direct public support is through the grants, procurement contracts and prizes. The use of one or the other is highly context specific. Indirect public support may be through such measures as tax exemptions.

A framework for financing options for R&D considers two dimensions.

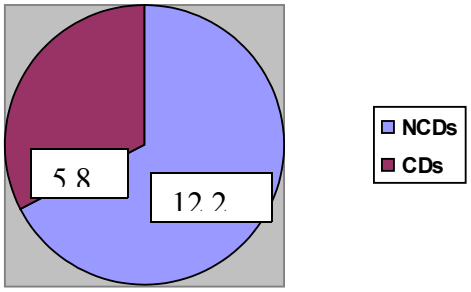
i. The first dimension is whether the knowledge required by the poor already exists. If it does, then the challenge is mostly associated with ensuring the diffusion of knowledge. If it does not exist yet, then the challenge is to ensure that it is generated.
ii. The second dimension is whether the innovations (knowledge) are relevant for the poor only, or are relevant both for the developing and industrial countries.

The most troubling situation occurs when knowledge that is predominantly applicable to the problems of the poor developing countries does not exist and therefore needs to be developed.

The approaches to be considered are those that bring together the technological capability of public and private actors mainly in developing countries. Apart from tax credits, orphan drug legislation and mobilizing the research capacity of developed country national research establishments, the most promising approach is through the formation of public/private partnerships. PPPs are now managing increasing amounts of research funding and probably represent the best way to stimulate the R&D necessary for tackling the Type II and Type III diseases that affect the poor disproportionately.

Note: Progress in stimulating R&D for the diseases of the poor must emphasize more the role of the public sector, introducing more firmly the visible hand of the state into the market.

The financing of R&D was examined, dividing diseases into the noncommunicable and the communicable groups for ease of analysis and because the data sources lent themselves to this analysis more readily than if the taxonomy of Types I, II and III had been used. Three categories of funding were examined. Public (France, Germany, Japan, UK and USA), industry and Charity/private foundations. There were limitations in the data sources, but there are enough data to allow general conclusions.



public sectors in the five countries-$ International 12.2 million to NCDs and 5.8 to CDs.

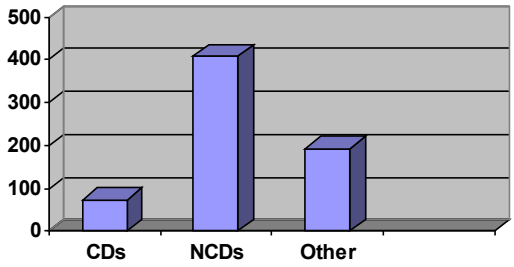
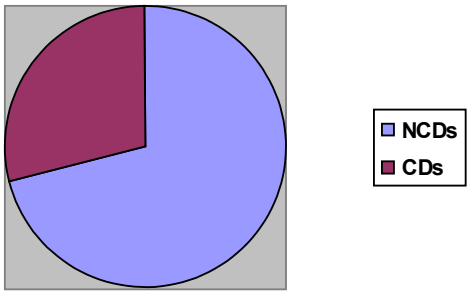


Figure 2 shows the number of drugs in development by 10 major pharmaceutical firms for Communicable, noncommunicable and other diseases. The R&D budget for these companies for 2008 at $ 43.9 Billion was 62.4 % of the whole Pharmaceutical industry's R&D budget for R&D.



A total of US $ 2.5 billion was identified as investment by private not-for profit institutions and was distributed by percentage as shown in figure 3

The total sector investments in R&D by category reflect the predominance of funding dedicated to noncommunicable diseases. (Table1) For all sectors expenditure on cancer dwarfed expenditure in all categories.

Table 1
Total Sector Investments in Health R&D by Category in International $ (2008)

	Public Sector		Private Sector		Not-for-profit		Total	
Category	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent
Non-Comunicable Total	$12'168.7	67.8%	$29'390.0	68.4%	$1'650.4	66.7%	$43'209.1	68.2%
Communicable Disease Total	$5'766.2	32.2%	$13'590.0	31.6%	$822.9	33.3%	$20'179.1	31.8%
Total	**$17'934.9**	**100.0%**	**$42'980.0**	**100.0%**	**$2'473.3**	**100.0%**	**$63'388.2**	**100.0%**

Resource tracking is seen as indispensable for any attempt at monitoring coordination of financing for R&D. This relatively new field has been pioneered by the Commission on Health Research for Development which initially in 1986 estimated that the world spent $US 80 billion on health R&D but about 5% of that sum was being applied to the health problems of the developing countries. Currently there are increasing amounts of data on ODA and the financial flows to health but a comprehensive system for analysis of the flows to R&D is sadly lacking and should be established.

Coordination of Research and Development

Similarly, there is no global coordination of R&D for diseases generally and less so for Types II and III. Analysis of coordination by disease, health area or by product could elucidate examples in each area, but there was no overall coordination mechanism. Each of the examples chosen could demonstrate coordination internal to the area usually through committees, Boards and technical specialist groupings.

There has been more progress in policy coordination for R&D and various fora have been established to allow international funders and AID agencies to coordinate and harmonize their efforts. One such example is ESSENCE (Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts) which is a collaborative framework for

funding agencies to ensure synergies in addressing research capacity needs. It aims to improve the impact of investment in institutions and enabling mechanisms that address the identified needs and priorities within national strategies on research for health. The secretariat is hosted by TDR, and the initial executive group includes development cooperation agencies – the United Kingdom Department for International Development (DFID), International Development Research Centre (IDRC), the Ministry of Foreign Affairs of the Netherlands, Norwegian, Agency for Development Cooperation (Norad), the Swedish International Development Cooperation Agency (Sida) – plus the Bill & Melinda Gates Foundation, the Wellcome Trust and NEPAD Science, Technology & Innovation.

A series of mapping tools have been developed to map initiatives in R&D and provide information to interested donors and researchers. One such example is The Council on Health Research for Development's Health Research Web, a web-based, interactive and growing source of information on the structure and organisation of research for health in and for low and middle income countries. The tool is aimed at maximizing the impact of research on health, equity and development in low and middle income countries is a response to the problem that there is no single source of information on research for health that is organised from the perspective of low and middle income countries; it is organised to provide integrated information on research for health at country and regional levels in order to strengthen national health research capability. Users can search by country for information on ongoing health research, health research priorities, key institutions, financing and partnerships, resources and country background, among others.

The World Health Organization itself has recognized the need for coordination of research internally and has initiated a process for coordination of the eight health research organizations and initiatives that have some role in the oversight and reporting on research globally, although they are not themselves engaged in research The eight selected were

- The Alliance for Health Policy and Systems Research (AHSPR)
- The Council on Health Research for development (COHRED)
- The Global Forum for Health Research (GFHR)
- The Special Program of Research, Development and Research Training in Human Reproductive health (HRP)
- The Initiative for Vaccine Research (IVR)
- WHO Secretariat on Public health, Innovation and Intellectual property (WHO PHI led IGWG process)
- The Special Program for Research and training in Tropical Diseases (TDR)Research

Any global coordination of R&D is challenging and will need identification of priority areas for action; in the distribution of the needed research effort between the different competent entities and in the financing of the R&D.

A proposal is made for a structure to satisfy these deficiencies that would involve establishing oversight and technical working groups. But the main element would be the creation of a Global Health Research and Innovation Fund (GHRIF) to provide funding for:

- targeted R&D for new drugs, vaccines, diagnostics, and intervention strategies against priority health conditions of the poor – including both CDs and NCDs that are prevalent in LMICS and for which adequate interventions are not presently available.
- a range of research areas primarily conducted in LMICs that are essential underpinnings of interventions to improve health, including: health policy and systems research, social science and behavioral research, implementation/ operational research and research on the determinants of health. The funding would combine capacity building with focused research to support key national health programs such as health systems strengthening, improving reproductive health, eradicating target diseases and responding to health threats such as climate change.
- enhancing innovation capacities and environments in LMICs, to enable countries to strengthen their the national innovation systems;

-operating a Global Health Research Observatory, to ensure that disease monitoring and R&D resource tracking could be carried out regularly and accurately, to provide both the inputs to the priority setting processes and the means of monitoring progress.

This would have to be accompanied by the establishment of a structure mandated with the responsibility to collect, collate, analyze, interpret and disseminate information with regard to funding for R&D.

To cover these functions, the GHRIF would need to be financed at a level of between US$ 3 billion and US$ 15 billion per year.

Proposals for new and innovative sources of financing

A plethora of proposals, over ninety, are currently in circulation or already implemented. Around half of these are pure financing proposals, a further nearly-half are not financing proposals at all. They include proposed structures to centralize, manage and disburse funds to health R&D (if funds were to be available), but they do not have mechanisms to raise these funds. A small number of proposals both raise and allocate funds. Each proposal was assessed for suitability to its stated disease and product target, and for its likelihood of incentivizing developers to commence or increase their R&D activities.

It is important to note that the amount of funding needed for any health R&D activity depends on several key factors:

Does the disease have a substantial market/ some market/ no market?
Does the disease have a sound science and technology (S&T) base?
What kind of R&D is needed?
How well does the proposal match the needs of the target group?

These groups each have very different cost structures, business models and needs and as a result of these differences, it is unlikely or impossible that a single allocation proposal could efficiently address all disease and product needs, and the requirements of all relevant development groups.

A suite of proposals has been chosen that cover R&D from basic research through to distribution; that are best suited to maximizing R&D activity by all potential target

groups; and that deliver maximum public health return for any given investment. The three main criteria for analysis were DC impact, financial aspects and operational efficiencies. These form a shortlist of:

- four financing mechanisms that will triple available funds for R&D for neglected diseases of the developing world;
- five funding allocation mechanisms that we believe will optimally allocate both existing funds and new funds raised by the four proposed financing mechanisms
- two efficiency proposals aimed at cutting R&D costs across the board.

FINANCING PROPOSALS

The following fundraising options have been put forward based on the likelihood they can generate new funds for health R&D in a sustainable way:

- A new indirect tax (a consumer based tax)
- Voluntary business and consumer contributions
- Taxation of repatriated pharmaceutical profits
- New donor funds for health R&D

A new indirect tax

Indirect taxes involve a small tax being imposed on specified products or transactions and could potentially raise very significant amounts of revenue. Examples given include:

- A 10% tax on the arms trade market might net about $5bn per annum.
- Digital tax or 'bit' tax: Internet traffic is huge and likely to increase rapidly; this tax could yield tens of billions from a broad base of users.
- Brazil's CPMF: a tax on bank account transaction, set at 0.38% levied on paying bills online and major withdrawals, it was raising an estimate $20bn per year and funding some 87% of the Government key social protection program – Bolsa Familia, before it was voted down.
- The airline tax has raised around $660m over 2 years (from France) this is expected to increase as more countries join (e.g. Portugal in 2009). Possible total revenues could amount to the low billions.

Using the airline tax as a guideline, the introduction of an indirect tax, (e.g. a very low digital tax) could be estimated to raise funds in the low billions. Introducing a new tax or expanding an existing tax may require legal changes, nationally and internationally, depending on the tax, and ongoing regulation to ensure compliance. As with the introduction of any tax there are trade-offs. For example, there is only moderate certainty over revenue forecasts as actual revenue will depend on the response of providers and consumers to price rises associated with the tax and scope of the tax.

Voluntary business and consumer contributions

Voluntary consumer contributions are donations made by individual consumers and operate in three different ways:

1) Voluntary linking of a donation to the payment for a service (e.g. payment of mobile phone bills or payment of income tax).
2) Automatic donations directly to a particular recipient (e.g. standing order payments to Oxfam)
3) Voluntary but non-automatic donations (e.g. private giving campaign or endowment). An income tax donation allows an individual to make a contribution from their income which government will match with the income tax that would have been paid.

Voluntary contributions have less certain funding streams than a tax, but once established are reasonably predictable. The size of revenue raised varies:

- Airline ticket voluntary solidarity contribution is expected to raise about US$980 million/annum, although these expectations have since been revised downwards. [1]

- Mobile phone voluntary solidarity contribution would raise from 200m – 1.3bn Euros according to the Millennium Foundation.

- De Tax could raise are up to $2.2 billion based on a base on 26 countries and 5% business uptake[2]

Using product RED as a guide, the introduction and use of voluntary business sector contribution could be estimated to raise in the order of US$40m annually; using the airline voluntary solidarity contribution as a base to estimate voluntary consumer contributions, these could be around $1bn per annum. A combined estimate of both brings this to around $1bn per annum. Introducing voluntary contribution schemes, like the airline ticket voluntary solidarity contribution is not expected to have any legal obstacles, nor require amendments to international laws. However, other mechanisms, like De-Tax do require changes to law.

Taxation of repatriated pharmaceutical profits

Funds would be raised through direct taxation of pharmaceutical company profits within countries that join. The Brazilian proposal aims for governments of "associated countries" (i.e. any country that agrees to sign up, DC or Western) to tax non-domestic pharmaceutical companies that undertake activities in their territories. The tax would be on all profits remitted to the overseas parent company.

Initial estimates suggest if profits from the pharmaceutical industry from LMIC are in the order of $16 billion per annum and if the tax rate was applied at 1% across these countries, then revenue regenerated could be in the order of $160 million per annum. This

[1] http://www.internationalhealthpartnership.net/CMS_files/userfiles/FS_DeTax_raffaella%20final%20final.pdf

[2] http://www.internationalhealthpartnership.net/CMS_files/userfiles/FS_DeTax_raffaella%20final%20final.pdf

figure would increase if profits from very significantly if profits from one or more of the HICs were included. However, there are trade-offs:

- Like all taxes it is subject to some political uncertainty, however this uncertainty is potentially reduced the greater the number of countries involved in the scheme.
- Once the proposal had achieved political commitment, implementing the tax system, at a national level would require administrative and legislative changes.
- Would also require confirmation with WTO that it was not seen as an unfair subsidy, whereby revenue is collected in one jurisdiction and given to some countries but not others.

New donor funds for health R&D

This mechanisms considers three main sources of funding

- Additional funding from new donors, non traditional donors, who are not currently included in OECD's Development Assistance Committee (DAC), such as China, India and Venezuela.
- Additional funding from existing (DAC) donors (for example, earmarking a percentage of GDP for health R&D)
- Additional funding from philanthropics

This differs from diverting existing resources in that is based on projected additions to funds raised that could be allocated to health in the future. Estimates on additional funding for health might amount to some $7.4bn by 2015 from traditional donors (optimistic assumptions), and that Southern contributions *might be* in the range of $9.5bn to $12.1bn per annum. [3] Using these estimates, removing the potential for double counting from the indirect tax, and assuming 10% could be earmarked for health R&D, new donor funds could amount to between $1.5bn and $1.75bn per annum.

Conclusion

The proposed suite of fundraising mechanism provides a balance between:

- consumer, government and the pharmaceutical industry
- voluntary and non-voluntary (i.e. taxes) contributions
- some that would require managed and sustained political commitment: new donor funds and taxes; while others would not: voluntary consumer and business contributions
- some that would need effort to be operationalise: new taxes; while others have less operational requirements: voluntary contributions
- taxes would provide greater certainty once in place than voluntary contributions.

[3] North South Institute 2009 Non-DAC donors and reform of the international aid architecture Lama Hammad and Bill Morton. (See also Working Group 1 Taskforce)

Potential estimates from this combination are in the order of $US4.6 to US4.9bn. All of these funding alternatives and decisions ultimately rest with national governments and individual philanthropic organizations.

FUNDING ALLOCATION PROPOSALS

The following five proposals provide optimal funding allocation across all R&D stages and developers, in a manner that is best designed to maximize public health returns in the developing world:

- Funding via Product Development Partnerships (PDPs)
- Direct grants to small companies and grants for DC trials
- Milestone Prizes
- End-Prizes (cash)
- Purchase or procurement agreements

Funding via Product Development Partnerships

PDPs operate on a not-for-profit basis and as 'quasi venture capital funds' in the domain of developing world health. They raise funds from a wide range of public and philanthropic sources, select the projects that offer the likely highest health return for investment, and closely monitor and manage the progress of the portfolio they have invested in. They have large product portfolios across many Type II and III disease areas (but only marginal activity in Type I disease areas), and currently manage around nearly 30% of global neglected disease R&D grant funding in 2007; and around half of global grant funding, if the NIH is excluded. As a result, they act as a major consolidator of public funding, of investment risk, and of global coordination on R&D in their given field. PDPs predominantly invest in product discovery and development. Currently, PDPs have no reliable revenue stream, being entirely reliant on annual donor funding. As a result, three proposals are in circulation to provide reliable, long-term funding to PDPs; and to automate or centralize funding decisions across PDP portfolios to a lesser or greater degree. These are:
Fund for R&D in Neglected Diseases (FRIND)
Industry R&D Facilitation Fund (IRFF):
PDP Financing Facility (PDP-FF):

The proposed PDP funding mechanisms performed variably on DC impact, and operational efficiency and feasibility. Overall, PDPs score very highly on DC impact due to their focus on developing affordable suitable products for DC use; their routine practice of working with DC researchers and developers; and, to varying degrees, their capacity building efforts in DCs. Donors are increasingly favoring PDPs as their vehicle of choice to disburse neglected disease funding, while smaller donors may disburse

virtually all their funding in this manner (likely reflecting PDP's ability to minimize donor management needs).

Conclusion.
The PDP route offers high DC health impact and operational efficiency, and is the only mechanism that successfully stimulates early and ongoing MNC involvement. However, a mechanism is needed to assist donors to fund across PDPs in a far simpler manner than is currently possible. PDPs do not cover all areas of Type II and III need, and not all PDPs are equally efficient.

Direct grants to small companies & grants for DC trials

Many countries and some philanthropists provide direct grants or contracts to small companies (SMEs) in areas of public health importance where Venture Capital may be either sub-optimal or lacking entirely

Direct grants are vital for cash-constrained small firms, which need push funding in order to conduct R&D. Small company funding schemes fall into two categories: grants or contracts to Western companies to conduct R&D relevant to developing countries; and grants within developing countries (especially IDCs) to conduct locally relevant R&D.

Typical schemes in circulation or submitted to the EWG (although many others exist[4]) include:
Western grant/ contract schemes for SMEs:

- US Small Business Innovation Research Programme (SBIR). Funded through the US government -NIH to provide early stage finance for small innovative businesses to bring technologies to market.

- UK Small Business Research Initiative –(SBRI) - a program that provides innovative solutions to specific issues identified by the public sector, by engaging a broad range of companies in competitions for ideas that result in short-term development contracts..

DC/ IDC grant schemes

- São Paulo state funding agency (FAPESP) funds R&D projects through its Technological Innovation in Small Businesses (PIPE) program
- Indian Small Business Innovation Research Initiative (SBIRI), initiated by the Department of Biotechnology promotes high-risk pre-proof-of-concept research and end-stage development by SMEs

In terms of DC health impact, Western-based schemes performed less well since they do not clearly and specifically target DC needs and define DC-relevant outputs. Small developers (SMEs, IDCs and diagnostic firms) gave unanimous support to direct grant programs, rating this as one of the two incentives most likely to stimulate them to commence or expand developing country R&D programs. Large companies were less

[4] See Mclaughlin Rotman proposal (http://www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf)

likely to respond, although they noted that grant programs would be a very welcome support to subsidize the costs of large-scale clinical trials in developing countries. These grant schemes were rated very highly by all donors, public and philanthropic, Western and DC.

Conclusion

Western and DC grant schemes are a clear priority to encourage broad SME participation in DC-relevant R&D, with DC-based schemes being particularly promising.

Milestone prizes

Milestone prizes are cash prizes given for reaching interim steps along the development pathway and are best suited to solving basic research and technical questions, but are unlikely to be useful for clinical development. Only one pure prize proposal was presented to the EWG. However a number of more complex proposals include a milestone prize element:

- InnoCentive is a pure prize. It is an online marketplace where 'seekers' (public, private and philanthropic) can post challenges. The award is paid to the solver who best meets The award is paid to the solver who best meets the solution requirements, and a commercial agreement is then negotiated with the 'seeker'.

. InnoCentive performed particularly well on DC capacity-building, with over one-third of InnoCentive's solvers being located in the developing world.

Milestone prizes are easy to put in place, scalable and have no administrative or legal hurdles. Their operational efficiency and feasibility scores were therefore high, and would likely be higher if data gaps had not existed. The InnoCentive milestone prize system is also strikingly cost effective, with an average of 300 problems posted per year (and around 130 solved) for an annual cost of $6-9 million

Conclusion

InnoCentive style milestone prizes are a highly cost-effective way to encourage small firms to generate innovative solutions to basic research questions and technical problems up to the point of clinical development, however maximum buy-in from the private sector is likely to be obtained by managing prizes within the IP system. Prize design is crucial to generating high DC-impact.

End-Prizes (cash)

Cash end-prizes propose providing a large lump sum at the end of the development process as a reward for product development. The prize can be awarded as a pure reward for innovation, allowing the IP-holder to retains rights to their product, or as a 'fee' to purchase the IP from the developer to allow free exploitation by the prize-giver. Although the notion of cash end-prizes has been generally discussed, only one such proposal was

submitted to the EWG, the Prize Fund for development of a low cost Rapid Diagnostic Test for TB (TB-RDT). The TB-RDT proposal is rather complex, involving a $100 million prize fund, which is used to fund a $90 million end-prize for development of a TB RDT, as well as an open information reward and a range of interim prizes

The TB-RDT proposal performs very well on DC impact, since the product profile is designed to best suit DC needs, and the licensing approach encourages low-cost manufacture and distribution; DC researchers are also prioritized, and the proposal requires hand-over of both IP rights and technical know-how to generic manufacturers, many of whom will be in DCs. However, the complexity of the proposal and the requirement for groups to administer the fund, administer the licenses, assess market penetration and administer the various prizes and grants mean it scores very poorly on operational efficiency and feasibility.

Conclusion

End-prizes are likely only suitable for diagnostic development, where prizes sufficiently large to reward developers are within reach of public funders. The DC health impact of the prize would be optimized by IP-buyout prizes rather than prizes purely as a reward for innovation.

Purchase or procurement agreements

Purchase or procurement agreements are contracts between a purchaser (often a government, regional or multilateral group) and product developers, which set out the price at which a product will be purchased and/or the volume of product that will be supplied. The majority of agreements applies to generic products, and is designed to secure bulk price discounts and security of supply, but they do not stimulate R&D.
A more recent innovation is purchase agreements for novel products or products still in development. Examples of such agreements include:

- Minimum Volume Guarantee
- Minimum Volume Guarantee (MVG) for a novel product:
- Affordable Medicines Facility - malaria (AMFm)
- Advance Market Commitment (AMC) pilot, whereby donors commit to price and volume purchase contracts with companies for as-yet-undeveloped vaccines that meet public health requirements. Developers are assured of higher initial prices (with the patient price subsidized by donors), in return for a lower unsubsidized tail price. Negotiations can be complex since they require advance definition of the desired product profile and contracts are locked in before the vaccine is made.

Performance of purchase agreements for novel products varies significantly depending on the design of each agreement. The AMC performs least well, due to its failure to preferentially incentivise low cost-of-good products and thus low prices, and its weak technology transfer stimulus; it is also operationally complex and scored low on political feasibility as it would be extremely difficult to scale up for broad use.
The AMFm has the highest rating of all, since it uses bulk procurement to secure lowest price, and also requires participating countries to ensure access to even the poorest populations as part of their national product roll-out plan:

All purchase commitments for novel DC products struggle to achieve financing, with donors and recipients historically accepting a long wait for cheaper generic versions. From a financial perspective, the most viable option is for straight purchase contracts between developers and DC countries who can afford their product (likely MICs such as Brazil where this is not possible (most LIDCs), donors will need to provide the necessary purchase funds as GAVI and the GFATM currently do for a range of products. The sums required would be very large and this option is therefore likely only viable for a few priority products, in particular vaccines for high-mortality DC diseases.
Developers gave purchase commitments the highest ranking of all the proposals reviewed, with a unanimous top rating by large and small companies, IDC firms, diagnostic companies and PDPs. All developers felt that purchase commitments – or rather, demonstrated government willingness to purchase products – was the best advance signal of demand they could have, and would incentivize them to conduct R&D.

Conclusion

Purchase funds for novel products are a vital factor in stimulating increased R&D ad providing large-scale access to new products; they are also well suited to steering existing programs towards DC needs, for example, R&D programs for Type I diseases that would otherwise focus on Western product profiles and on production capacity to meet Western needs. However, purchase agreements do not have a mechanism to decrease the price of new products, particularly if there is limited or no competition with similar products. Better outcomes may be achieved by pooled price negotiations or by early signals to developers as to the desired DC-friendly (and DC price-friendly) profile for the final product.

EFFICIENCY PROPOSALS

The following two proposals reduce R&D costs across the board, and thus reduce overall future R&D funding needs, and expedite access to new products by developing world patients:

- Regulatory harmonization (DC-focused)
- Pre-competitive R&D platforms

Regulatory harmonization (DC-focused)

A large proportion of the cost of developing and marketing a new product relates to regulatory requirements to establish that the product is safe, effective and of high quality

before it is administered to patients in large numbers. An additional 'quasi-regulatory' stage is in place courtesy of WHO processes aimed at assessing registered products for their suitability for DC use. Developing country regulatory harmonisation has begun in some regions, but progress is slow

DC regulatory harmonization is likely to have a very high DC impact, since the single act of harmonization facilitates more rapid registration of many products (both generic and brand) in many countries, and may lead to product registration in countries that would otherwise not have had access to that product at all.

Harmonization is feasible. However, it ranks only moderately in terms of operationality. Disparate national legislative frameworks are a substantial obstacle; regional countries may not have sufficiently high levels of trust to move to a harmonized system (it took the European Medicines Agency nearly 40 years); national sovereignty issues raise their heads; and loss of income from regulatory fees can pose difficulties for resource-poor nations. Product developers consistently rated regulatory efficiencies as a number one priority.

Conclusion

Political will to move forward on DC regulatory harmonization and integration would be a major cost-saving and greatly increase DC access to quality products.

Pre-competitive R&D platforms

Development of pre-competitive R&D platforms delivers high-value efficiencies, but requires up-front investment. They are tools to increase the efficiency of R&D across many products, for instance development of a new animal model that more accurately predicts the value of a TB vaccine in humans, or of surrogate markers that accurately predict the effect of a HIV drug, without requiring months or years of follow-up.

Examples of pre-competitive platform research include:

- The European Commission's Innovative Medicines Initiative (EC-IMI), co-funded by the European Union and the European Federation of Pharmaceutical Industry Associations (EFPIA), which awards research grants to European public-private collaborations working to develop platform breakthroughs.
- PATH, a US-based PDP, develops enabling and platform technologies that are made available to all companies making relevant products for its programs. .

Both companies and PDPs ranked investment into pre-competitive platforms as a top priority, noting for instance that "ways to reduce the cost of, and simplify, R&D is a real gap", and that "surrogate marker work is incredibly important to accelerate R&D".

Conclusion

Investment into pre-competitive R&D platforms targeted at DC products can deliver substantial cost-savings for all development programs in that disease area, but tends to be poorly supported due to public-good/ free-rider issues. Political will in this area would make a substantial difference.

Other Proposals

A number of promising proposals were analyzed which included:

- Open Source; Patent Pools(UNITAID model); Health Impact Fund; Priority Review Voucher and Orphan Drug Legislation

CONCLUSIONS AND NEXT STEPS

The proposed allocation and efficiency mechanisms provide coverage of Type II and III diseases in an efficient manner, and are well suited to maximizing developer activity. If the provisos noted are taken into account, they are also expected to provide good public health and capacity building results for the developing world. Some of the recommended approaches are already in place, or the general approach is in place to act as a framework, host or model for a developing-country specific version of the mechanism (e.g. PDPs; grant schemes; milestone prize vehicles; purchase or procurement funds hosted by GAVI, GFATM and others; regulatory harmonization and integration initiatives; and isolated pre-competitive platform initiatives within individual organizations). Other proposals would require implementation, including mechanisms to fund PDPs and cash end prizes.

Unlike many lower-performing proposals that have been discarded, none of the recommended mechanisms have a revenue stream, with all currently relying on donor contributions and philanthropy. The financing mechanisms proposed in this report are, however, well suited to address these funding deficits

Type I disease products do not fare so well. The recommended mechanisms cover DC-relevant adaptations of Type I products fairly well, but are less effective in ensuring low prices for these. However, as noted above, there were no effective proposals to address gaps in DC access to patented Type I products.

The next steps might be to proceed to a working phase which could involve an in-depth review of the proposals recommended and setting up of a funder group to test the acceptability of those most appropriate. It is also essential to carry out additional work on DC access to Type I products and explore the role of the IDC commercial sector.

Introduction

This is a report to the Director-General of the World Health Organization and as such must be framed within the possibilities of action of that organization. WHO, as mandated by its constitution, has logically been central to or an active participant in all the debates swirling around the changing panorama of health, particularly the health of the developing countries and more specifically the health inequities which exist. Several Commissions and Working Groups have been established in recent years to examine one or other facet of the difficult problem of how to change this panorama for the better. The problem is bedeviled by the fact that much of the improvement in health lies in areas that traditionally have not been under the purview of the traditional health sector. In spite of the evidence of the inseparable bidirectional link between health and all the other facets of human development, it has been a slow process galvanizing global attention to the fundamental aspects of the problem and the possible solutions. One of the issues that is assuming ever increasing prominence is the cost of and lack of access to essential health products and the extent to which these problems are linked to the processes currently underlying technological innovation. In particular, many of the technological developments have come from the developed countries and are hedged around by numerous restrictions that place them beyond the reach of the world's poor.

This report was crafted by a time-limited Expert Working Group established by the Director General with specific limited responsibilities, given the enormous amount of writing about the subject and germane areas in recent years. Stress is laid on the limitations, as it was decided from the beginning to adhere strictly to the mandate as given and not to address the several issues that remained unresolved from the work of other groups. Thus the Report is structured to address:

- Current financing of R&D
- Coordination of R&D
- Proposals for new and innovative sources of financing to stimulate R&D.

The working group had to complete its work within a year. It held three face-to-face meetings in Geneva in January, June/July and November/December, 2009, and much of its work was done by soliciting public comment and submission electronically as appropriate.

The first meeting entertained a series of presentations from groups and organizations which have interest or expertise in the area. It commissioned several background papers to inform its work. All presentations as well as the background papers and the individual submissions to the EWG are available on the WHO website. Subsequent meetings discussed and evaluated the extensive material presented. Most of the work between meetings was by virtual consultations on various tools, proposals and report drafts. It was gratifying and an indication of interest that there was much comment through public hearings. The membership of the EWG as shown in the Annex was drawn from a wide cross section of countries and disciplines.

We are grateful to those who made submissions and contributed to our work but special thanks must be given to the WHO Secretariat for intellectual and logistical support to this effort.

1-Background

There is now abundant and incontrovertible evidence of the double burden of disease being borne by the developing countries. It is also clear that many large countries represent virtual spaces and there are significant differences in health status within countries. The tyranny of the averages hides much of the ill health that affects the world's poor. The old paradigm of the infectious diseases affecting the developing countries and the poor and the chronic noncommunicable diseases (NCDs) affecting only the rich has been put to rest.

Since the 1980s, the burden of noncommunicable diseases (NCDs) has been rapidly increasing in low- and middle-income countries (LMICs). Whereas NCDs accounted for 47% of disease burden in 1990, this is projected to increase to 69% by 2020 [5]. Conversely, whereas communicable diseases (CDs) accounted for 42% of disease burden in 1990, they are expected to decrease to approximately 17% by 2020 (ibid.). NCDs are now the leading cause of morbidity and mortality in every region of the world except sub-Saharan Africa – where they are prominent, but overshadowed by communicable, maternal, perinatal and nutritional conditions.

Of the global deaths in 2005, 60% were caused principally by cardiovascular diseases and diabetes (32%), cancers (13%), and chronic respiratory diseases (7%). The burden of NCDs is felt especially in LMICs, where 23 selected countries[6] account for 80% of worldwide deaths from NCDs[7] . NCDs were responsible for an estimated 49% of the total worldwide burden of disease in 2005, and 46% of the disease burden in LMICs. Coronary heart disease and stroke account for 21% of disability-adjusted life-years (DALYS) in this group, cancer for 12% and respiratory diseases for 8% [8]. Endocrine disorders (primarily diabetes) account for 3.7% of the disability-adjusted life-years attributed to non-communicable diseases, and this proportion is predicted to rise sharply to 5.4% by 2030, with much of the increase in low-income countries [9] . Neuropsychiatric

[5] Boutayeb, A. (2006). The Double Burden of Communicable and Non-communicable diseases in Developing Countries. *Royal Society of Tropical Medicine and Hygiene*, 100: 191-199.

[6] Countries include: Argentina, Bangladesh, Brazil, Burma, China, Colombia, Democratic Republic of the Congo, Egypt, Ethiopia, India, Indonesia, Iran, Mexico, Nigeria, Pakistan, Poland, Philippines, Russia, South Africa, Thailand, Turkey, Ukraine and Vietnam.

[7] Abegunde, D.O., Mathers, C.D., Adam, T., Ortegon, M., Strong, K. (2007) The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet*, 370: 1929-38

[8] Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M.R., Rahman, A. (2007) No Health Without Mental Health. *Lancet*, 370: 859-77

[9] Mathers CD, Loncar D. (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 3: e442. Doi: 10.1371/journal.pmed.00304424

conditions account for up to a third (28%) of disability-adjusted life-years attributed to noncommunicable diseases, although the size of this contribution varies between countries and according to income level [10] .

Although the disease burden per person of communicable diseases fell by 20% from 1990 to 2001, HIV/AIDS, TB, malaria and neglected diseases remain significant causes of morbidity and mortality [11]. Particularly in LMICs, HIV/AIDS, tuberculosis, malaria and diarrhea conditions caused by communicable diseases are among the leading 10 causes of death, accounting for a combined 14.8% of deaths in 2001.

The rapidly increasing burden of these diseases is affecting poor and disadvantaged populations disproportionately, contributing to widening health gaps between and within countries. 15-19 year olds in LMICs face a 30% greater risk of death from NCDs than their counterparts in HICs. Just under half of total deaths from NCDs in LMICs occurred in people younger than 70 years, compared with only 27% in high income countries[12] . The contributions to disability in LMICs from conditions such as cardiovascular and chronic respiratory diseases, and long-term consequences of communicable diseases and nutritional deficiencies are also higher in LMICs [13]. In these countries moreover, communicable diseases still cause substantial death and disability. In 56 of the 58 countries where the bottom billion live, virtually every person has at least one neglected tropical disease [14] . According to the Global Fund to Fight AIDS Tuberculosis and Malaria [15], 95% of the estimated 33 million individuals living with HIV live in LMICs (68% in sub-Saharan Africa). 27% of new cases of and 31% of registered deaths from tuberculosis were in Africa [16].

The cost of disease to societies, particularly LMICs, has serious implications for poverty reduction and economic development. People who are already poor are the most likely to suffer financially from chronic diseases, which often deepen poverty and damage long-term economic prospects[17] . Abegunde and colleagues estimate that US$ 84 billion of national income will be lost from heart disease, stroke, and diabetes alone in 23

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[10] See Reference 5

[11] Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J.L. (2006) Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, 367: 1747-57

[12] See Reference 3

[13] See Reference 7

[14] Hotez, P. J., Fenwick,A., Molyneux, D.H. and Savioli, L. (2009). Rescuing the Bottom Billion Through Control of Neglected Tropical Diseases. *The Lancet*, 373: 1570-1575.

[15] The Global Fund for AIDS, Tuberculosis and Malaria. (2009). Fighting HIV/AIDS. [Online]. Available from: www.theglobalfund.org/en/hivaids/ [Accessed 11 October 2009].

[16] WHO (2005) Preventing Chronic Diseases: a Vital Investment. World Health Organization

[17] See Reference 12

selected LMICs between 2006 and 2015, if nothing is done to reduce the risk of noncommunicable diseases.[18] Achievement of the global goal for prevention and control of chronic diseases would avert 36 million deaths by 2015 and would have major economic benefits. Furthermore, because most of the averted deaths would be in LMICs and about half would be in people younger than 70 years, it would have major economic benefits, including extension of productive life and reduction in the need for expensive care [19] .

The first of the recent WHO Commissions that addressed health concerns globally was the Commission on Macroeconomics and Health (CMH) which emphasized and adduced data to show the link between health and economic growth. The CMH pointed out the need for global knowledge to fight disease which is of particular relevance to the work of this EWG [20]. Its Report said:
"The fight against disease requires important investments in global public goods, beyond the means or incentives of any single government and beyond the sum total of national level programs. One of the most important kinds of public goods is those that involve the production of new knowledge, especially through the investments in research and development."
The Report went on
"We believe that at least $3.0 billion per year should be allocated toward R&D directed at the health priorities of the world's poor. Of that amount, $1.5 billion per year should be allocated toward targeted R&D for new drugs, vaccines, diagnostics and intervention strategies towards HIV/AIDS, malaria, TB, reproductive health and other priority conditions of the poor".
The Commission went on to explore various mechanisms for mobilizing these resources and the institutional framework for dispensing and monitoring their use.

The promotion of health and the promotion of development beyond economic growth go hand-in-hand. This was acknowledged by Member States, which met in 2000 and subsequently committed to addressing a series of development challenges classified as Millennium Development Goals (MDGs). The MDGs provide a timeframe for addressing challenges, such as poverty, illiteracy, the reduction of child and maternal mortality and the reversal of the incidence of HIV/AIDS, malaria and other diseases. In relation to this, governments have also recognized the moral and legal issues in ensuring general access to drugs for those in need and who also have limited means to combat burdensome diseases, such as HIV/AIDS. Such need relates largely to socio-economic inequalities and imbalances with regards to both demand and supply of new drugs and vaccines.[21]

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[18] See reference 3

[19] Beaglehole, R., Ebrahim, S., Reddy, S., Voûte, J., Leeder, S. (2007) Prevention of chronic diseases: a call for action. *Lancet*, 370: 2152-57

[20] CMH (2001) *Macroeconomics and Health: Investing in Health for Economic Development.* Commission on Macroeconomics and Health. Geneva, World Health Organization. www.cid.harvard.edu/archive/cmh/. Accessed 9.11.09.

[21] See Fig 4.1 and 4.2 in CIPIH report, p 98-99 - the mortality from AIDS in the US (Fig 4.1) fell from 17 per 100,000 to 5 per 100,000, b/w 1995 and 1998, through treatment and reduced infection. By contrast, during the same period, in most developing countries the epidemic continued unabated, rising from deaths

1.1 The Commission on Intellectual Property Rights, Innovation and Public Health

Against the backdrop of increasing awareness of the global disease situation, the importance of reducing poverty and addressing the social determinants of ill-health, an international debate concerning the wider aspects of the relationship between intellectual property rights (IPRs), innovation and public health has been taking place. The emphasis has been on the specific contribution that innovation in the public health field can make to improving human health in developing countries, especially for the poorer and more vulnerable segments of the population. Mobilizing research and development that responds to the needs of these populations is crucial, as the contribution that innovation can make will only be meaningful if products are acceptable, affordable and accessible.[22]

In response to this public concern, in May 2003, the World Health Assembly decided to establish an independent time-limited body, The Commission on Public Health, Innovation and Intellectual Property Rights (CIPIH) to collect data and proposals from different actors involved and produce an analysis of intellectual property rights, innovation and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries.[23] The Report which the Commission submitted to the member states in April 2006 contained 60 recommendations grouped into 5 categories: discovery, development, delivery, fostering innovation in developing countries and the way to support a sustainable global effort.

The Commission concluded in its report that intellectual property rights provide important incentives for the development of new medicines and medical technologies. Those rights, however, do not provide an effective incentive when patients are either small in number or poor. As a result, there is a gap in the innovation cycle; in some cases no product exists to address the health needs of the poor; in other cases, products exist, but little effort is made towards making them affordable for poor communities. [24] To address this gap, there is a need for other incentives and financial mechanisms to be put in place and ways in which different stakeholders can work together. Defining the conditions necessary for products to be accessible is, therefore, an important part of the report.[25]

1.2 The recommendations of the CIPIH and its follow up activities

of over 1 million to approx. 1.75 million, due to the unavailability of drugs that existed in the West (Fig. 4.2).

[22] CIPIH report, pp 97, 98

[23] Resolution WHA 56.27

[24] CIPIH report, See Fig 1.4, pp 23.

[25] Turmen, Tomris and Clift, Charles, *Public health, innovation and intellectual property rights: unfinished business,* WHO Bulletin, 84(5) (May 2006)

Discovery: With regard to the discovery of new health-care products, the Commission reviewed some of the science of disease control and the economic and policy choices facing countries, in particular the scientific, institutional and financial issues arising in the process between basic research and identification of a lead compound. The Commission sought to determine the gaps in this process for diseases principally affecting developing countries, and policy measures that might be appropriate to fill those gaps. It concluded that it is in the interest of all countries to promote health research that addresses the health needs of developing countries and to set specific and measurable targets in this regard.

Development: The most expensive part of the process is development: taking the candidate product through all the required stages of pre-clinical and clinical research and the regulatory process. The Commission recognized the increasing attention being given to the drug development and regulatory process, but stressed the strengthening of clinical trials and regulatory frameworks in all countries. It also recognized the role of new players and public- private partnerships. It examined the range of activities, from optimization of a lead compound through to regulatory review of the safety, efficacy and quality of a new product, and identified several key issues that need careful consideration.

Delivery: Successful efforts to develop new products will be of no value if they cannot be made available and accessible to those who need them. The Commission examined the factors affecting the introduction of new and existing products into developing countries, including health delivery systems, regulation, pricing, intellectual property and policies to promote competition.

Fostering innovation in developing countries: The Commission observed that lessons can be learnt from those countries that have made significant progress in developing innovative capacity for health research. It also affirmed the significant contribution the most scientifically and technologically advanced developing countries were making to biomedical research and development. It recognized the massive indigenous resource in developing countries in the form of traditional medicine, better use of which could be made through wider availability and application of knowledge to accelerate development of new treatments. The Commission's recommendations focused on building capacity in developing countries in the fields of science and technology, regulation, clinical trials, the transfer of technology and traditional medicine, as well as intellectual property. [26]

The way to support a sustainable global effort: The Commission defined the important role and responsibilities for WHO as the lead international agency for public health, including developing a global plan of action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that proportionately affect developing countries. There is a need to ensure enhanced financing on a sustainable basis for innovation and access and promote synergy between different partners. Ultimately, it is really the responsibility of governments to see that these

[26] A/PHI/IGWG/1/2, p 2

objectives are achieved. However, it is seen to be appropriate that WHO should take the lead in promoting a more sustainable and better-funded effort.[27]

The Fifty-ninth World Health Assembly welcomed the report of the CIPIH and as a follow-up, adopted resolution WHA 59.24 on "Public Health, Innovation, Essential Health Research and Intellectual Property Rights: towards a Global Strategy and Plan of Action.[28] Among other proposals, the Resolution requested the Director-General of WHO to establish an inter-governmental working group open to all interested Member States to draw up a global strategy and plan of action in order to provide a medium-term framework based on the recommendations of the Commission.[29]

1.3 Development of a global strategy and plan of action

The Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) was mandated to develop a global strategy and plan of action aimed at, inter alia, securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area.[30] In fulfilling this mandate, the IGWG became the first forum to simultaneously address the issues of innovation and access.

In May 2008, the World Health Assembly adopted the global strategy and the agreed parts of the plan of action on public health, innovation and intellectual property as shown in resolution WHA61.21.[31]

The global strategy proposes that WHO should play a strategic and central role in the relationship between public health and innovation and intellectual property within its mandate. To achieve this principle, Member States endorsed by consensus a strategy designed to promote new thinking in innovation and access to medicines, which would encourage needs-driven research rather than purely market-driven research to target diseases which disproportionately affect people in developing countries.

The global strategy is comprised of eight elements, the development of which was guided by a set of principles established and agreed upon by Member States. In particular, the elements of the global strategy are designed to promote innovation, build capacity, improve access and mobilize resources and will:

(a) provide an assessment of the public health needs of developing countries with respect to diseases that disproportionately affect developing countries and identify their R&D priorities at the national, regional and international levels

[27] CIPIH report / Turmen and Clift, Bulletin of the World Health Organization, 84 (5), p 338 (May, 2006)
[28] Fifty-ninth World Health Assembly: Resolution WHA 59.24
[29] Ibid
[30] Ibid
[31] The global strategy was approved. The plan of action was approved except for a small number of actions, which remained open until the adoption of Resolution 62.16 in May 2009.

(b) promote R&D focusing on Type II and Type III diseases and the specific R&D needs of developing countries in relation to Type I diseases

(c) build and improve innovative capacity for research and development, particularly in developing countries

(d) improve, promote and accelerate transfer of technology between developed and developing countries as well as among developing countries

(e) encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the R&D needs of developing countries, protects public health and promotes access to medicines for all, as well as explore and implement, where appropriate, possible incentive schemes for R&D

(f) improve delivery of and access to all health products and medical devices by effectively overcoming barriers to access

(g) secure and enhance sustainable financing mechanisms for R&D and to develop and deliver health products and medical devices to address the health needs of developing countries

(h) develop mechanisms to monitor and evaluate the implementation of the strategy and plan of action, including reporting systems.

The plan of action, linked to the global strategy, identifies stakeholders, lead stakeholders and timeframes for implementation, thus providing a roadmap for carrying forward this important work in fostering innovation and improving access relevant to diseases that disproportionately affect developing countries.

1.4 The Expert Working Group

In recent years donors have provided additional funding to promote access and R&D relevant to diseases affecting developing countries. Nevertheless, further funding on a sustainable basis is essential to support the long-term R&D efforts that are needed to meet the health needs of developing countries.[32] In this context, the global strategy called for the establishment of a results-oriented and time-limited expert working group under the auspices of WHO and linking up with other relevant groups to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate R&D related to Type II and Type III diseases and the specific R&D needs of developing countries in relation to Type I diseases.[33] In response to this request, the Director-General established the present Expert Working Group. The Resolution emphasized R&D related to type II and Type III diseases and the specific R&D needs of developing countries in relation to type I diseases. The EWG debated as to whether that taxonomy of disease that was developed by the Commission on Macroeconomics and Health was still valid and in some of its work elected to be less rigid in its separation of diseases into these specific categories.

[32] Resolution WHA61.21, paragraph 40 of the annex
[33] Resolution WHA61.21 paragraph 42 of the annex

The process leading to the establishment of the EWG entailed considerable debate and discussion in various fora and structures and there has been expectation that the Group would consolidate and clarify the various proposals on R&D and financing that have been the subject of recommendations in the various previous Commissions and Groups.

2- Financing of R&D

2.1 Context

The adoption of the Millennium Declaration in 2000 (UN 2000) and the subsequent mobilization of multilateral and bilateral development agencies around the Millennium Development Goals (MDGs) brought a renewed focus to the resources that would be required to advance development. In parallel, the question of how to mobilize the required resources generated a number of studies and initiatives. Broadly lumped together under the label "innovative sources of financing for development," several initiatives and ideas proposed in these and other studies continue to be part of the discussions and debates on how to enhance the mobilization of resources to finance the MDGs and promote development. Some of the ideas branded as "innovative" are actually quite old and reemerge regularly after some time in the shadows. One example is the "Tobin tax," the idea of imposing a levy on some financial transactions (for example, on foreign exchange transactions). [34]

Kaul and Conceição expanded the analysis of financing beyond resource mobilization and considered a range of options to enhance resource allocation, both to promote development and to enhance the provision of global public goods.[35] This broadened perspective led to the consideration of a range of possible mechanisms and tools that were intended not only to increase the *volume* of resources, but also the *efficiency* and *effectiveness* of their allocation. Also beyond mobilizing and spending money, a range of risk management tools must be considered to optimize the intertemporal allocation of resources (e.g. the International Financing Facility), and tools to mitigate markets failures and enhance incentives (e.g. Advanced Market Commitments).

The predictability and stability of financing must be enhanced. The fact that the MDGs have set target dates to be achieved, along the potential of high-returns of frontloading certain investments, led to the proposal of creating an International Financing Facility (IFF). In fact, donor countries have promised to increase ODA over time, so if it were possible to "advance" these commitments to take advantage of high returns from frontloading, there would be potential efficiency and effectiveness gains. The IFF would mobilize financing from capital markets by selling bonds backed by commitments from governments of future financial flows that would service the debt linked to the bonds over time. Initially, this was an open-ended proposal, intended to mobilize significant resources to frontload investments to meet the MDGs.

[34] Tobin J. (1978) A proposal for international monetary reform. Eastern Economic Journal. 4: 153-159
[35] Kaul, Inge and Pedro Conceição. 2006. *The New Public Finance: Responding to Global Challenges*. New York: Oxford University Press

A more modest proposal, the International Finance Facility for Immunization (IFFIm), has been implemented. IFFIm placed bonds backed by long-term legally-binding commitments from seven countries: France, Italy, Norway, South Africa, Spain, Sweden and the United Kingdom. Backed by these commitments, the IFFIm sold bonds (borrowed) from international capital markets and has been able to raise $2 billion since IFFIm was launched in the end of 2006 and is expected to raise approximately $3.3 billion through 2015. The resources from IFFIm are channeled to GAVI (the Global Alliance for Vaccines and Immunization) to fund vaccine purchases and other health interventions. This type of innovative financing is limited in its potential to generate *additional* resources: it is mostly intended to frontload commitments. It is also costly, because there are administrative and debt servicing costs. It would be cheaper to channel funds directly from participating countries to GAVI, but given the practical reality that these funds are not always forthcoming, the costs have to be weighed against the benefits from frontloading and having secured predictable financing (which may result, for example, in cost advantages from being able to establish long term purchase agreements with vaccine manufacturers).

One set of market failures relates to inadequate risk management. For example, one of the challenges of development is that technologies that specifically address the problems of poor countries fail to be developed, both because the national public interest of rich countries in subsidizing those technologies is small or heavily discounted, and because the private incentives are absent given that the markets where these technologies would be sold are thin and small. This has long been recognized as a problem in terms of health interventions, especially medicines and vaccines for diseases that affect almost exclusively developing countries, but it is also present in other areas, like agriculture, for example.

One specific idea to mitigate these problems, in the specific case of vaccines, is to establish Advance Market Commitments for vaccines (AMC). The idea is for a group of donors to make a binding commitment to buy a vaccine, if and only if this vaccine is developed. This "creates a market" for the vaccine that is expected to encourage private investment into developing the vaccine. It is important to note that this is essentially a "risk management" tool. What an AMC in effect does, is to move the market risk away from the private developer, given that market demand is guaranteed by the public/philanthropic sectors. The market risk is not entirely removed, given that the vaccine is not free, but is subject to a "demand test" that implies that part of the cost must be supported by the developing country – although heavily subsidized. But, from the point of view of the private developer, the market risk is substantially reduced. In June 2009, the Pilot AMC for Pneumococcal Diseases was launched. Italy, UK, Canada, Russia, and Norway, along with the Bill & Melinda Gates Foundation pledged $1.5 billion to enhance access to vaccines against pneumococcal disease. The Pilot AMC for Pneumococcal Diseases backs commitments to purchase new pneumococcal vaccines that meet a number of criteria that ensure effectiveness and safety. While the pilot is an important step forward, there is still uncertainty about how effective it will be in stimulating investments in vaccines and other technologies that require longer and more substantial investments than for pneumococcal diseases.

The report of the Taskforce on Innovative Financing for Health Systems considered the proposals outlined above and also identified measures to catalyze private voluntary giving.[36] New ideas are emerging in this area, including voluntary donations linked to air travel or mobile telephone use (as proposed by the Millennium Foundation for Innovative Financing for Health). The idea is to tap into very small individual contributions that have very large volume, and where the providers of goods/services are concentrated to minimize the transaction costs of the initiative.

2 Incentive Structures to Stimulate Research and Development in Light of Market and Policy Failures in the Production and Diffusion of Knowledge

Public policy is important to stimulate research and development. Without direct public subsidies or incentives for private engagement in research, the public (more precisely, non-rival) nature of knowledge implies that it will be undersupplied in decentralized markets. But the arrangements that exist at present could perhaps be improved upon to enhance the efficiency and the equity in the global production and diffusion of health-related knowledge. There are practical implications relating to the incentive structures that encourage health-related research and development that benefits developing countries.

It is puzzling that the current incentives for the production of knowledge may have resulted in under provision at the global level. The nature of knowledge is such that any innovation, wherever produced, could in principle be immediately and easily made available to the whole world. According to the taxonomy proposed by Sandler [37], the production of knowledge follows a best-shot aggregation technology of production. That is, in principle – ignoring restrictions to access to knowledge for the moment – it is enough for a single country to contribute to knowledge generation for knowledge to be fully provided.

However, there is an under provision of knowledge, there are large asymmetries in the ability to access existing knowledge, and there is a large unevenness across countries in the engagement with research and development. One hypothesis is that both the under provision of knowledge and access problems result in part from the fact that policies and activities oriented to the development of science and technology have not given enough consideration to the global asymmetries in the supply and diffusion of knowledge. Since knowledge-generating activities are costly and build on scientific and technological capabilities, most poor countries cannot afford and do not have the ability to generate

[36] World Health Organization (2009) Report of Taskforce on Innovative International Financing for Health Systems

[37] Sandler, Todd. 2003. "Assessing the Optimal Provision of Public Goods: In Search of the Holy Grail." In Inge Kaul, Pedro Conceição, Katell Le Goulven and Ronald U. Mendoza, eds., *Providing Global Public Goods: Managing Globalization*. New York: Oxford University Press.

knowledge specific to their contexts. In addition, the national focus has limited the incentives for producing technologies with large global spillovers, or that would bring benefits to poor countries.

The lack of consideration of the global dimension has also created problems of access to *existing* knowledge. Often, this is the result of intellectual property rights (IPRs). IPRs, designed to stimulate innovation in rich countries, often impact on the price and on the variety of goods available in developing countries for consumption and for production. Yet, even knowledge that is not formally restricted through IPRs often fails to be diffused[38]. Quah notes: "one of the most significant aspects in economic development is not knowledge's over-dissemination, but instead the opposite, even in the absence of explicit IPRs. Knowledge — something economists have expended so much effort studying how to restrict — turns out, puzzlingly, to be one of the most difficult things to disseminate."[39] National incentive structures may often be insufficient to provide knowledge efficiently and equitably at the global level, and international collective action might be helpful in producing incentive structures for global knowledge generation and diffusion.

2.2 Implications of the Public Nature of Knowledge

The *public* good nature of knowledge implies that, as Arrow (1962) indicated, it will be undersupplied in decentralized markets.[40] The reason for undersupply in competitive markets is simple: the costs of production are decoupled from the benefits of consumption. This is true also for knowledge embodied in tangible goods.

The lack of incentives for knowledge production in competitive markets does not mean that it cannot be privately supplied nor does it imply that it must necessarily be produced by the state. Rather, it entails that some type of incentive structure must be put in place to reward the efforts of creation. It is also crucial to point out that the analytical argument is not that in the absence of these incentive structures no knowledge would be produced. However, the amount of knowledge supplied would certainly not be as abundant as it would be with institutionalized incentive mechanisms that compensate creative efforts oriented towards the production of knowledge.

[38] For example, the polio vaccines were never patent protected. In developed countries, polio incidence was reduced by 86% between 1955 and 1957; a comparable reduction was only achieved in poor countries after an eradication effort was launched in 1988. See Arhin-Tenkorang and Conceição (2003).

[39] Quah, Danny T. 2001. "Demand-driven Knowledge Clusters in a Weightless Economy." London School of Economics Department Working Paper. London, UK: Center for Economic Performance of the London School of Economics.

[40] Arrow, Kenneth J. 1962. "Economic Welfare and the Allocation of Resources for Inventions." In Richard R. Nelson, ed., *The Rate and Direction of Inventive Activity. Economic and Social Factors*. Princeton, NJ: Princeton University Press.

2.3 The Evolution of Incentive Structures to Stimulate Research and Development

Simply, two main incentive structures (the establishment of intellectual property rights and public support) have emerged to stimulate the production of knowledge. Following David in the medieval and Renaissance traditions of alchemy the objective was to discover some formulae that would bring power over material things. These formulae would be kept secret and would be used only for the benefit of the discoverer. Geographical knowledge (trade routes, more accurate maps) would be kept from the public domain to be used only by the merchants or rulers who had discovered this new knowledge, from which military or mercantile gains could be extracted. Craftsmen kept close watch over the technologies used in their trade, even when no formal guild restrictions applied.[41]

Secrecy continues to be used today as a means to protect knowledge but the same principle of attributing to the discoverer the power to exclude others from access to new knowledge has been institutionalized in the incentive structure of IPRs. Secrecy is rather limited as a means of restricting others from using knowledge, since it may be possible to understand the underlying knowledge embodied in a product or associated with a certain process of production. With IPRs, knowledge is made excludable, since the creator has the right to exclude others from access to the creation. In this case, private market incentives work: the creator provides access to knowledge only to those who are willing to pay for access and/or usage.

At the same time that IPRs were taking hold in the US, a second institutionalized way to provide incentives for knowledge generation was emerging in Europe. In post-Renaissance Europe a system of aristocratic patronage by rulers and nobles (both lay and ecclesiastical) concerned with the "ornamental" benefits of the discoveries of the philosophers and savants they sponsored planted the seeds for a research culture of open science[42]

Rather than keeping the discoveries private, the incentives were oriented towards the rapid and wide dissemination of the new achievements, to enhance the prestige and power of the patron. Those that were sponsored by others in turn scrutinized these discoveries, to make sure that the claims to grandeur were legitimate. The philosophers who consistently showed ability to produce important discoveries gained a reputation that was based on the wide dissemination and scrutiny of their discoveries.
Today the rules of engagement of the scientific community are based on this second incentive structure.

[41] David, Paul A. 2001. "From Keeping 'Nature's Secrets' to the Institutionalization of 'Open Science'." *University of Siena Lectures on Science as an Institution and the Institutions of Science*.

[42] Ibid

2.4 Incentives for the Provision of Knowledge at the National Level

These two incentive mechanisms tend to separate knowledge into two categories. People and firms are willing to pay for knowledge for which substantial private benefits exist or are perceived to exist. These private benefits create market demand for knowledge, making it attractive to attempt to produce that knowledge so that it can be sold after IPRs have been awarded to the innovator. For other types of knowledge, on the other hand, the benefits are so widespread, uncertain or long-term that no one will pay enough for having it produced. Thus, the two institutional mechanisms tend to create knowledge of two types: one that remains in the public domain (that which is paid for by the public, or sometimes, voluntarily provided) and one that is private (protected by IPRs or by secret). This dichotomy can be identified, in a very crude way, as the distinction between "science" and "technology"[43]. The national structuring of public support to science and technology introduces imbalances in the global production of knowledge that are of real consequence. The imbalance in the global production of science has direct consequences for the welfare of specific countries. The issues that receive public support are those of more relevance to national concerns. R&D to produce knowledge that addresses problems in poor countries is under funded and knowledge specific to their needs is under provided.

This balance between IPRs and public support should not be confused with other, different issues associated with the interaction of public and private actors in the production of knowledge. In particular, public support does not have to be provided exclusively by the state. Clearly, resources need to be mobilized from agents that are willing to have knowledge remain largely in the public sector. For example, private philanthropic organizations – especially foundations both in the US and Europe – have, for a long time, played important roles in supporting health related research and development, and continue to do so.

2.5 Mechanisms to Deliver Public Support to Research and Development

Direct public support to science and technology can be deployed through a variety of ways, including through three mechanisms that, individually or in combinations, are used very frequently: **grants**, **procurement contracts** and **prizes**. **Grants** are typically given as a result of a competitive process of proposal submission. Proposals are judged based on their scientific merits. Funding is allocated with few strings attached as long as the scientific program of the proposal has been complied with. **Procurement** for a specific technology or scientific solution for a national problem entails contracting with an R&D performer – however, depending on the goal of public procurement, there are instances in which access to knowledge is restricted, so in this case public support to R&D does not always result in the knowledge being made public. Finally, **prizes** are combination of the

[43] Dasgupta, Partha and Paul David. 1994. "Toward a New Economics of Science." *Research Policy* 23: 487-521.

grant and the procurement approach. The government decides on which problem it wants to see addressed (as in procurement) but instead of a procurement contract commits to pay a prize to whoever solves the specific scientific or technological problem.

Indirect support to increase the overall level of R&D has also been provided through public support, often through incentives oriented towards the private sector. The rationale behind public support to privately executed R&D is associated with the large positive spillovers that are presumed to be associated with R&D. Although the evidence at the micro or industry level on the existence of spillovers is controversial at the aggregate country level,[44] the existence of spillovers is well established [45]. Indirect support is often provided through tax exemptions or tax credits on private expenditure on R&D. There is not a single mechanism that is superior in every circumstance to the others.

The issue is not only the lack of access that over-reliance on IPRs may cause. If the concern with access to existing knowledge is deep-seated, there is also the solution of public buying out of patents[46] and even of compulsory licensing. The issue, rather, is that without "push" and, specifically, without grants, fundamental knowledge for the overall progress of science and technology may never, or take much longer to be discovered.

2.6 A Possible Framework to Consider Financing Options

The deficiencies in health R&D targeting the problems of the poor exists because the current (public and private) incentives to produce and diffuse innovations required by the poor are inadequate:

- Private incentives, associated with intellectual property rights, have limited effectiveness because developing countries markets are small and "thin";
- Since developing countries are severely resource constrained, they devote very limited resources, in a sustained way, to research and to technological innovation;
- Additionally, industrial countries' contributions to research to address problems specific to poor countries are very limited, due to mismatch between costs of undertaking research and the scope of benefits, as elaborated upon above;

The disease environment faced by developing countries is different from the one that developed countries face as has been noted above. Infectious and parasitic diseases account for one third of the burden of disease in developing countries, but only 3% of the

[44] David, Paul A., Bronwyn H. Hall and Andrew A. Toole. 2000. "Is public R&D a complement or substitute for private R&D? A review of the econometric evidence." Research Policy. 29 (4-5): 497-529.

[45] Jones, Charles I. and John C. Williams. 2000. "Too Much Of A Good Thing? The Economics of Investment In R&D." *Journal of Economic Growth* 5(1):65-85.

[46] Kremer, Michael. 1998. "Patent Buy-Outs: A Mechanism for Encouraging Innovation." *Quarterly Journal of Economics* 113(4):1137-1167.

burden in high-income countries. Non-communicable conditions, such as cancer and cardiovascular disease, while also important in the developing world, account for more than 80% of the burden of disease in developed countries. But non-communicable diseases are now assuming an even greater importance in the developing countries. 1998 was the last year in which communicable diseases caused more deaths than NCDs globally and in the LMIC, the NCDs now account for more than 50% of all deaths.

In developing an analytical framework through which to analyze financing options for health R&D, two dimensions can be considered:

iii. The first dimension is whether the knowledge required by the poor already exists. If it does, then the challenge is mostly associated with ensuring the diffusion of knowledge. If it does not exist yet, then the challenge is to ensure that it is generated.
iv. The second dimension is whether the innovations (knowledge) are relevant for the poor only, or are relevant both for the developing and industrial countries.

The consideration of these two dimensions in conjunction explains that the health R&D gap results from four different sets of challenges, with each set belonging to one of the four quadrants in Figure 1.

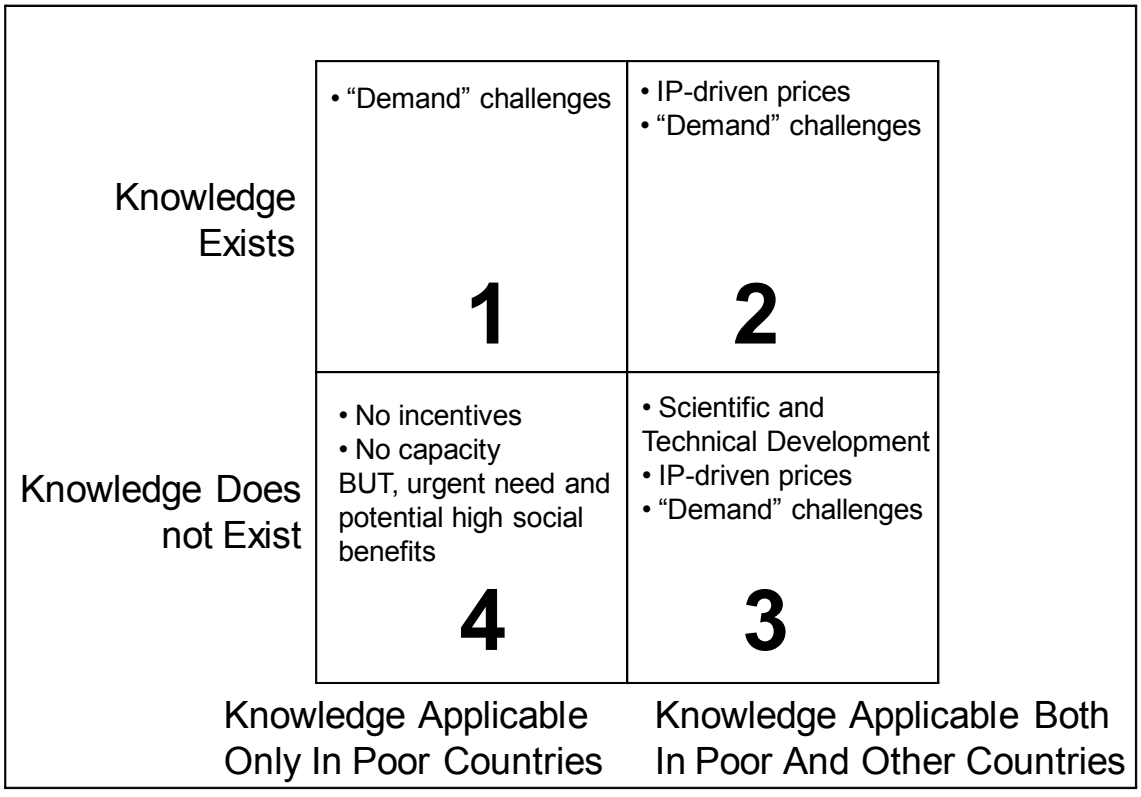


Figure 1- A Framework to Identify Missing Incentive Structures for the Production and Distribution of Knowledge

The concrete challenges that, in each quadrant, contribute to the health R&D gap can be summarized as follows:

1. When knowledge exists and is relevant mostly to poor countries, challenges are predominantly associated with the nature of demand. It may be that, very simply, developing countries do not have the resources to acquire knowledge. Or volatile demand may detract public and private agents from investing in the production of the goods and services that would permit the deployment of knowledge. IPRs challenges may exist as well, but perhaps smaller in impact.

2. When knowledge exists, but is relevant both to industrial and developing countries, the demand challenges outlined above also contribute to impede access to this type of knowledge by the poor. But in this case, an additional barrier is, in all likelihood, the existence of intellectual property (IP)-driven prices. Knowledge in this quadrant is likely to be subject to intellectual property protection, with the rights to access and use of knowledge being held mostly by private agents (but also in some cases by public entities) that seek to be compensated for the investments made to generate the knowledge by charging IP-drive prices, which will price the poor out of accessing knowledge.

3. When knowledge does not yet exist, and is relevant both to poor and industrial countries, challenges are a combination of technical and scientific issues and demand challenges. Additionally, IP-issues may also play a role, both in the way IPRs may impede access to existing knowledge. Moreover, IP-issues have to be considered here to avoid, or limit the possibility, that once knowledge has been generated (moving, then, to quadrant 2) IP-prices will not price the poor out of access.

4. Perhaps the most vulnerable quadrant is the situation depicted in quadrant 4, when the knowledge relevant only to the poor does not exist. In this case, not only is there an almost absolute lack of incentives, but there is no capacity in developing countries to develop, by either private or public agents, the knowledge required.

The Figure below illustrates with suggestions the generic situations described above.

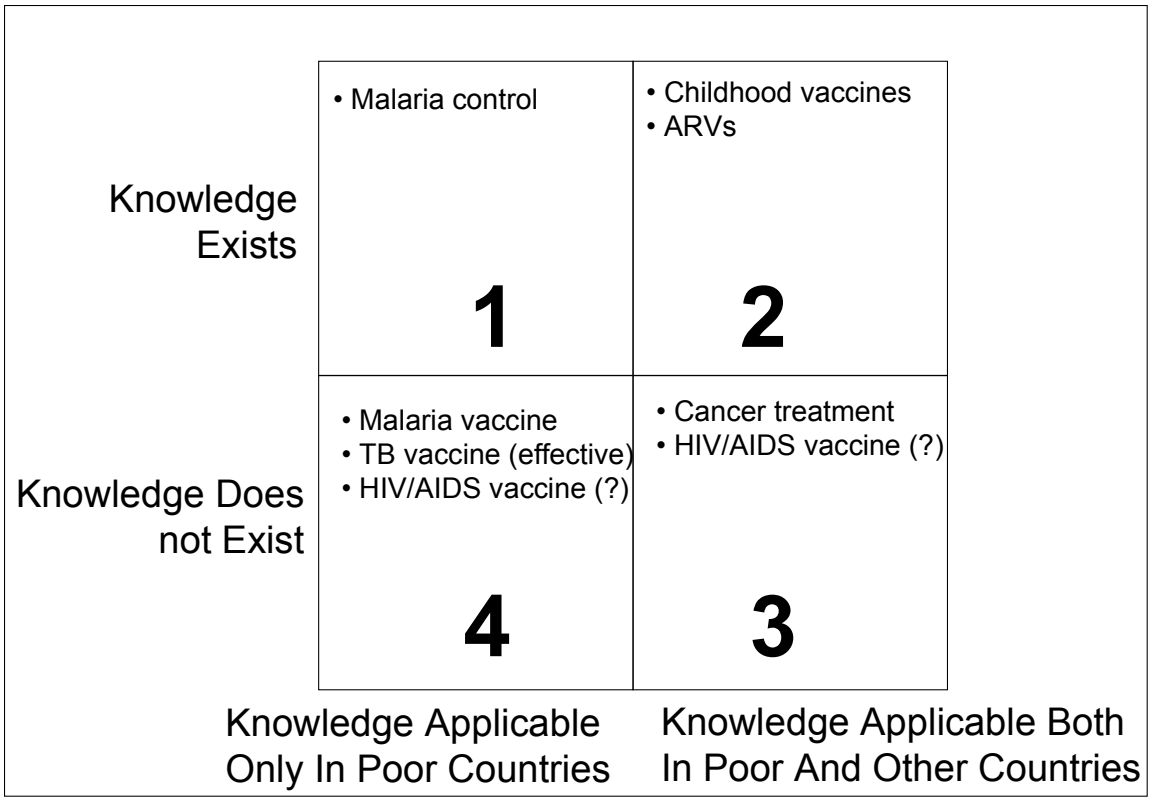


Figure 2-A framework to identify missing incentive structures for Health R&D (Examples)

1. There is now sufficient knowledge to use a combination of therapeutic drugs and prevention measures (including insecticide impregnated nets) to control malaria, but this knowledge fails to be deployed effectively in poor countries. Lack of resources and volatile demand for the goods and services needed to deploy this knowledge impede the application of this existing knowledge.

2. Many childhood vaccines are no longer subject to patent protection. They are relevant in both developed and developing countries, but they still fail to be deployed effectively in developing countries. Challenges associated with demand (especially its volatility) impede access. Antiretrovirals for HIV/AIDS, on the other hand, have been subject to IP-pricing barriers to access, in addition to the demand challenges that afflict childhood vaccines.

3. The cure for many types of cancer and an HIV/AIDS vaccine are examples of knowledge that does not yet exist, and would be relevant the world over. It is not certain that an HIV/AIDS vaccine that works to stimulate the immunological response against the strain of the HIV virus that is prevalent in Europe and North America would also work for the strain of the virus that is prevalent in Africa, thus there are some questions that an HIV/AIDS vaccine would have the same effective everywhere (thus, the question mark). The constraints in this case are mostly scientific and technical.

4. Examples of knowledge that is completely absent include vaccines for malaria and an effective vaccine for TB in the context of developing countries. Perhaps, as indicated above, there would also be the need to develop an HIV/AIDS vaccine for the strains of the HIV virus that are prevalent in Africa.

2.7 Applying the Framework to Financing Options

Within the framework provided above, there are a number of concrete initiatives, proposals and ideas that aim at closing the knowledge gap.

In quadrant 1, the major issue is to meet the challenges associated with demand. Options to improve access to this knowledge by the poor are typically associated with generating reliable demand on a scale that is commensurate with the requirements of those who produce the goods and services that need to be deployed to apply this knowledge. One option is to pool purchasing funds for medicines. The result is not only that these funds allow for the deployment of medicines in developing countries, but they also contribute, through economies of scale in consumption and enhanced bargaining power, to price reductions, in a virtuous cycle of enhanced access. Resource pooling and bulk purchasing have been options that, in the health area, have been pursued by initiatives such as GAVI, the Global Fund, and the Global TB Drug Facility. There is an excellent example of pooled purchasing by small countries in the Eastern Caribbean through their Drug Facility. These small countries pool purchases.

When knowledge is relevant both to the poor and to others (quadrants 2 and 3), challenges may be related to IP-drive prices, or to demand challenges, as outlined above. For demand challenges, the options would be very similar to the ones described in above for the case when knowledge is relevant both to the poor and to the others. When the challenges are related with IP-driven prices, the general thrust of options to meet restrictions to access related with IP is the segmentation and differentiation of the two markets, poor and others. If knowledge exists, access can be improved by adopting differential pricing for patented technologies. This option is efficient (Pareto improving) since developed countries would not be worse off (they would still pay the same they pay now, or even slightly less), with developing countries facing a substantially reduced price (based on ability to pay and the marginal costs of production). The differential pricing for some critical technologies has come up against the decisions of some groups of low and lower middle income countries to seek to obtain a single price.

If knowledge does not exist, differential patenting (the Lanjouw proposal) would be an option. Basically, firms accept ex ante the licensing of their technologies to the poor, while retaining the usual property rights in developed countries. This proposal has been advanced to solve problems of access to pharmaceuticals, but could be generalized to other types of innovations. It could be implemented within the current system of IP

protection, if firms were to file foreign license statements along with their patent application.

As mentioned above, quadrant 4 is perhaps the most vulnerable one. The options highlighted here consider how the scientific power and technological capacity of private and public actors in developed countries could be mobilized to focus on problems of the poor. They do not address the longer-term need to build endogenous capacity to allow the poor to become fully-fledged active participants in the knowledge economy. Several options have been considered to meet these challenges. One consists of Advanced Market Commitments (AMCs), a commitment by developed countries to purchase vaccines for neglected diseases as discussed above.

Basic research and efforts to get to new fundamental scientific results upon which later technological development can be built require a different type of incentives, with "push" incentives probably being more effective for this purpose. One possibility, which taps again the scientific capabilities of the private sector in developed countries, is to offer tax credits on research and development expenditures associated with efforts oriented towards the diseases affecting predominantly developing countries (such legislation has been proposed at times in the US Congress and in the UK). Another possibility is offering tax credits to developed countries' pharmaceutical firms for sales of new vaccines to address conditions specific to developing countries, which provides an incentive not only for vaccine discovery, but also for its distribution and sales to those in need. A pharmaceutical company in a rich country could receive one dollar in tax credits for each dollar of sales to a poor country. This would correspond roughly to putting half of the burden of the cost with the government. However, this burden would have to be incurred not only if the vaccine is discovered, but also if it were sold, which, in principle, would only happen if it were to be effectively applied. For a more detailed discussion see Attaran, Kremer, Sachs and Sievers[47].

Of course, incentives such as a commitment purchase do not pay for opportunity costs. That is, why should a firm, which has limited resources and time, engage in R&D for a vaccine, even if there is a purchase commitment, when it could be investing in much more rewarding projects? The size of the purchasing commitment may be important to overcome the opportunity cost, but there may also be a need for grants for clinical trials or even R&D. Note that the orphan drug legislation combines marketing exclusivity with, precisely, clinical trial grants. More broadly, government funding (through direct grants or tax credits) for R&D may often be required as a "push" mechanism.

[47] Attaran, Amir, Michael Kremer, Jeffrey Sachs and Sara Sievers. 2000. *A Tax Credit for Sales of HIV, Tuberculosis, and Malaria Vaccines*. Cambridge, Mass.: Harvard University, Center for International Development.

Another possibility, still oriented to private firms, is extending national orphan drug legislation to the international level. National orphan drug legislation gives access to special public funds for research oriented towards diseases that affect only a minority of the national population (along with special treatment in the regulatory drug approval process and other benefits once the medicine actually exists). Bringing the same principle to be applied not only to diseases that affect only a few nationally, but also to those that have been neglected in developing countries, would provide added incentives for research.

Yet another possibility is to tap into the research capacity of national laboratories and research universities by establishing at the international level the equivalent to the National Institutes of Health in the US or the Medical Research Council in the UK.

But perhaps the most promising approach to date for linking the capacity of public and private actors to address the problem as seen in quadrant 4 is through the development of product development partnerships.

2.5 Product Development Partnerships

Product Development Partnerships (PDPs) represent one class of Public Private Partnerships (PPP). In PPPs a government service or private business venture is funded and operated through a partnership of government and the private sector. They typically involve a contract between a public sector authority and a private party, in which the private party provides a public service or project and assumes substantial financial, technical and operational risk in the project with the guarantee of adequate return on the private investment. See 6.4.1 for further description of PDPs
Examples of successful PDPs include the Medicines for Malaria Venture (MMV), a Swiss foundation whose mission is to bring public, private and philanthropic sector partners together to fund and manage the discovery, development and delivery of new medicines for the treatment and prevention of malaria in disease-endemic countries and the International Aids Vaccine Initiative. (IAVI). IAVI is an ambitious non-profit entity with truly global reach which works to accelerate the development of an AIDS vaccine in addition to promoting expansion of universal access to prevention, treatment and support in HIV. IAVI implements a major part of its research, policy, and advocacy programs in developing countries, where 95% of new HIV infections are occurring.[48]

A PDP Donor Coordination Group (DCG), comprising Irish Aid, UK DFID, Wellcome Trust, World Bank, DGIS (Netherlands), BMGF, SDC (Switzerland), Rockefeller Foundation, CIDA (Canada), NORAD (Norway), USAID and US National Institutes of Health (NIH), was established in April 2004 to facilitate donors in supporting and monitoring the performance of PDPs through information sharing, policy analysis and advocacy. An additional rationale for the DCG was that donors and PDP representatives

[48] http://www.iavi.org/about-IAVI/PAGES/what-we-do.aspx/ Accessed 2 October 2009

agreed on the need to reduce monitoring and engagement transaction costs on both sides, through coordinated monitoring initiatives. Three years later, Irish Aid highlighted what it saw as the advantages of the DCG: (i) improved quality of decision-making; (ii) policy influence as part of a larger group of donors; (iii) reduced transaction costs; and (iv) increased capacity of Irish Aid to oversee and monitor the PDP field. However, Irish Aid also noted that work to date had not produced criteria or clarified for donors how they can make comparative judgments and choices between different PDP options. They also saw the need to involve WHO and other relevant normative multilateral agencies as full partners with the PDP; and to avoid addressing the upstream-downstream interface on a product-by-product case, or only by individual PDPs, which carries the risk of product or disease-specific verticalisation. [49]

3-Coordination of R&D Financing

As of today, there are no good sources of information on investments in both communicable and noncommunicable disease research[50]. Resolution WHA61.21 refers to the division of diseases into types I, II and III, but for ease of analysis it was decided to deal with communicable and noncommunicable diseases here. Total global financing for health R&D exceeded US$ 160 billion in 2005, with the private for-profit sector accounting for 51% of this, the public sector 41% and the private not-for-profit sector 8%[51] . Lack of reporting mechanisms, inconsistent data, the lack of publicly available information and the need for resources to examine reports in multiple languages pose significant challenges in data collection. It must be noted, however, that in recent years strides have been made in identifying investments by disease category and by region, such as the work of G-Finder [52] or the HIV Vaccines and Microbicides Resource Tracking Group [53]. Nevertheless, at this moment there is no global understanding of investments in CDs and NCDs.

[49] Irish Aid (2007), Strategy for supporting Global Health Partnerships 2006 – 2010. www.irishaid.gov.ie/hivandaids/downloads/Irish_Aid_GHP_Strategy.doc . Accessed 18.10.09.

[50] The organization of much of the data in this section was done by Marta Feletto as a part of the Report to the EWG " Global R&D financing for communicable and noncommunicable diseases" by Marta Feletto and Stephen Matlin.

[51] Global Forum for Health Research (2008) Monitoring Financial Flows for Health research 2008. Prioritizing Health Research for Health Equity. Available from www.globalforumhealth.org/layout/set/print/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2008-Prioritizing-research-for-health-equity

[52] Moran, M. , Guzman, J., Ropars, A.L., McDonald, A., Jameson, N., Omune, B., Ryan, S., Wu, L. (2009) Neglected Disease Research and Development: How much are we really spending? PLoS Med 6(2): e1000030

3.1 The major research funders

This is an overview of the largest government, pharmaceutical and not-for-profit research funders in the world during 2008, across CDs and NCDs. Through publicly available sources, relevant funding into NCDs and CDs were tracked for the following: 1) the United States, Japan, the United Kingdom, Germany, and France, collectively contributing to 80% of global public spending on health R&D, 2) the top ten pharmaceutical firms by revenue, collectively contributing to over 60 % of global industry spending on R&D, and 3) the largest private international foundations, as well as the largest charitable organizations of the aforementioned five high-income countries. The inclusion of other funders' research portfolios would add to the overall landscape of global research on NCDs and CDs. However, obtaining these data was not feasible, given the short time span and resources available. Further research is desirable to broaden the scope of this exercise.

While no CDs have been excluded from the analysis, the focus is on those NCDs that make the largest contribution to mortality in the majority of LMICs: cardiovascular diseases (CVD), cancers, chronic respiratory diseases (CRD) and diabetes. These diseases also share the characteristic of being largely preventable by means of effective interventions that tackle shared risk factors [54]. Mental and neurological disorders, as important chronic conditions that share a unique set of features, and whose dual diagnosis with other health conditions is inadequately appreciated, were also included in the analysis [55]. With respect to NCDs, the study focuses on cardiovascular diseases, chronic respiratory diseases, cancer, diabetes, and mental health. Any NCD-related figure refers to these outlined categories and excludes all other NCDs.

All financial figures are expressed in 2008 international US$[56]. Absolute figures of R&D funding, as well as relative proportions of specific disease R&D are reported for the public and not-for-profit sector. These figures need to be interpreted with caution, as only a share of total public and private not-for-profit spending on CD and NCD research could be tracked from publicly available sources and, more importantly i) the size of this share varies among observed countries and ii) how untracked funds are distributed to different disease areas remains unknown. While absolute R&D figures are not exhaustive of national public and private not-for-profit spending, relative shares allocated to disease-specific research might change substantially if the overall spending by these sectors was to be tracked.

[53] HIV Vaccines and Microbicides Resource Tracking Group (2009). Report Archive. [Online]. Available from: www.hivresourcetracking.org/resources/report_archive [Accessed 14 September 2009].

[54] See Reference 12

[55] See Reference 4

[56] In recent years it is unlikely that the trend in $ exchange rates bears much resemblance to trends in the price of carrying out R&D; we thus used purchasing power parity (PPP) rates against the US$ as they are adjusted for general internal price levels between countries and reflect the opportunity cost of committing funds to R&D. Figures are first converted from local currencies into constant 2008 values (Kumaranayake, 2000) and (www.imf.org/external/pubs/ft/weo/2009/01/ weodata/weoselgr.aspx) and then into international $ by applying PPP conversion rates (www.oecd.org/dataoecd/61/54/18598754.pdf).

3.1.1 Publicly funded R&D for NCDs and CDs

To estimate the breadth of research funded by the public sector, the study focuses on five high-income countries - the United States, Japan, the United Kingdom, Germany, and France - that accounted for 80% of global public spending in health R&D according to the latest available OECD data [57]. In each of the five countries the largest public funders of health R&D were identified. In order not to constraint or bias the research, rather than addressing solely English-translated information, original language budgets and reports across the US, the UK, France, Germany and Japan were accessed through public portals. The lack of standardization in R&D reporting and availability of disease-disaggregated research information between and within countries posed a significant challenge.

For each country, a total public R&D budget envelope is provided when available, as well as a share that could be classified as CD and NCD-related research. Included is a more detailed review of the process by which funding was identified and categorized in the United States in order to give a clear indication of the process used for other countries. The data are given in PPP-converted figures (2008 international dollars).

Financial R&D figures are reported in Table 1. The US is the biggest public funder. Germany's and Japan's absolute figures are understated as these are the two countries for which the lowest portion of public funding was tracked. Moreover, UK figures include the three most important philanthropic organizations' R&D budgets. Public funding in the UK would lower substantially if we subtracted the relative contribution of the not-for-profit organizations (as estimated by their annual R&D budget). Public institutions in France receive a mix of funds from public and private donors; public funding would lower if we estimated the portion allocated solely by the public sector.

Table 1 Public Sector Health R&D funding by Category and by Country (international $, 2008)

[57] See Reference 32

Category		France	Germany	Japan	United Kingdom	United States	Total
NCD	Cancer	$211.4	$21.5	$50.8	$324.1	$4'573.8	$4'970.3
	Cardiovascular Diseases	$110.1	$6.2	$18.7	$159.1	$1'538.4	$1'722.4
	Chronic Respiratory Diseases	$110.1	n.a.	$2.2	$23.6	$587.8	$613.6
	Diabetes*		n.a.	$8.2	$47.1	$613.9	$669.2
	Mental Health	$103.6	$30.2	$23.1	$259.3	$3'864.1	$4'176.6
	Non-Communicable Diseases Tot	$535.1	$57.9	$103.0	$813.1	$11'178.1	**$12'152.1**
CD	HIV/AIDS			$11.1		$2'905.0	$2'916.1
	Other Communicable Diseases			$40.7		$2'809.4	$2'850.1
	Communicable Diseases Total	$110.6	$23.1	$51.8	$147.3	$5'714.4	**$5'766.2**
Total		**$645.8**	**$81.0**	**$154.8**	**$960.4**	**$16'892.4**	**$17'918.3**

*Research on diabetes is included in CVD research

3.1.2 Industry-funded R&D for NCDs and CDs

To estimate the breadth of research on NCDs and CDs funded by the private sector, the study focused on the top ten pharmaceutical companies, based on their 2008 revenues.[58] These companies' R&D investments collectively account for 62.38% of the whole 2008 pharmaceutical industry's R&D (US$ 90.49 billion) according to the European Federations of Pharmaceutical Industries and Associations[59] (2009). Each firm's pipeline was retrieved from the company's website and compounds in active development, either in clinical trials or at the registration stage, were grouped into CD or NCD drugs, based on the product's primary therapeutic indication[60]. Compounds being actively tested in multiple trials within the same phase were counted as a single project. 72.6% of drugs in development by the ten firms were classified as related to the therapeutic areas of interest to this project. The financial cost incurred in 2008 for the development of drugs in noncommunicable and communicable therapeutic areas was estimated by a correlational analysis.

Based on ten companies' pipelines, the number of NCD and CD drugs in development in each phase of clinical trial was computed, as shown in the table below (Table 2). The table also reports each company's annual R&D budget for 2008, converted to 2008 international $.

Table 2 Number of Active Drug Development Projects by Category and Phase in International $ (2008)

[58] Pfizer, Novartis, GlaxoSmithKline, Sanofi-Aventis, Johnson & Johnson, Roche, Merck, AstraZeneca, Amgen, Eli Lilly.

[59] European Federation of Pharmaceutical Industries and Associations (2009) The Pharmaceutical Industry in Figures: key data.2009 Uptake. Available from www.efpia.eu/content/default.asp?pageID=559&DocID=4883

[60] Novartis and Johnson & Johnson disclose only a sample of their pipeline ; this comprises 50 out of 152 of projects in development for the former and a selected number of entities in later stages of development for the latter.

Company	R&D Budget ($bn)**	Communicable Disease Phases I	II	III	CD Total	Non-communicable Disease Phases I	II	III	NCD Total	Other Disease (Total)	Totals Phases I	II	III	Company Total	Project Average ($bn)**
Johnson & Johnson***	$8.4			8				11					23		
Pfizer	$7.9	3	5	3	11	31	21	8	60	29	40	33	27	100	$0.08
Novartis****	$6.1	5	1	11	17	0	9	20	29	4	5	16	29	50	$0.12
GlaxoSmithKline	$5.6	4	4	0	8	20	15	16	51	77	41	49	46	136	$0.04
AstraZeneca	$5.2	7	2	1	10	23	22	8	53	13	38	29	9	76	$0.07
Sanofi-Aventis	$5.0	4	7	8	19	10	5	16	31	14	17	16	31	64	$0.08
Merck	$4.8	1	3	1	5	21	11	7	39	3	22	16	9	47	$0.10
Eli Lilly	$3.8	0	0	0	0	32	14	7	53	13	39	19	8	66	$0.06
Amgen	$2.9	0	0	0	0	7	10	7	24	16	13	13	14	40	$0.07
Roche	$2.5	2	1	1	4	32	20	17	69	13	42	23	21	86	$0.03
Total	**$43.9**	**26**	**23**	**25**	**74**	**176**	**127**	**106**	**409**	**182**	**257**	**214**	**194**	**665**	**$0.07**

* " Other" includes diseases that not selected as explained in section A2.

** Adjusted US PPP (2008)

*** J&J reports only selected drugs in later stages (phase III or registration) without providing the total number of drugs in development; and therefore excluded from the analysis

**** Novartis reports details for only 50 out of their total of 152 projects

While these companies disclose their last financial year's R&D budget, they do not provide any indication of the share of R&D expenditure devoted to NCD or CD drugs development. Therefore, the financial cost incurred for the development of drugs in these two therapeutic areas over 2008 had to be estimated.

3.1.3 Charity- and private foundation-funded R&D for NCDs and CDs

The Global Forum for Health Research estimated that US$12.2 billion was invested in 2005 in health-related R&D by the private not-for-profit sector, which includes charities, foundations and higher education.[61] Within that figure, private university funding was estimated to amount to US$ 3.1 billion (ibid.). The present study centered on major foundations and charities and had to disregard private funding of universities, as they do not systematically report on R&D funding by category of disease.

Foundations were identified through reviews of donor funding of health R&D, as done by Shiffman [62], and ranked by the size of their endowment. Subsequently, the largest 50 U.S. and 40 European foundations were examined on the basis of three criteria: i) available information on health R&D investments, ii) available information on health R&D investments by disease and iii) investments in excess of US$ 5 million. Due to these inclusion criteria, merely 5 foundations were included in the study. This is a challenging sector to examine, since unlike charities, few of them disclose their investments in R&D.

Although charities normally report on specific R&D allotments, their sheer number also makes this a challenging group to report upon. According to the National Center for Charitable Statistics, in 2008 there were 1,536,134 registered non-profit institutions in the United States of which 974,337 were public charities and 115,340 were private foundations [63]. A review of 372 U.S.-based charities, identified through Charity

[61] See Reference 32

[62] Shiffman J.(2006) Donor funding priorities for communicable disease control in the developing world. Health Policy and Planning 21(6) 411-420

[63] National Center for Charitable Statistics (2009). Number of Nonprofit Organizations in the United States, 1998-2008. [Online]. Available from:

Navigator, excluded those for which R&D funding could not be attributed to specific NCDs or CDs, resulting in the inclusion of 34 charities. The remaining charities either did not have a clear link to a disease group examined, or were focused on advocacy and support, rather than research. All identified U.S. charities reported R&D investments under programme activity within their financial statements.

Moreover, the study sought to provide representation of the major charities based in the UK, France, Germany and Japan, as these countries were also considered in the public sector funding review. In the United Kingdom, charities are regulated by the Charity Commission, which is a government body that ensures that charities remain transparent and accountable to donors. There are 166,807 registered charities with a combined annual income of £51.1 billion. Although the Charity Commission does not maintain a register of charities by sector, it is possible to search various charities by keywords for objectives and activities. A search of charities by keywords "health", "medical" and "research" was undertaken and the sample further restricted to charities with a total income of over £10 million, resulting in 256 charities. The 14 charities providing disease-disaggregated information on R&D funding were retained. French charities with annual research activities accounting for over €33 million were also included. The search for Germany- and Japan-based charities, based on the same criteria held above, was inconclusive.

Of greatest interest in the private not-for-profit sector are the results from both the United Kingdom and the United States, since there are very clear definitions of charities and foundations, which are actively monitored by government agencies and interest groups. When examining the total for private foundations and charities included as part of this study (US$ 2,473.3 million), a total of 66.7% (US$ 1,650.4 million) was allotted to NCDs and 33.3% (US$ 822.9 million) to CDs. In total, cancer is the leading category of investments for NCDs, accounting for 44.2% (US$ 1,092.7 million) followed by cardiovascular diseases with 12.7% (US$ 313.5 million) and diabetes with 9.3% (US$ 230.8 million). Chronic respiratory diseases and mental health, both account for less than 1% of investments. (Table 3)

Table 3 Private Not-for-profit Sector Investments in Health R&D by Category in international $ (2008)

http://nccsdataweb.urban.org/PubApps/profile1.php?state=US [Accessed 5 October 2009].

Category	R&D ($mn)	Per Cent of Total
Cancer	$1'092.7	44.2%
Cardiovascular Diseases	$313.5	12.7%
Chronic Respiratory Diseases	$12.9	0.5%
Diabetes	$230.8	9.3%
Mental Health	$0.4	0.0%
Non-communicable Diseases Total	$1'650.4	66.7%
Infectious Diseases	$822.9	33.3%
Communicable Diseases Total	$822.9	33.3%
Total	**$2'473.3**	**100.0%**

3.1.3.1 The United States

Considering both charities and private foundations in the United States, a total of US$ 1,537.6 million (2008) was spent on relevant research, of which 61.1% (US$ 939.3 million) was for NCDs and 38.9% (US$ 598.3 million) was for CDs. The majority of funding for CDs came from private foundations such as the Bill and Melinda Gates Foundation, whereas funding for NCDs come mostly from charities. Investments in NCDs include: cancer (US$ 508.1 million), diabetes (US$ 223.0 million) and cardiovascular disease (US$ 199.78 million), while chronic respiratory disease (US$ 8.0 million) and mental health (US$ 0.4 million) remain less funded. If we exclude private foundations, charities invested a total of 88.1% (US$ 907.5 million) in NCDs and 11.9% (US$ 113.62 million) in CDs. (Table 4)

Table 4 USA Private Not-for-profit Sector Investments in Health R&D by Category in International $ (2008)

Category	R&D ($ mn)	Per Cent of Total
Cancer	$508.1	33.0%
Cardiovascular Diseases	$199.8	13.0%
Chronic Respiratory Diseases	$8.0	0.5%
Diabetes	$223.0	14.5%
Mental Health	$0.4	0.0%
Non-communicable Diseases Total	$939.3	61.1%
Infectious Diseases	$598.3	38.9%
Communicable Diseases Total	$598.3	38.9%
Total	**$1'537.6**	**100.0%**

3.2 Conclusions on funding

These are estimates of global R&D spending in 2008, across the spectrum of considered NCDs and CDs. Due to the limited time and resources available for this work, only the largest sources, responsible for the majority of global funding, could be considered. Moreover, this study can only report the data that were publicly available. This is a limitation to the extent that the study relies on what and how countries, organizations and industries choose to report. In order not to constrain or bias the research, rather than addressing solely English-translated information, original language budgets and reports across the US, the UK, France, Germany and Japan were accessed through public portals. Nonetheless, public funders variably report on disease-specific R&D budgets. Moreover, foundations as well as private universities generally do not report on disease-specific research funding. Industries disclose their project pipelines (in some cases only a sub-sample) as well as information on the therapeutic significance of active drugs in development, but not information on R&D flowing into specific-disease drugs. The study manages to classify a share of disease-relevant R&D funding from less than half (in Germany) to as high as 95% (in the US) of public funding; over 70% of industry investments and, finally, the largest funding by foundations and charities (although these do not account for the majority share of not-for-profit spending, given the sheer number of organization holding modest budgets).

Another challenge faced was the lack of standardization in reporting and classification systems between and within countries. Public bodies may report on budget appropriations, requests or commitments. Research expenditures may be aggregated across variably defined groups of diseases. Compounds in development might be classified across variably defined primary indications. Funding sources may not be discernable.

While the results are therefore tentative and the relative share of R&D funding across diseases should not be generalized, they show a consistent 2:1 ratio in R&D funding that is allocated to NCDs and CDs respectively, across sectors (Table 5).

Table 5 Total Sector Investments in Health R&D by Category in International $ (2008)

	Public Sector		Private Sector		Not-for-profit		Total	
Category	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent	R&D ($mn)	Per Cent
Non-Comunicable Total	$12'168.7	67.8%	$29'390.0	68.4%	$1'650.4	66.7%	$43'209.1	68.2%
Communicable Disease Total	$5'766.2	32.2%	$13'590.0	31.6%	$822.9	33.3%	$20'179.1	31.8%
Total	**$17'934.9**	**100.0%**	**$42'980.0**	**100.0%**	**$2'473.3**	**100.0%**	**$63'388.2**	**100.0%**

There are large variations in public spending flowing into NCDs and CDs across the countries examined, with NCDs receiving from 65% to over 80% of national public budgets. Cancer research alone absorbs in all countries the equivalent of, or more than what flows into research for all communicable diseases.

While an estimate of the cost for the development of the aggregate classes of industry NCD and CD drugs was developed, the sample was not large enough to allow the estimation of the cost of disease-specific drugs. However, the distribution of active projects across diseases can provide some indication of the industry R&D commitment to different diseases. Of all CD and NCD projects in development in 2008 in the top ten pharmaceutical industries by revenue, 84% were NCD-related and 15.3% were CD-related (Table 2). The distribution of drugs in development across NCDs is consistent with the relative magnitude of NCD research funded by the public sector: cancer drugs constitute 31.5% of drugs in development (regardless of the development stage); mental health and CVD drugs represent respectively 22.4% and 11% of disease-relevant projects. While being limited to the ten largest pharmaceutical companies by revenue, the sampled pipeline analysis is consistent with results provided by FierceBiotech [64]: of the 2,900 medicines in development in the U.S. in 2008, 750 (25%) compounds were cancer drugs, 312 (10%) for heart disease and stroke and 109 (3.7%) for HIV/AIDS.

In the private not-for-profit sector, communicable disease funding remains primarily in the realm of private foundations (63.3%), while noncommunicable diseases are widely covered by charity funding (98.1%). 44% of the overall not-for-profit R&D commitment goes to cancer research. Interestingly, mental health - which is significantly targeted by public as well as private R&D - is neglected by the not-for-profit sector even in those countries where it constitutes an important item on the public research agenda, such as the US and the UK.

It is beyond the scope of this study to link this mapping of R&D to the mapping of burden of disease. However, a few considerations are worth making. According to the UK Clinical Research Collaboration, the general distribution of public and not-for-profit funding across diseases in the UK broadly follows the pattern of burden of diseases as measured by DALY rates for the country in 2006.[65] Similarly, Manton et al. found consistent longitudinal correlation between the level of investment in NIH research and population changes in the risk of specific diseases (CVD, stroke, cancer, and diabetes) over the last five decades.[66]

However, the extent to which this research can address the risk or burden of these diseases in LMICs remains unknown. Data from this study shows that the US NIH's disbursement for HIV/AIDS research amounted to almost US$3 billion, and Ravishankar

[64] R&D Spending by U.S. Biopharmaceutical Companies Reaches Record Levels in 2008 Despite Economic Challenges' posted March 10, 2009 by FierceBiotech website. Retrieved September 30, 2009 from www.fiercebiotech.com/press-releases/r-d-spending-u-s-biopharmaceutical-companies-reaches-record-levels-2008-despite-econo

[65] UK Clinical Research Collaboration (2006) UK Health Research Analysis, United Kingdom. Available from www.ukcrc.org/PDF/UKCRC_Health_Research_Analysis_Report.pdf [Accessed 28 September 2009].

[66] Manton, K.G., Gu X.L., Lowrimore, G., Ullian, A., Tolley, H.D. (2009) NIH Funding Trajectories and their correlations with U.S. health dynamics from 1950 to 2004. Available from www.pnas.org/cgi/doi/10.1073/pnas.0905104106

et al.[67] estimated that Development Assistance for Health (DAH) funding for HIV/AIDS amounted to a total $5.1 billion in the United States in 2007. According to Moran et al. however, NIH funding for neglected diseases specifically targeted to developing-country-specific presentations (including HIV/AIDS) was an estimated US $1.06 billion in 2007.[68] This gap shows the extent to which research that is relevant to LMIC health needs is severely under-funded. A similar conclusion can be drawn by comparing research funding for communicable diseases across sectors. For example, the G-Finder estimate of US$2.5 billion spent on LMIC-relevant neglected disease R&D is rather small, when this study finds $20 billion (Table 5) allocated to all CD research in an incomplete sampling of HICs. The gap between LMIC-relevant R&D and all health R&D is considerable.

4 Coordination of R&D for communicable and noncommunicable diseases.

4.1 Material

Qualitative research methods were used for much of this assessment; these comprised of archival analysis, review of published and grey literature and informant interviews. As a first step, an inventory of R&D financing initiatives was developed drawing on information from three sources; i) the list of initiatives provided in a draft report commissioned by the Secretariat of the Expert Working Group on R&D Financing in the first quarter of 2009;[69] ii) from the catalog of initiatives reflected in a paper prepared for the WHO Commission on Intellectual Property Rights and Health;[70] and iii) from the listing of industry partnerships in the databases of health partnerships developed by the International Federation for Pharmaceutical Manufacturers and Associations. (IFPMA)[71]. The list was supplemented by additional search on published sources and initiatives' websites; where information was incomplete, respective initiatives were contacted for further details. A WHO Internal Document titled "*Geneva Health Research Cluster: In Search of Alignment & Synergies"* which was prepared for a discussion on 15-16 December 2009 was invaluable in providing budget and background information about UN health research coordinating mechanisms. In addition, in contacting initiatives for further information, some suggestions were received concerning other relevant initiatives and these were also incorporated into the final inventory. The complete list of initiatives examined can be found in the background document. ( )

4.2 Background

[67] Ravishankar, N., Gubbins, P., Cooley, R.J., Leach-Kemon K., Michaud, C.M., Jamison, D.T., Murray, C.J.L. (2009) Financing of global health: tracking development assistance for health from 1990 to 2007. *Lancet*, 373(2113-2124)

[68] See Reference 46

[69] Ariane McCabe. Survey of R&D Coordination and Financing Mechanisms for Type II and Type III Diseases". World Health Organization in January 2009.

[70] Public-Private Partnerships for Product Development: Financial, scientific and managerial issues as challenges to ensure success" by Elizabeth Ziemba for the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health, March 2005.

[71] http://www.ifpma.org/healthpartnerships/, accessed 1 June 2009.

Coordination, which implies a slightly more active approach than collaboration, can be defined as *"synchronization and integration of activities, responsibilities, and command and control structures to ensure that the resources are used most efficiently in pursuit of the specified objectives*".[72] The need for collaboration or the more demanding coordination of R&D is close to a matter of faith and has been sought almost as a Holy Grail for at least decades. The thesis is accepted that research produces knowledge that is a public good and as such, that knowledge should be shared. It is the means of generating that knowledge and the possession of the knowledge generated that give power of one or other sort and therefore exacerbates the intrinsic difficulty in collaborating. It is only when there is clear mutuality of interest that those who have the means to generate knowledge are willing to share. It is part of the remit of organizations like WHO with its constitutional mandate to coordinate to demonstrate the mutuality of interest and provide a neutral forum for the interchange or be the impartial broker that is a conduit for sharing the necessary information. The other means of ensuring the sharing of knowledge or the means of generating it is through a dictamen from an agency which provides the funding for the knowledge generation.

The primary objective of coordination should be to ensure that, when new drugs, vaccines and diagnostics are needed to treat diseases prevalent in LMICs, products are developed that are safe, effective, affordable and suitable to the conditions in which they will be used, thereby contributing to better health and health equity globally. Secondary objectives could include:

- avoiding unnecessary duplication of effort
- avoiding waste of funding
- enabling priority efforts to be directed to urgent or neglected areas by assisting policy makers and donors in setting and management of global priorities and in selecting the most productive areas for attention along the innovation pipeline – e.g. where there is insufficient priority for specific areas of basic science, inadequate funding for lead uptake and product development, or lack of funding or capacity for clinical trials at appropriate locations; or where competing product development pipelines within and between specific diseases necessitate choices to be made.
- facilitating cooperation between public and private sector actors
- promoting inclusion of a wider range of actors in the R&D process – e.g. ensuring involvement of LMIC researchers in developing solutions to problems in their own countries; and/or R&D capacity building in LMICs.

The difficulty of coordination is emphasized in, ***The Disease Control Priorities in Developing Countries,*** where the relevance of research, especially that which is population based was stressed and emphasis was placed on the fact that health research is product of individual or institutional effort rather than being derived from nation states. It was said[73]

[72] http://www.businessdictionary.com/definition/coordination.html, accessed 3 June 2009.

[73] Bloom BR, Michaud CM, LaMontagneJR, SimonsenL. Priorities for global research and development of interventions. In Disease Control Priorities in Developing Countries, edsJamison DT et al. Oxford University Press and The World Bank, 2006

"No simple answer is available regarding the best ways to ensure effective collaboration in relation to global health. Global collaborations can be difficult, they are not inexpensive and their successes are limited in number…One set of lessons still to be learned is what the best forms of collaboration are: individual scientist, institutional, transnational or multinational"
Perhaps the truth lies in the nature of the problem to be solved. While the discovery phase may be addressed by all four, the development phase is more likely to be a product of one or other or all of the last three.

The Bamako ***"Call to Action on Research for Health"*** [74]was a major milepost along the way to stimulating global action in health research and with respect to collaboration, said: *"research activities of the private and the public sectors, including international product development partnerships, together with an increased involvement of civil society, can be mutually supportive and complementary in furthering health development and security globally".*
It also was conscious of the need to
"Mobilize all partners and players (public, private, civil society) to work together in effective and equitable partnership to find needed solutions".

4.4 Resource tracking and coordination

While they may not be concerned exclusively with financing, any efforts at the coordination of health R&D must be based on an understanding of the resources needed to tackle the targeted health problems, coupled with knowledge of the resources already available and how they are being used. Thus, coordination approaches in general require resource tracking as an indispensable tool to aid problem formulation, priority setting, program planning and monitoring of progress.

The field of global resource tracking for health R&D is relatively new. The first estimate of worldwide spending on health R&D was made by the Commission on Health Research for Development [75]. The Commission estimated that in 1986 the world spent US$ 30 billion on health R&D, of which only about 5% was being applied to the health problems of LMICs, where 93% of the world's preventable deaths occurred. Since 2001, the Global Forum for Health Research has been regularly and systematically tracking and reporting global financial flows for health R&D, producing a biennial total, conducting studies of resource flows in relation to specific diseases, conditions, actors and geographies and, since 2008, publishing an annual Report Card on the performance of funders against targets and commitments [76].

[74]The Bamako Call to Action on Research for Health http://www.bamako2008.org/dmdocuments/Call %20to%20Action%20_E.pdf Accessed November 17, 2009

[75] Commission on Health Research for Development (1990). *Health Research: Essential link to equity in development.* New York, Oxford University Press.
www.cohred.org/node/311?DocumentId=2834. Accessed 18.10.09.

[76] Landriault E, Monot JJ & Matlin SA (Eds) (2009) *Monitoring Financial Flows for Health Research 2009,* Geneva: Global Forum for Health Research, in the press.

Interest in monitoring financial flows for particular aspects of health R&D has grown significantly in the last decade, some specific examples including:

- Groups dedicated to tackling a specific disease like HIV/AIDS [77], TB [78] or malaria [79] have assessed funding flows and needs;
- Countries have made assessments of research funding, either as a single exercise to benchmark activity and compare with burden of disease [80] [81]; , as a tool for advocacy towards policy makers [82], or as part of a systematic annual approach to prioritizing national funding for health research [83];
- The Bill and Melinda Gates Foundation (BMGF) has funded the G-FINDER project at the George Institute in Sydney to track global resources for a set of neglected diseases over a 5 year period [84] .
- The private sector has reported on its own contributions to health in LMICs, estimating the combined value of its donations to drug access programs (excluding R&D on neglected diseases) to be in the region of US$ 4.4 billion[85] [86].

[77] HIV Vaccines and Microbicides Resource Tracking Working Group (2009), www.hivresourcetracking.org. Accessed 18.10.09.

[78] Agarwal N (2009) *TB Research & Development: A Critical Analysis of Funding Trends 2005-7, An Update*, New York: Treatment Action Group. www.treatmentactiongroup.org/uploadedFiles/About/Publications/TAG_Publications/2009/TAG%20TB%202009%20web-version2.pdf. Accessed 18.10.09.

[79] Malaria R&D Alliance (2005). *Malaria Research & Development: An Assessment of Global Investment*. Malaria R&D Alliance. www.malariaalliance.org/PDFs/RD_Report_complete.pdf Accessed 18.10.09.

[80] See reference 45

[81] Families USA 2008, The World Cant Wait: More Funding Needed for Research on Neglected Infectious Diseases, Washington DC: Families USA Foundation. www.familiesusa.org/assets/pdfs/global-health/the-world-cant-wait.pdf. Accessed 18.10.09.

[82] Research!America (2009). www.researchamerica.org. Accessed 18.10.09.

[83] de Azevedo Gesteira AS (2006) Flows of Financial Resources for Health Research and Development in Brazil 2000-2002, Geneva: Global Forum for Health Research. www.globalforumhealth.org/Media-Publications/Publications/Flows-of-Financial-Resources-for-Health-Research-and-Development-in-Brazil-2000-2002. Accessed 18.10.09.

[84]Moran M, Guzman J, Ropars A-M, McDonald A, Sturm T, Jameson N, Wu L, Ryan S & Omune B (2009) *Neglected disease research & development: How much are we really spending?* Sydney: The George Institute for International Health. www.thegeorgeinstitute.org/shadomx/apps/fms/fmsdownload.cfm?file_uuid=409D1EFD-BF15-8C94-E71C-288DE35DD0B2&siteName=iih. Accessed 18.10.09.

[85] IFPMA (2006) *Partnerships to Build Healthier Societies in the Developing World*. Geneva: International Federation of Pharmaceutical Manufacturers & Associations, www.ifpma.org/pdf/IFPMA_Building_Partnerships_Eng_18Jul06.pdf. Accessed 18.10.09.

[86] Kanavos P (2006) *The IFPMA Health Partnerships Survey: A critical appraisal*. International Federation of Pharmaceutical Manufacturers & Associations. ww.ifpma.org/Documents/NR4467/IFPMARelease_Partnerships_

4.5 Current arrangements

At present, there is no global coordination of R&D for communicable and noncommunicable diseases. The field is highly fragmented, with most actors working either in isolation or as a part of small groupings or networks involving a very limited sub-set of entities with shared goals. Thus, there are partial efforts to coordinate selected aspects of the overall system, often involving predominantly just a section of the innovation pipeline.

A ground-breaking new approach to collaboration among national research agencies engaged in basic research emerged in mid-2009 with the announcement of the formation of the Global Alliance for Chronic Diseases. This involves six of the world's leading health agencies (Australia National Health and Medical Research Council; Canadian Institutes of Health Research; Chinese Academy of Medical Sciences; UK Medical Research Council; and US NIH – specifically its National Heart, Lung, and Blood Institute (NHLBI), and the Fogarty International Center), collectively managing an estimated 80% of all public health research funding, collaborating in NCD research to tackle cardiovascular diseases (mainly heart disease and stroke), several cancers, chronic respiratory conditions and type 2 diabetes. Work of the Alliance will focus in particular on the needs of LMICs, and on those of low-income populations of more developed countries. The Indian Council of Medical Research will be invited to join the Alliance as a member. Research agencies from other countries and private funders may be invited to join in a second wave and WHO is joining the Alliance as an observer. The proposed priorities were identified by Daar et al.[87]

It is possible to analyse cooperation or coordination of research and development in several ways, all of which may be classed as vertical.

- By disease
- By health area
- By product.

Alternatively it may be divided according to whether the cooperation takes place at the national or international level, and finally there is a need also for coordination of research or research management within organizations such as WHO itself. ;
Examples of research coordination in the various categories are given as it is beyond the scope of this analysis to detail all the possible initiatives in each category.

4.6 Coordination by theme

4.6.1 By disease –malaria

LSE_08Mar06.pdf. Accessed 18.10.09.

[87] Daar AS et al (2007) Grand Challenges in Chronic Non-Communicable Diseases, *Nature* Vol 450, 494-6. www.nature.com/nature/journal/v450/n7169/pdf/450494a.pdf. Accessed 18.10.09.

The European Malaria Vaccine Initiative was established in 1998 by the European Commission and interested European Union Member States in order to address identified structural deficiencies in public funded malaria vaccine development. The initiative aims to provide a mechanism through which the development of experimental malaria vaccines can be accelerated within Europe and in developing countries. It seeks *"to bridge the conceptual and operational gaps between the bench product i.e candidate molecules and further validation, limited production and clinical testing, thus making further industrial development and production feasible"* It facilitates and contributes financially and technically to nationally and internationally funded malaria vaccine research and development, and will provide a mechanism to see candidate molecules through to limited industrial production and clinical trials in close collaboration with the African Malaria Network Trust (AMANET), as well as providing a forum for scientists and policy makers engaged in malaria vaccine research and development. It is not a research undertaking per se. The basic research to produce the candidate molecules is produced through national or international research.

Coordinating mechanism. Coordination is a feature of its governance and it is a major focal point of the major European malaria vaccine development efforts. It coordinates both nationally supported and EC supported malaria vaccine efforts. There is Board, an independent Scientific Advisory Committee and a Secretariat one of whose specific functions is to ensure international collaboration with major players". [88]

4.6.2 By health area-Human Reproduction

CONRAD (Contraceptive Research and Development) was established in 1986 under a cooperative agreement between Eastern Virginia Medical School (EVMS) and the U. S. Agency for International Development (USAID), but also receives funding through interagency agreements between USAID and the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the National Institute of Allergy and Infectious Diseases. Partnerships with a variety of for-profit entities for specific projects have been established, including., Personal Products (J&J), Polydex, ReProtect, Biosyn, Schering AG (now Bayer Schering Pharma), Laboratorios Silesia (now part of Andromaco Group), Gedeon Richter, Aplicaciones Farmaceuticas, and Integra LifeSciences.

The organization's overall goal is to improve reproductive health, especially in developing countries. Its main objective is to help develop safe, acceptable, affordable products and methods that provide contraception and/or prevent the sexual transmission of HIV/AIDS and other infections. Accordingly, the organization works by nurturing promising research in institutions worldwide; engaging in preclinical research; conducting clinical trials; partnering with private industry to get new products on the market; collaborating with other agencies, foundations, and non-governmental

[88] http://www.emvi.org/, accessed 27 May 2009.

organizations; and training investigators throughout the world in preclinical and clinical research techniques.[89]

In 1995, CONRAD established the Consortium for Industrial Collaboration in Contraceptive Research (CICCR) to help revitalize the pharmaceutical industry's commitment to developing new contraceptives. CICCR supports research and development of methods that specifically address the needs and perspectives of women, with particular emphasis on three priority areas: male methods, monthly methods for women, and vaginal methods that prevent pregnancy and sexually transmitted infections

Coordinating mechanism. This is apparently done internally by technical monitors' assessments and meetings of various thematic working groups. External oversight is through a Scientific Advisory Committee comprised of independent experts in the relevant disciplines which provides guidance, monitors progress, assists in making critical product development decisions and advising donors.

4.6.3 By product(s)

Vaccines: The WHO Initiative for Vaccine Research (IVR) aims to guide, provide vision, enable, support, and facilitate the development, clinical evaluation and world-wide access to safe, effective and affordable vaccines against infectious diseases of public health importance, especially in developing countries. IVR's role includes inter alia providing a source of guidance and vision for the world-wide vaccine R&D efforts; facilitating and co-ordinating clinical trials, ensuring proper scientific and ethical standards; providing normative guidance, standards and reagents; building capacity, providing training and facilitating technology transfer; addressing the issues of access and introduction of new vaccines; and encouraging partnerships.[90] IVR will focus on critical steps, leveraging on existing research, developments and management opportunities, proactively identify and promote set of targets for each stage of development to shape the global portfolio at every stage.

One of the major activities of the initiative is the organization of the Global Vaccine Research Forum.[91] The conference began in Morges, Switzerland in June 1996 and was known then as the Technical Review Meeting for Vaccine Research and Development. Since then it has grown in size and reputation and at the first meeting in the new millennium, it became known as the Global Vaccine Research Forum. The conference brings together every year a world-wide selection of top researchers and scientists and serves as a forum for the partners of GAVI (Global Alliance for Vaccines and Immunization) to discuss vaccine research and development issues, and to update research agendas. Revision of these conferences shows exchange of information on existing initiatives and some view of future developments, but in spite of rhetoric to the contrary and several initiatives, there is no evidence anywhere of a structured approach to genuine coordination of research and development in this area. Some measure of control

[89] http://www.conrad.org/, accessed 30 May 2009.
[90] http://www.who.int/vaccine_research/en/, accessed 21 May 2009.
[91] http://www.who.int/vaccine_research/about/gvrf/en/, accessed 2 October, 2009

is exerted through the need to comply with the requirements of the global norms and standards through the WHO Quality Assurance and Safety of Biologicals.

There is still echo of the comments made by UNICEF and WHO 13 years ago in "The state of the World's Vaccines and Immunization".[92]

"The world has become inured to the topsy-turvy notion that, while antibiotics may be expensive, vaccines should come cheap…But today things are changing. Today vaccines belong not , as Salk resolutely maintained "to the people" but to a complex web of biotechnology companies, universities, public and private sector research institutes and pharmaceutical companies".

4.7 Policy Coordination

As pointed out previously, the nature of the R&D process makes coordination intrinsically difficult, but there seems to be some limited policy coordination across this sector more recently. Recent initiatives do aim to coordinate policies between funders and across various initiatives better. For example, in 2008 SIDA hosted a meeting on Capacity-Building for Research in Health[93] which addressed how to better achieve policy alignment and harmonization Various forums have also been established to allow international funders and aid agencies to coordinate and harmonize their efforts and policies, e.g. ESSENCE and IFORD.

The following are examples of some of the current programs aimed at coordinating research in given areas.

- The Alliance for Health Policy and Systems Research (AHPSR) is an international collaboration based in the Health Systems and Services Cluster of WHO which aims to promote the generation and use of health policy and systems research as a means to improve the health systems of developing countries. Its governance structure consists of the Board (Max 8 members, meets 1/year), the Scientific and Technical Advisory Committee (STAC) (8 members) and the WHO Advisory Committee on Health Research which offers oversight to the Board.[94]
- ESSENCE (Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts) is a collaborative framework for funding agencies to ensure synergies in addressing research capacity needs. It aims to improve the impact of investment in institutions and enabling mechanisms that address the identified

[92] State of the world's vaccine and immunization" World Health Organization, United Nations Children's Fund. Geneva 1996

[93] Meeting on Capacity Building for Research for Health, Stockholm, Sweden 3-4 April 2008. 31 representatives of funding agencies and African partners met to address how to improve support and activity for capacity building for research in resource-constrained countries.

[94] http://www.who.int/alliance-hpsr/en/, accessed 25 May 2009.

needs and priorities within national strategies on research for health. The secretariat is hosted by TDR, and the initial executive group includes development cooperation agencies – the United Kingdom Department for International Development (DFID), International Development Research Centre (IDRC), the Ministry of Foreign Affairs of the Netherlands, Norwegian, Agency for Development Cooperation (Norad), the Swedish International Development Cooperation Agency (Sida) – plus the Bill & Melinda Gates Foundation, the Wellcome Trust and NEPAD Science, Technology & Innovation. [95]

- UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) works with scientists throughout the world to undertake research guided and monitored by experts from many countries. Capacity-building efforts enable the participation of developing country institutions in seeking solutions to local problems. HRP works to ensure that it has strong connections in countries via its network of sexual and reproductive health and HIV/AIDS advisors, a bottom-up approach which draws upon developing country policy-makers, programme managers, service providers, consumers and scientists to define research and technical activities that respond to the priorities of the poor and disadvantaged, and effective partnerships with a global network of scientists and health professionals in universities, professional and other nongovernmental organizations, the private sector and government bodies as well as foundations and multilateral development agencies. Within HRP, several complementary oversight and advisory bodies ensure accountability: the Policy and Coordination Committee, the Scientific and Technical Advisory Group, the Gender and Rights Advisory Panel, the Regional Advisory Panels and the Scientific and Ethical Review Group Panel. [96]
- The Special Programme for Research and Training in Tropical Diseases, (TDR) is an independent global programme of scientific collaboration that helps coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. Established in 1975, TDR, is sponsored by UNICEF, UNDP), the World Bank and WHO. TDR is governed by a unique board made up of representatives from governments in funding and receiving countries, ensuring equal representation regardless of economic level. In addition, TDR has a scientific and technical review committee that oversees the mix and range of scientific priorities, and additional committees for specific research areas, made up of scientific experts from all over the world.[97]
- The International Forum for Research Donors (IFORD) is a network of research donors who informally share information and build research partnerships for international development. IFORD's mandate is to facilitate collaboration and information-sharing amongst policy-makers from within organizations that have a mandate to support research in low and middle-income countries.
- The Institutional Centre for South-South Cooperation in Science, Technology and Innovation (ISTIC) opened in March 2009 and the ISTIC program for 2009-2010

[95] http://apps.who.int/tdr/news-events/news/pdf/essence.pdf, accessed 2 June 2009.
[96] http://www.who.int/reproductive-health/hrp/publications/hrp_brochure.pdf, accessed 20 May 2009.
[97] http://apps.who.int/tdr/, accessed 27 May 2009.

will cover the areas of S&T policy and STI human capacity building within the framework of UNESCO program for natural sciences. Among its planned 2009 activities are a Research and Development Management Programme for High Level Policy Makers.[98]

- Heads of International Research Organizations (HIROs) is an informal policy organization bringing together major government and philanthropic biomedical research funders for an annual meeting to exchange information and views and discuss possible joint activities among major health research organizations. Annual meetings are held to discuss relevant issues; the 2008 meeting discussed pandemics, sharing of worldwide database knowledge (for example on genome testing), cross-border funding, peer review, clinical research training, open access publishing, and bio-security and biosafety.[99]

4.8 "Mapping" Initiatives

Additionally, it should be noted that there are a number of tools which attempt to map existing initiatives in the field and facilitate coordination by sharing of information. These include the following health research databases:

- The Council on Health Research for Development has developed Health Research Web, a web-based, interactive and growing source of information on the structure and organisation of research for health in and for low and middle income countries. The tool is aimed at maximizing the impact of research on health, equity and development in low and middle income countries and to improve the lives of underserved populations everywhere. Health Research Web is a response to the problem that there is no single source of information on research for health that is organised from the perspective of low and middle income countries; it is organised to provide integrated information on research for health at country and regional levels in order to strengthen national health research capability. Users can search by country for information on ongoing health research, health research priorities, key institutions, financing and partnerships, resources and country background, among others. [100]
- The Global Health Progress Initiative seeks to bring research-based biopharmaceutical companies and global health leaders together to improve health in the developing world. Its programs and initiatives database is searchable by keywords as well as dropdown menus allowing users to search by disease, by background information (including geographical basis) and by global health community and partners. [101]

[98] http://istic-unesco.org/, accessed 20 May 2009.

[99] CIHR 2003, *Meeting of Heads of International Research Organizations (HIRO)*, Ottawa: Canadian Institutes of Health Research. www.cihr-irsc.gc.ca/e/18769.html. Accessed 18.10.09.

[100] http://www.cohred.org/HRWeb/, accessed 29 May 2009.

[101] http://www.globalhealthprogress.org/programs/search.php?first=yes&parent=programs, accessed 1 June 2009.

- HRP publishes the WHO Reproductive Health Library on the Internet and on CD-Rom which includes inter alia systematic reviews of research.[102]
- The International Federation for Pharmaceutical Manufacturers and Associations (IFPMA) has developed a database of health partnerships, searchable by country, program type, disease area, and partners (http://www.ifpma.org/Healthpartnerships/), which provides a synopsis of programs and links to appropriate websites. The same site offers access to a clinical trials portal which is free of charge and easy-to-use interface containing comprehensive information on ongoing clinical trials, clinical trial results and complementary information on related issues. Resources like this serve to increase industry transparency as well as to reduce duplication of efforts.[103]
- The Special Programme for Research and Training in Tropical Diseases (TDR) has established TropIKA.net as a global knowledge management electronic portal to share essential information and to facilitate identification of priority needs and major research gaps in the field of infectious diseases of poverty. Despite immense scientific advances, researchers and policy makers face the other problem of haphazard flow of scientific information for which they lack time to screen, awareness of what is relevant and essential for their domain of activities and skills for interpretation and application in health interventions. Beginning in 2004, TDR undertook surveys and consultations to underpin the development of this knowledge management platform (TropIKA.net). TropIKA is designed to enhance access and to share essential knowledge with health researchers and policy makers dedicated to improving control of infectious diseases of poverty. [104]

5. Collaborative arrangements for Global Health Research

The World Health Organization and many other global health stakeholders have been engaged in a number of discussions and analytical exercises to assist with improving collaboration within the space of these partnerships, global health initiatives and health research in particular.[105,106] An attempt is being made to identify opportunities, challenges and methods of achieving successful collaboration. It appears logical that the first level of rationalization, cooperation and synergizing needs to be sought within the domain where there is one authority—WHO—and as a next step, initialised in the UN group of organizations. WHO as a result of several discussions on the need for more collaboration, commissioned FSG Social Impact Advisors recently to analyse the potential for collaboration among eight health research organizations and initiatives that have some role in the oversight and reporting on research globally, although they are not themselves engaged actively in research and development directly. The eight selected were

[102] http://www.who.int/reproductive-health/hrp/publications/hrp_brochure.pdf, accessed 1 June 2009.
[103] http://www.ifpma.org/, accessed 29 May 2009.
[104] http://www.tropika.net/, accessed 29 May 2009.
[105] FSG report Social Impact Advisors Report.
[106] WHO commissioned McKinsey Report

- The Alliance for Health Policy and Systems Research (AHSPR)
- The Council on Health Research for development (COHRED)
- The Global Forum for Health Research (GFHR)
- The Special Program of Research, Development and Research Training in Human Reproductive health (HRP)
- The Initiative for Vaccine Research (IVR)
- WHO Secretariat on Public health, Innovation and Intellectual property (WHO PHI led IGWG process)
- The Special Program for Research and training in Tropical Diseases (TDR)Research

It is expected that the analysis will outline the areas such as capacity strengthening and resource mobilization in which collaboration among themselves and coordinated technical cooperation to member countries in these areas would be of immense benefit.
A recent paper by WHO has mooted the idea of an effective global health governance structure—a multi-level, multi-party, multipurpose partnership framework of global health governance, a platform coordinated by WHO and supported by high-level political commitment and policy coherence; it is envisaged that the platform could be operationalized ultimately through an effective implementation mechanism of global action networks (GANs).[107] Ideas for the construct of a new arrangement are also being mooted by independent and country experts.[108]

6. General conclusion and comment

From the description of the several initiatives above, it is evident that many "local" R&D coordinating arrangements are currently in place. Coordination within the respective initiatives is aimed at varying objectives and is structured either through more formal governance and oversight arrangements or is ordered through initiatives that are more flexible and quasi prescribed in nature. Some are internal to organizations' management hierarchies, whereas others are outside of it. Broadly, these fall into three categories:

First, many initiatives described in the sections above have governing arrangements—boards, councils, committees with broad-based representation, both with respect to geographic considerations as well as subject domains and institutional backgrounds. These entities, in majority of the cases are internal to the organization/initiative and are mandated in governance and oversight roles. Although they are not, as such, mandated to 'coordinate' R&D at the global level, as perceived in the given context, they nevertheless constitute an important resource. These multi-stakeholder-characterized governing arrangements should be leveraged while exploring the need for and in the event of establishing a global coordinating arrangement.

[107] Sridhar D, Khangram S, Pang T. Are existing structures equipped to deal with today's global health challenges—towards systemic coherence in scale up. Global Health Governance, Volume II, No. 2 http://www.ghgj.org

[108] Røttingen JA, Buss PM, Davies S, Touré O. Global-health research architecture--time for mergers? Lancet. 2009 Jan 17;373(9659):193-5.

Second, many initiatives have mechanisms in place to draw on the strength and expertise of technical partners; as a result task forces, expert groups and scientific and technical advisory committees are usually part of most of them. These structures tend to have broad-based representation in an attempt to draw on the best possible advice and expert opinion from around the world or region. As in the previous case, these arrangements are not mandated to coordinate globally; however they do have a knock on effect owing to the common platform that they provide for sharing information informally.

The third category includes the plethora of informal networks of researchers, and related stakeholders that have an opportunity to share experiences from time to time informally either at the platform of meetings convened by agencies such as WHO, or their affiliate initiatives such as TDR.

In addition to existing coordinating arrangements, there are many structures in place to map ongoing activities, develop inventories and manage information. There are also a number of structures in place to coordinate arrangements at the policy level, albeit predominantly involving donor and development agencies that fund research and their key research-performing collaborators.

At present, however, there is no "global" coordination of R&D for major diseases and any possible Global Health Research and Innovation System (GHRIS) is highly fragmented. Four kinds of failures can be seen in the system, leading to a lack of effective treatments for health problems and to the persistence of large health disparities within and between populations: failures in science, in the market and in public health and failure to collect, consolidate, interpret and disseminate information.

To overcome these failures, a globally coordinated approach to R&D is proposed, which would involve three elements:

- Coordination in the identification of priority areas for action
- Coordination in the distribution of research efforts between different entities, which may be located in the public or private sectors and in different geographies.
- Coordination in the financing of R&D for them.

These elements can be regarded as sequential. In particular, the coordination of financing of R&D for diseases prevalent in LMICs would require considering both identifying the priority diseases and determining which actors should receive the financing. Consequently, there is an argument for a comprehensive approach involving all three elements and requiring an arrangement such as the following:

- Establishment of Working Groups and an Oversight Group to collectively draw up research agendas and set priorities, based on information gathered from a range of sources including a new Global Health Research Observatory.
- Decisions by the Working Groups and Oversight Group about the distribution of elements of the required R&D among a diverse range of researchers working in different settings, including basic research laboratories, development/scale-up plants, clinics, health services and communities, in public and private sector environments in HICs and LMICs.

- Creation of a Global Health Research and Innovation Fund (GHRIF) to provide funding for:
  - targeted R&D for new drugs, vaccines, diagnostics, and intervention strategies against priority health conditions of the poor – including both CDs and NCDs that are prevalent in LMICS and for which adequate interventions are not presently available.
  - a range of research areas primarily conducted in LMICs that are essential underpinnings of interventions to improve health, including: health policy and systems research, social science and behavioral research, implementation/ operational research and research on the determinants of health. The funding would combine capacity building with focused research to support key national health programs such as health systems strengthening, improving reproductive health, eradicating target diseases and responding to health threats such as climate change.
  - enhancing innovation capacities and environments in LMICs, to enable countries to strengthen their the national innovation systems;

-operating a Global Health Research Observatory, to ensure that disease monitoring and R&D resource tracking could be carried out regularly and accurately, to provide both the inputs to the priority setting processes and the means of monitoring progress.

- Establishment of a structure mandated with the responsibility to collect, collate, analyze, interpret and disseminate information with regard to funding for R&D

To cover these functions, the GHRIF would need to be financed at a level of between US$ 3 billion and US$ 15 billion per year.

However there is likely to be great difficulty in creating any single over-arching governance structure for coordinating global R&D. The nature of the research and development processes and the varying structure of the world's economies make it extremely challenging. This does not negate a very important role for WHO. To the extent that the collection and wide dissemination of information can facilitate dialogue and understanding, this is the role that the organization should seek to play more aggressively. The fact that this may cause consideration of modifying the governing structure of the Organization to take account of a more plural state should not inhibit it from addressing the issue.

6 Innovative Sources of Financing.

6.1 INTRODUCTION

A plethora of proposals, over ninety, are currently in circulation or already implemented. Around half of these are pure financing proposals that is they raise monies that could be allocated to any cause, but are not yet used to fund health R&D. A further nearly-half are not financing proposals at all, but are rather allocation proposals. They include proposed structures to centralize, manage and allocate funds to health R&D (if funds were to be available), but they do not have mechanisms to raise these funds. A small number of proposals both raise and allocate funds.

The vast majority of proposals in circulation, operation or submitted to the EWG are focused on public researchers and Western product developers – and thus formed the bulk of the comparative work we undertook. However, to the extent possible we sought to examine these with an eye on R&D capacity in developing countries, particularly Innovative Developing Countries (IDCs) since it seems to us that these will increasingly be the source of new products for their own needs.

6.2 **Background**

Before reading this report, it is important to note that the amount of funding needed for any health R&D activity depends on several key factors:

Does the disease have a substantial market/ some market/ no market?

Products for diseases with a substantial Western market (sometimes called Type I diseases) generally require less funding, since R&D for the developing world can be "piggybacked" onto existing commercial programmes. Diseases with no commercial market (Type III diseases) will require full funding, while Type II diseases, which have small Western markets, sit somewhere in between.

Does the disease have a sound science and technology (S&T) base?

Products for diseases with a sound S&T base (e.g. pneumonia vaccines) are less risky investments. However, diseases with a weak S&T base are highly risky thus donors will need to fund the R&D themselves or provide incentives that are highly inflated for risk.

What kind of R&D is needed?

If basic research is needed, per project costs are relatively small (in the hundreds of thousands to perhaps $2-3 million), however, scientific uncertainty tends to drive overall costs up, with multiple projects failing and being replaced by others before success is reached. For all products, early development (preclinical testing and smaller clinical trials) is relatively cheap, costing in the hundreds of thousands for diagnostics, to tens of millions for drugs and vaccines. By contrast, late development (large-scale clinical trials and manufacture) is far more expensive, costing a few millions for diagnostics, but up to $150-250 million[i] for drugs; and $500-800 million for vaccines, if plant construction costs are included. [ii]

How well does the proposal match the needs of the target group?

Different types of R&D require different skill sets and are carried out by different actors. Basic research is generally conducted by academics and public institutions; product discovery predominantly by small and large companies and Product Development Partnerships (PDPs) although public groups also play a role; and large-scale product development by large companies and PDPs. DC firms dominate manufacturing and distribution for the developing world, and IDC firms are increasingly moving into product discovery and development.

These groups each have very different cost structures, business models and needs. For instance, large multinational companies can invest more of their own resources and take higher risks before they receive a return on investment, or may even be able to conduct not-for-profit research. On the other hand, most small companies live hand-to-mouth: they need ongoing capital during the R&D process and cannot afford to do not-for-profit work. Commercial groups will also invariably require larger incentives than not-for-profit groups.

As a result of these differences, it is unlikely or impossible that a single allocation proposal could efficiently address all disease and product needs, and the requirements of all relevant development groups.

Notes on methodology

Financing and allocation proposals are very different and are therefore reviewed separately. Fundraising proposals were sorted into like groups, and each proposal within that group was then assessed for its capacity to raise funds, additionality, likelihood that the funds would be accepted as suitable for allocation to health R&D and ease of implementation. Allocation proposals were also sorted into like groups, with each proposal within the group being assessed for its DC impact, operationality, financial aspects, and for its likelihood of incentivizing developers to commence or increase their R&D activities, including both developing country and Western groups. Performance rankings are identified by symbols (three symbols being a high score; two a good score; one a moderate score; and none a low score). Based on this assessment process, we were able to determine which fundraising and allocation approaches worked best overall. Within these approaches, the highest performing proposals were then selected. We note that performance of proposals within groups varied significantly depending on their design, with most performing better against one criterion than another. These variations are themselves telling, helping to identify which design features deliver the best outcomes. (See Methodology section for details.)

While the shortlist of final proposals was largely based on their assessed performance, other factors were also considered, in particular their ability to offer a broad solution across many diseases and products. We also sought for overall balance among the shortlist, with proposals selected to collectively provide good coverage of the R&D field and those working within it, and a reasonable balance of public and private risk.

Such a review could not have been completed without the efforts of those who came before us. Thus, our review of financing proposals drew heavily on the extensive work of the Taskforce on Innovative International Financing for Health Systems Working Groups 1 & 2 (WG1/2), and we are indebted to the assistance of an analyst on that Group, whose input reduced duplication and inefficiencies in our own review. We also drew on many sources to develop the criteria against which proposals were assessed. Thanks must go particularly to the Brookings Institute for their Innovative Financing for Global Health report, as well as to WG2 for their development of financing effectiveness criteria. However, finally, our R&D criteria could not have been successfully developed without the extensive input of the public, private, philanthropic and civil society

stakeholders who participated in the EWG consultation process. (See Methodology section).

One important areas of health R&D (operational research) is not covered by this report, due to lack of proposals; and we have included basic research proposals only to the extent that they are additional to existing programmes run by most national governments.

As noted above, no one allocation proposal could efficiently address the needs of all diseases, products and developers. We have therefore chosen a suite of proposals that cover R&D from basic research through to distribution; that are best suited to maximizing R&D activity by all potential target groups; and that deliver maximum public health return for any given investment.

These form a shortlist of four financing mechanisms that would nearly triple available funds for R&D for neglected diseases of the developing world; five funding allocation mechanisms that we believe will optimally allocate both existing funds and new funds raised by the four proposed financing mechanisms and two efficiency proposals aimed at cutting R&D costs across the board;. All shortlisted mechanisms are examined in more detail in the following section.

We caution that the financing and allocation mechanisms cannot be paired at this point. This is because the allocation proposals, their scope (disease and products), and timeframe need to be finalized in order to specifically determine dollars needed per year for each mechanism. (In the absence of this information, we have used a target figure of two to three times existing spend on neglected disease programmes as a guide.) We therefore urge donors to move quickly to make decision on which disease and product areas they wish to target in what priority, so that appropriate amounts of funding can be quickly mobilized and allocated to achieve those goals.

6.3 FINANCING PROPOSALS

The following fundraising options have been put forward based on the likelihood they can generate new funds for health R&D in a sustainable way:

- A new indirect tax (a consumer based tax)
- Voluntary business and consumer contributions
- Taxation of repatriated pharmaceutical profits
- New donor funds for health R&D

6.3.1 A new indirect tax

Indirect taxes involve a small tax being imposed on specified products or transactions. Typically the tax is paid by the consumer or user of the product/transaction, collected by the retailer and forwarded to the taxation authority. Once in place they are compulsory and offer varying degrees of diversity depending on the tax. These mechanisms aim to

raise revenue and, in the cases of the tax on the arms trade and excise duties on tobacco and alcohol, to discourage the (excess) consumption of a particular product. In these cases there are likely to be positive spill-overs in terms of health gains. The digital tax involves a charge on traffic over the internet. It was first discussed in the 1990s and various proponents have put forward different versions of this tax. Examples include a tax of one US cent on every 100 e-mails of 10 KB sent, a charge per specific number of email messages (eg 10 cents per 1000 messages), a charge per SMS message and a charge by the quantity of information sent/received (eg for internet telephony and video). The key element is a very low charge.

Performance

Fund-raising capacity and additionality: An indirect tax could potentially raise very significant amounts of revenue:

- A 10% tax on the arms trade market might net about $5bn per annum.
- Digital tax or 'bit' tax: Internet traffic is huge and likely to increase rapidly; this tax could yield tens of billions from a broad base of users.
- Brazil's CPMF: a tax on bank account transactions, set at 0.38% levied on paying bills online and major withdrawals, it was raising an estimate $20bn per year and funding some 87% of the Government key social protection programme – Bolsa Familia, before it was voted down. However, there is scope globally for bank transactions taxes to be expanded.
- The airline tax has raised around $660m over 2 years (mostly from France) this is expected to increase as more countries join (e.g. Portugal in 2009). Possible total revenues could amount to the low billions. At the end of 2008, Chile, Côte d'Ivoire, Democratic Republic of Congo, France, Madagascar, Mauritius, Niger and the Republic of Korea had implemented the airline tax; in addition Norway allocates part of its airline emissions tax to UNITAID.
- Tobacco taxes: Low-income countries are estimated to raise around $13.8bn in taxes on tobacco. Of 152 countries with tobacco taxes in place the tax rate is less than 25% in around a quarter of the countries. A 5-10% increase to the tax rate could net $0.7-1.4bn per annum. A similar increase in developed countries would net $5.5-11bn. Alcohol taxes are already widespread.

While funding projections can be made, ultimately revenue will depend on responses to price rises associated with the tax. Any government decision to implement or expand one of these taxes for the purposes of directing the revenue stream to developing world health would result in additional funds.

In order to estimate the size of the funds that could potentially be raised we take the example of the introduction of a very low indirect digital tax, which could be estimated to conservatively raise funds in the low billions per annum (US$3bn).

Likelihood: There is a more obvious link between the source of the funds and the purpose (health R&D) for the tobacco, alcohol and arms trade related taxes. However, as the airline tax has shown, such a link is not always necessary to appeal to both politicians and consumers. An indirect tax like a type of digital tax can be appealing to politicians and consumers who accept a small tax across a broad base with an altruistic purpose.

Operationality: Introducing a new tax or expanding an existing tax may require legal changes, nationally and internationally, depending on the tax, and ongoing regulation to ensure compliance. A new global tax would take longer to implement than expanding an existing tax within a country. A tax that is global in scope allows for developing countries to contribute to fundraising, and there is a willingness to do so as demonstrated by the airline tax. This framework could be applied to a type of digital tax.

As with the introduction of any tax there are trade-offs:

- There is only moderate certainty over revenue forecasts as actual revenue will depend on the response of providers and consumers to price rises associated with the tax and scope of the tax. Furthermore, as seen with the withdrawal of Brazil's bank transaction tax there are occasions, although rare, when a tax is removed.

- Some of these taxes could potentially create perverse incentives. For example, the tax on arms trade is likely to result in an increase in illicit arms trading, (and therefore reduce the size of revenue); an excessively high tax on alcohol could encourage people to consume illicit and often dangerous alcohol products. An arms tax may have less political appeal than others as governments are essentially taxing themselves.

- Achieving a wide geographical coverage by some of these taxes internationally might be difficult as governments might be resistant to introducing them (e.g. The US is a notable omission from the airline tax citing problems with the tax dimension, but they are trying to capture the revenue through voluntary airline contributions rather than a mandatory tax.)

- The digital tax has additional operational hurdles to overcome, in that monitoring internet traffic in a cost-effective manner in order to tax consumers might prove to be a challenge. The digital tax could place a high burden on companies that depend heavily on use of the internet and sending large amounts of data over the internet. However, this could be overcome by appropriate scoping of the tax.

6.3.2 Voluntary business and consumer contributions

This approach proposes voluntary donations made by individual consumers. It can operate in three different ways:

4) Voluntary linking of a donation to the payment for a service (e.g. payment of mobile phone bills or payment of income tax).

5) Automatic donations directly to a particular recipient (e.g. standing order payments to Oxfam)

6) Voluntary but non-automatic donations (e.g. private giving campaign or endowment). An income tax donation allows an individual to make a contribution from their income which government will match with the income tax that would have been paid.

Voluntary business contributions are donations whereby the business sector donates a share of its revenue or a share of its profits for charitable causes or provides pro bono in-kind support to charitable activities. In return the business earns goodwill for doing "good things" which may lead to extra sales and profits or it may do it for more altruistic corporate-social-responsibility related reasons. De-Tax, a new mechanism combining waiver of tax and voluntary business contributions, and product RED are examples of such a mechanism.

Voluntary contributions have less certain funding streams than a tax, but once established are reasonably predictable.

Performance

Fundraising capacity and additionality: Size of revenue raised varies:

- Airline ticket voluntary solidarity contribution is expected to raise about US$980 million/annum, although these expectations have since been revised downwards. [109]

- Mobile phone voluntary solidarity contribution would raise from 200m – 1.3bn Euros according to the Millennium Foundation.

- Private giving already raises significant amounts for development. Estimates suggest some $17bn in OECD countries in 2001 and $34bn in the US in 2004 (including faith based organizations and universities[110]). More of these existing funds could be diverted into health R&D.

- The World Bank (2009) estimates that the UK and Belgian lotteries transferred $66m to developing countries in 2007.[111]

- Product Red has raised more than $ 40m per annum since 2006[112]

[109] http://www.internationalhealthpartnership.net//CMS_files/documents/working_group_2_-_report_EN.pdf
[110] http://news.bbc.co.uk/1/hi/uk/7946518.stm
[111] http://www.internationalhealthpartnership.net/CMS_files/userfiles/FS_DeTax_raffaella%20final%20final.pdf
[112] http://www.joinred.com/Home.aspx

- Internet advertising expenditure is growing rapidly in absolute terms and as a share of total advertising revenue.

- De Tax could raise are up to $2.2 billion based on a base on 26 countries and 5% business uptake[113]

The introduction of a voluntary fundraising mechanism would largely be additional, although consumers could change their voluntary contribution preferences away from an existing offering.

For the purposes of this exercise, we give the example of using two of the above proposals to raise funds for health R&D. Using product RED as a guide, the introduction and use of voluntary business sector contribution could be estimated to raise in the order of US$40m annually; using the airline voluntary solidarity contribution as a guide to estimate voluntary consumer contributions, these could be around $1bn per annum.

Likelihood: Both the introduction and take up of product RED and the airline ticket voluntary solidarity contribution demonstrate consumer and business willingness to make global health-based altruistic contributions. In order to direct this to health R&D, they need a mechanism to do so. (See allocation proposals).

Operationality: Introduction of voluntary contribution schemes, like the airline ticket scheme, is not expected to have any legal obstacles, nor require amendments to international laws. However, other mechanisms, like De-Tax do require changes to law. De-Tax is being formally supported by the Taskforce for Innovative Financing for Health R&D and is being piloted by Italy[114] - but for funds to be allocated to DC health systems. Voluntary contributions face few political hurdles and are likely to be sustainable long term, they are applicable in both the West and DCs.

6.3.3 Taxation of repatriated pharmaceutical profits

This approach proposes raising funds through direct taxation of pharmaceutical company profits within countries that join. The Brazilian proposal aims for governments of "associated countries" (i.e. any country that agrees to sign up, DC or Western) to tax non-domestic pharmaceutical companies that undertake activities in their territories. The tax would be on all profits remitted to the overseas parent company.

Performance

Fundraising capacity and additionality: Initial estimates suggest that if profits from the pharmaceutical industry in LMICs are in the order of $16 billion per annum and if the tax rate was applied at 1% across these countries, then revenue regenerated could be in the order of $160 million per annum. This figure would increase very significantly if profits

[113] http://www.internationalhealthpartnership.net/CMS_files/userfiles/FS_DeTax_raffaella%20final%20final.pdf

[114] http://www.internationalhealthpartnership.net/CMS_files/userfiles/FS_DeTax_raffaella%20final%20final.pdf

from one or more of the HICs were included. These funds would be additional for health R&D. Like other taxes, once in place payment is compulsory. Given the embryonic nature of this proposal the certainty of revenue is untested, and depends on the uptake of the mechanism by countries.
Likelihood: The clear link between the source of the funds and the purpose, makes this option particularly attractive to fund health R&D.
Operationality: By setting a low tax rate over a broad base the proposal aims to minimize any distortionary tax effects, and therefore increase sustainability. Existing entities could be used to implement the mechanism at the country level.
However, there are trade-offs:

- Like all taxes it is subject to some political uncertainty, however this uncertainty is potentially reduced the greater the number of countries involved in the scheme.
- Once the proposal had achieved political commitment, implementing the tax system, at a national level would require administrative and legislative changes.
- It would also require confirmation with WTO that it was not seen as an unfair subsidy, whereby revenue is collected in one jurisdiction and given to some countries but not others.

6.3.4 New donor funds for health R&D

This approach considers three main sources of funding

- Additional funding from new non- traditional donors, who are not currently included in OECD's Development Assistance Committee (DAC), such as China, India and Venezuela.
- Additional funding from existing (DAC) donors (for example, earmarking a percentage of GDP for health R&D)
- Additional funding from philanthropics

Performance
Fundraising capacity and additionality: The Taskforce on Innovative International Financing for Health Systems Working Group 1[115] estimates that additional funding for health from governments might amount to between $US28-37 bn by 2015 as donors meet their Gleneagles G8 commitments and close the health funding gap. Using these estimates and assuming that 10% of these new funds could be earmarked for health R&D, new donor funds could amount to around $US 0.6bn per annum.
Likelihood: New funding from the traditional donor group could be allocated to health R&D, because it is generally easier to fund new activities out of additional resources than

[115] http://www.internationalhealthpartnership.net//CMS_files/documents/working_group_2_-_report_EN.pdf

at the expense of existing activities. These funds would by design be additional for health R&D. Support from non -traditional donors currently tends to be in non grant form and in support of infrastructure, these preferences would need to broaden for resources to go into health R&D. As philanthropics are already significant contributors, a case would need to be made for increases from them.

Operationality: Directing new funds from traditional donors or nontraditional donors into developing world health needs is a policy allocation decision, and operationalising it will take different forms depending on individual country decisions. Many DAC countries are on track to reach 0.7% of GNI devoted to health by 2015. However, donors are not legally required to commit and disburse a certain amount of funding, so there is a low degree of certainty and sustainability over future funding – even more so in uncertain economic times.

Acceptability to funders

Overall, funders showed a strong preference for solutions that are broad-based and which include new sources of funding. Government funders were attracted to mechanisms that are simple, automatic, can be operationalised fairly easily, and are future-proofed. An international tax or levy was also viewed as more appropriate than a national tax, which could put implementing countries at a disadvantage to non-implementing countries. This would likely not be the case for the tax on pharmaceutical profits, since companies would continue to sell the products where there was a market for them.

The nature of the allocation component was very important to funders. They wanted and needed to know what the money would be used for (What will it deliver? When?), and to be able to assess the associated risk (i.e. the likelihood of a health return on their investment). This makes the choice of allocation mechanisms crucially important.

Conclusion

The proposed suite of fundraising mechanisms provides a balance between:

- developing country and Western contributions
- consumer, government and the pharmaceutical industry
- voluntary and non-voluntary (i.e. taxes) contributions
- developing country and Western contributions
- some that would require managed and sustained political commitment (new donor funds and taxes); others that do not (voluntary consumer and business contributions)
- some that would need effort to be operationalised (new taxes); others have lower operational requirements (voluntary contributions)

- taxes would provide greater certainty once in place than voluntary contributions.

Potential estimates from this combination are in the order of $US4.6 to US4.9bn per annum, which would nearly triple current neglected disease R&D funding for developing countries[116]. However, further analysis is needed to accurately determine potential revenue streams and their alignment to dollars needed. Further funds could be sourced by re-directing current expenditure on R&D funding allocation mechanisms assessed as ineffective by this review, to mechanisms assessed as more effective (see Funding Allocation section).
All of these funding alternatives and decisions ultimately rest with national governments and individual philanthropic organizations. They cannot be uniformly applied. For example, the UK is very unlikely to support new hypothecated taxes, and in the US the regionally based sales tax system would make national implementation complicated. Different governments will choose among these to select approaches that best suit their own political perspectives, objectives, budgetary cycles and taxation systems. As noted above, willingness to advance these fundraising proposals is also intimately tied to the presence of a vehicle that will allocate these funds in an efficient and high impact way. Approaches to do so are examined in the following section.

6.4 FUNDING ALLOCATION APPROACHES

The following five approaches provide optimal funding allocation across all R&D stages and developers, in a manner that is best designed to maximize public health returns in the developing world:

- Product Development Partnership (PDP)- linked funding
- Direct grants to small companies and grants for DC trials
- Milestone Prizes
- End-Prizes (cash)
- Purchase or procurement agreements

6.4.1 Product Development Partnership (PDP)-linked funding

PDPs operate as 'quasi venture capital funds' in the domain of developing world health. They raise funds from a wide range of public and philanthropic sources, select the projects that offer the likely highest health return for investment, and closely monitor and manage the progress of the portfolio they have invested in. All PDPs operate on a not-for-profit basis.

[116] Moran M, Guzman J, Ropars AL, McDonald A, Sturm T, Jameson N, Wu L, Ryan S, Omune B. *Neglected disease research and development: how much are we really spending?* The George Institute for International Health. February 2009

PDP's have large product portfolios across many Type II and III disease areas (but only marginal activity in Type I disease areas), and currently manage nearly 30% of global neglected disease R&D grant funding in 2007 and around half of global grant funding, if the NIH is excluded.[117] As a result, they act as a major consolidator of public funding, of investment risk, and of global coordination on R&D in their given field. PDPs predominantly invest in product discovery and development (although a few also fund basic research or R&D of platform technologies); including into projects conducted by academic research institutions, and large and small pharmaceutical companies, in both developed and developing countries.

Currently, PDPs have no reliable revenue stream, being entirely reliant on annual donor funding. However, it can be very difficult for donors to invest in the "right" PDP, since most do not have the resources to conduct the necessary due diligence on an annual basis, or to compare the widely differing product portfolios.

As a result, three proposals are in circulation to provide reliable, long-term funding to PDPs; and to automate or centralize funding decisions across PDP portfolios to a lesser or greater degree:

- *Fund for R&D in Neglected Diseases (FRIND):* Proposes a central fund (supported by donors) to finance discovery and development of drugs by PDPs, industry and public research institutes for 10 neglected diseases. A portfolio management committee allocates funds based on unmet need and scientific likelihood of success, replacing individual PDP or industry portfolio management. Commercial revenues and IP-derived income are fed back into the Fund through licensing agreements with development partners.

- *Industry R&D Facilitation Fund (IRFF):* Proposes a long-term fund (supported by donors) that automatically reimburses a fixed percentage (e.g. 80%) of the funds that PDPs disburse to Western or DC companies. Designed to encourage industry partnering with public-health driven PDPs, and thus provision of low or cost-price final products. Automatically allocates funds across all PDP drug portfolios globally, with most funding going to those who advance their portfolios most efficiently. PDPs retain portfolio management.

- *PDP Financing Facility (PDP-FF):* Proposes raising funds from the sale of bonds in private capital markets to support R&D conducted by three vaccine PDPs (HIV, TB and malaria). Bond-holders are repaid from royalties on sales in high- and middle-income countries, and donor-funded premiums on sales in low-income countries. To reduce risk to bondholders and allow the PDP-FF to borrow at low interest rates, the Financing Facility would back its borrowing with guarantees from donor governments and possibly foundations

[117] Moran M, Guzman J, Ropars AL, McDonald A, Sturm T, Jameson N, Wu L, Ryan S, Omune B. *Neglected disease research and development: how much are we really spending?* The George Institute for International Health. February 2009.

- Direct grant funding to PDPs (the current approach)

Performance

Overall, PDPs score very highly on DC impact due to their focus on developing affordable suitable products for DC use; their routine practice of working with DC researchers and developers; and, to varying degrees, their capacity building efforts in DCs (high for IAVI, DNDi and MVP, less so for MMV). Since they provide funding through PDPs, most PDP funding proposals also perform well on DC impact (however, see PDP-FF below), but proposals varied substantially in their operational efficiency and feasibility. The IRFF scored well on DC impact and very well on operational efficiency and feasibility, reflecting its automated fund allocation, linkage of funding with efficiencies, and use of existing PDP structures and practices.

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
Product Development Partnerships (PDPs)	🧍 🧍 🧍	★★★	
Industry R&D Facilitation Fund (IRFF)	🧍 🧍 1/2	★★★	
Fund for R&D in Neglected Diseases (FRIND)	🧍 🧍	★	??
PDP Financing Facility (PDP-FF)	🧍	★	?

Data gaps for the PDP-FF, and particularly for FRIND, meant they could only be partially assessed. FRIND performed well on DC impact, however a low operational score partly reflected lack of data, but also design issues. Under FRIND, a central group manages the global drug R&D portfolio for PDPs, industry and academics: this is a distinct advantage for global coordination, but is likely to be resisted by major funders (as well as by PDPs), who expect a high level of control over their multi-million dollar investments, as expressed at interview. Nevertheless, FRINDs high score despite data gaps suggests it has great promise.

The PDP-FF has more fundamental difficulties, as reflected in its lower scores for both DC impact and operational efficiency and feasibility. The key problem lies with its inclusion of HIV, TB and malaria vaccines, since it is unlikely that a sufficiently effective HIV or malaria vaccine will be available in the next 10 years to provide the planned 7-10% royalty-based revenue streams from Western markets. As a result, TB vaccine

revenues may need to cross-subsidise other areas. Alternatively, developing country markets will be squeezed for margins on less commercially successful vaccines (e.g. initial lower efficacy malaria and HIV vaccines) Since poor countries may not be able to pay higher prices (or only at the cost of reduced patient access), donors will likely need to pay the price premium on their behalf (their willingness to do so being a moot point). Bond purchasers, looking at these figures and delivery timelines, may also be disinclined to risk their funds. We note though that, if restricted to more commercially attractive Type II vaccines that are already in development (e.g. TB, pneumonia, meningitis), the PDP-FF would likely perform substantially better.

Financial aspects of the various proposals could not be reasonably compared due to differences in scope, therefore we only note their projected funding needs and outcomes:

	REVENUE STREAM (AND WHETHER SECURE)	ANNUAL INVESTMENT	ANNUAL PROJECTS	SCOPE
PDPs	No revenue stream Milestone based for recipients	~US$ 584m	Projects across more than 22 existing ND PDPs	Malaria, TB, HIV, helminths, helminths, kinetoplastids, dengue, meningitis, diarrhoeal diseases etc. Drugs, vaccines, diagnostics and insecticide devices
IRFF	No revenue stream Milestone based for recipients	US$130-190 m	To fund 80% of DC and Western industry inputs to all PDP drug projects	TB, malaria, kinetoplastids, helminths, diarrhoeal diseases. Drugs only
FRIND	No revenue stream Milestone based for recipients	US$600m- $1 bn	All neglected disease drug projects PDP, industry and academic	Likely to cover: Malaria, TB, kinetoplastids, helminths, Chagas', dengue, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis and sexually transmitted infections, TB/HIV co-infection. Drugs only.
PDP-FF	Yes, commercial bonds underwritten by government guarantees. Estimated - US$73-230m/year (US$2.2bn-6.9bn over 30 years)	~US$ 150m	For only HIV, malaria and TB vaccine R&D projects in IAVI, MVI and AERAS	TB, malaria and HIV vaccines only

We can however, make an assessment of the overall viability of PDPs as a funding route. As noted above, donors are increasingly favouring PDPs as their vehicle of choice to disburse neglected disease funding, while smaller donors may disburse virtually all their funding in this manner (likely reflecting PDP's ability to minimize donor management needs); for example, in 2007 Ireland channeled 100% of its neglected disease R&D funding through PDPs. This suggests a high willingness to support PDPs financially.

Acceptability

Provision of funding through PDPs was rated by MNCs as one of their two preferred approaches for product discovery and development: "PDPs work and provide a vehicle for the pharmaceutical industry to make contributions". Diagnostic firms and IDCs were moderately enthusiastic about PDP funding as an incentive to conduct R&D; however SME groups said they would not respond to additional funding routed through PDPs.

Conclusions

PDPs already coordinate and fund a great deal of neglected disease R&D undertaken globally. Providing funding through PDPs offers high DC health impact and operational efficiency, and is the only mechanism that successfully stimulates early and ongoing MNC involvement. However, a mechanism is needed to assist donors to fund across PDPs in a far simpler manner than is currently possible. We also note that PDPs do not cover all areas of Type II and III need, and that not all PDPs are equally efficient. In-depth analysis is needed to determine which of the above mechanisms, or combination of mechanisms, is best adapted to providing reliable, long-term, centralised PDP funding, and to link this funding to PDP efficiency.

6.4.2 Direct grants to small companies & grants for DC trials

Many countries and some philanthropists provide direct grants or contracts to small companies (SMEs) in areas of public health importance where Venture Capital may be either sub-optimal or lacking entirely e.g orphan diseases or, less often, neglected diseases of the developing world. When the innovation successfully reaches the end of the grant's scope (e.g. discovery of a promising lead molecule, or conclusion of Phase II trials), SMEs are expected to raise third party funding from private investors and capital markets or to seek additional public or philanthropic funding to bring the product forward to registration.

Direct grants are vital for cash-constrained small firms, who need push funding in order to conduct R&D. They are non-dilutive of company equity (a bonus for small companies) and can fit well within traditional national business grant funding schemes.

Grants are most commonly used for basic research, discovery and early development up to Phase II trials. Public grants are rare for expensive large-scale clinical trials and manufacture, although they can be the crucial tipping factor in a developer decision to undertake these trials; with large scale trial support almost invariably relying on philanthropic funding, often given via PDPs (e.g. for HIV, malaria and TB drug and vaccine trials). Indeed, one MNC noted that, without clinical trial grant support, they would NOT have undertaken the additional trials needed to develop their product for DC use.

Small company funding schemes fall into two categories: grants or contracts to Western companies to conduct R&D relevant to developing countries; and grants to SMEs in developing countries (especially IDCs) to conduct locally relevant R&D. These perform very differently in terms of their DC impact and likely funding needs and are therefore reviewed separately. Typical schemes in circulation or submitted to the EWG (although many others exist[118]) include:

Domestic grant/ contract schemes for Western SMEs:

- US Small Business Innovation Research Programme (SBIR). Under this US government scheme, the NIH provides early stage finance for small innovative

[118] See Mclaughlin Rotman proposal (http://www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf)

businesses to bring technologies to market. The scheme mainly addresses niche markets and needs e.g. West Nile virus, Hepatitis C, malaria

- UK Small Business Research Initiative (SBRI) is a programme that engages a broad range of companies in competitions for ideas that result in short-term development contracts. For example, projects to develop pathogen tests for hospital acquired infections

- DARPA contracts, an R&D arm of the US Department of Defense, funds unique and innovative research through the private sector, academic and other non-profit organizations as well as government labs. Programs funded include research into chronic as well as infectious diseases

- Wellcome Trust's Seeding Drug Discovery. Funds small and large pharmaceutical companies and not-for-profit research organisations to identify promising lead molecules in areas of unmet medical need such as cancer and neglected diseases research.

- IAVI Innovation Fund. Funds SMEs to conduct experimentation on pioneering/blue-sky ideas and technologies for an AIDS vaccine. Also includes technical and scientific support from IAVI, and funding and product development support for successful projects

- EMEA's SME support scheme provides financial and administrative assistance to SMEs, including reduction or deferral of regulatory fees, scientific advice, and regulatory support. It is designed as a contribution to costs, but is not intended to cover full costs of any development stage.

Grant schemes for SMEs in DCs:

- São Paulo state funding agency (FAPESP) funds R&D projects through its Technological Innovation in Small Businesses (PIPE) program Research grants awarded have covered diseases such as HIV, TB, Chagas' disease, helminths, Hepatitis C and cancer

- Indian Small Business Innovation Research Initiative (SBIRI), initiated by the Department of Biotechnology in 2005, promotes high-risk pre-proof-of-concept research and end-stage development by SMEs. Applications from the health sector have covered diseases such as cancer, typhoid, malaria and genetics research[119]

- Regional Health R&D Coordination Office in Southern Africa funds regional R&D projects working on pre-defined disease priorities such as diarrhoeal diseases and TB

[119] http://biospectrumindia.ciol.com/content/CoverStory/10806041.asp

- Proposal for an international SBIR-like grant scheme, where pooled funds from Western donors and IDC host countries will be provided to local SMEs in participating IDCs to address global health challenges. The scheme which is still in its early stages will fund a variety of projects based on global health needs as determined by the funding agencies.

Performance

In terms of DC health impact, Western-based schemes performed less well since they do not clearly and specifically target DC needs and define DC-relevant outputs, thus firms are likely to focus R&D on commercially-relevant needs (e.g. malaria products for travelers, Western disease strains etc). These schemes are unlikely to include or encourage technology transfer to, or capacity building with, DC groups; or to encourage recipients to take DC suitability and price issues into consideration. However, as seen by the superior performance of the IAVI Innovation Fund (which has a relatively high score despite significant data gaps), these issues can be improved by better targeting, although tech transfer and DC capacity building still remain unaddressed. Domestic grant schemes performed well across the board on operational efficiency and feasibility, even allowing for data gaps. We note, though, that some legislatures (e.g. US) might have difficulty extending existing schemes to diseases that are not a domestic priority.

The international SME grant scheme also performed well on DC impact and on some operational aspects (e.g. coordination of grant allocation), but would likely be more difficult to operationalise than national schemes as it would require multiple countries to set up local grant schemes, as well as a central group to manage funds and make allocation decisions to projects in multiple DCs. We could not assess DC-based grant schemes for SMEs as these are so many and diverse that time did not permit. However, in principle conclusions can nevertheless be reached based on the few schemes we examined. DC-based schemes offer the promise of significantly higher DC impact <u>if designed well</u>, in particular if the scheme includes requirements that the final product be affordably priced and meets high regulatory standards (which may be higher than those of some host DCs). All are, however, less likely to perform well on technology transfer, since most are nationally based rather than focused on international partnering.

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
IAVI Innovation Fund	🧍	★★	??
Grants (international) for SMEs in Innovative Developing Countries	🧍 🧍	★★	??
Domestic to SMEs in Developing Countries	🧍	★	???
Domestic to Western SMEs		★★★	
EMEA's initiative for SME's (regulatory, financial & scientific relief)		★★★	

Financial aspects could be readily assessed for Western grant schemes. Large scale Western schemes cost in the several hundred millions per year, while more targeted schemes involved tens of millions per year; with top-line outputs, for the US scheme in particular, appearing to offer a good return on investment. As noted, we only had limited data on DC schemes (the Indian scheme is noted in the Table below) so could not draw reliable conclusions as to their cost and output across the board. However, in principle, these schemes should not cost more than similar schemes in the West and may likely be substantially cheaper due to lower local research costs.

	REVENUE STREAM (AND WHETHER SECURE)	ANNUAL INVESTMENT	ANNUAL PROJECTS	SCOPE
Domestic grants to western SMEs	IAVI: Not mandated WT :Not mandated SBIR: Legislated. All US government agencies with R&D budgets >$100 million give 2.5% of their extramural research funds SBRI: Not legislated	IAVI: ~US$3m WT: £20 m SBIR: US$570m SBRI: Phase 1 - £50-100K for 6 months. Phase 2 – $250-£1 million for 2 years (size of each reward). Total value of grants unknown	IAVI: ~5 projects (15 projects over the 3 yrs) WT: No data SBIR: 2,069 grants awarded. Of grantees: 50% had at least 1 peer reviewed publication/ 40% led to a patented invention SBRI: No data	IAVI solely for HIV vaccines SBIR:– any diseases (but guided by donor preference) SBRI:– any diseases (but guided by donor preference)
Domestic grants to developing country (DC) SMEs	SBIRI: Not legislated	SBIRI: ~US$17m	SBIRI: ~18 projects (37 projects funded over 2 years). Includes some projects in the non health sector	SBIRI: any diseases

Acceptability

Small developers (SMEs, IDCs and diagnostic firms) gave unanimous support to direct grant programmes, rating this as one of the two incentives most likely to stimulate them to commence or expand developing country R&D programmes. Large companies were less likely to respond, although they noted that grant programmes would be a very welcome support to subsidise the costs of large-scale clinical trials in developing countries. These grant schemes were rated very highly by all donors, public and philanthropic, Western and DC.

Conclusion

Western and DC grant schemes are a clear priority to encourage broad SME participation in DC-relevant R&D, with DC-based schemes being particularly promising. Grant schemes should also be extended to fund large-scale clinical trials by other groups (e.g. MNCs). However, these recommendations come with provisos. DC-based schemes could consider opportunities to increase technology transfer; while Western-based grant schemes must be very carefully designed to maximize DC health impact. Failure to do so can lead to waste of substantial funds on products that will be neither suitable nor used in DCs.

6.4.3 Milestone prizes

Milestone prizes are cash prizes given for reaching interim steps along the development pathway, for example, solving a basic research problem, developing a new animal model or discovering a production technology that can reduce costs. The problem to be solved

may be defined more or less loosely by the group seeking a solution, and the IP may or may not be handed over at the point that the prize is paid out.
Prizes encourage out-of-the-box thinking, they mobilize far more activity than the value of the prize itself (since each group will invest up to the value of the prize), and they often help move the field forward by more clearly defining the problem at hand.
While milestone prizes can theoretically be applied at any point along the development pathway, they are best suited to solving basic research and technical questions, but are unlikely to be useful for clinical development. Prizes can be applied to any disease or problem, from broad-based prizes that are used for many diseases, to prizes specific to one disease, or even one product, as outlined below.
Only one pure prize proposal was presented to the EWG. However a number of more complex proposals include a milestone prize element:

- InnoCentive is a pure prize. It is an online marketplace where 'seekers' (public, private and philanthropic) can post challenges. The award is paid to the solver who best meets the solution requirements, and a commercial agreement is then negotiated with the 'seeker'.

- Prize fund for development of low cost Rapid Diagnostic Tests for TB: Interim prizes for technical and best contribution; amount is unclear but appears to be less than 10% of the total prize fund

- Chagas Disease Prize Fund: interim prizes for technical and best contribution, however amount dedicated to interim prizes is not noted

- Priority Medicines and Vaccines Prize Fund (PMV/pf): Interim prizes for technical and best contribution to the value of 20% of the total prize fund

Performance
With the exception of InnoCentive, the above proposals could not be properly assessed since their milestone prize elements were very sketchy. We have therefore assessed InnoCentive in detail, and can presume that any other prize model that follows a similar approach would perform similarly. We note though that all proposals apart from InnoCentive are part of mechanisms that propose pooling IP, raising the possibility that their IP management may <u>not</u> follow the same lines as InnoCentive's straight commercial approach.

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
InnoCentive	▪ ▪	▪ ▪	??

InnoCentive performed moderately well on DC impact; however an InnoCentive-type prize would deliver even higher benefits if two aspects were improved. Firstly, the prize question would need to be designed very carefully to ensure that DC-relevant factors such as suitability and cost-of-goods were addressed even at early research stages. A second factor relates to the fact that the commercial nature of the deal between seeker and solver leaves the seeker very much in control of what happens to any future product based on the solution. This could, however, be addressed if problems were posted by public-health oriented groups, including PDPs, who include up-front negotiations on lower DC prices as part of their contracts. InnoCentive performed particularly well on DC capacity-building, with over one-third of InnoCentive's solvers being located in the developing world (China -20%, India -15%) as well as in Russia (15%), with each 'solver' subsequently signing a deal with the Seeker company to take forward their research.

Milestone prizes are easy to put in place, scalable and have no administrative or legal hurdles. Their operational efficiency and feasibility scores were therefore high, and would likely be higher if data gaps had not existed.

The InnoCentive milestone prize system is also strikingly cost effective, with an average of 300 problems posted per year (and around 130 solved) for an annual operating cost of $6-9 million. However, it has been difficult to find prize funding or funds to support running costs for non-commercial disease areas, unlike InnoCentive's commercial arm which Is self-sustaining through user fees.

Acceptability

Large companies supported the idea of InnoCentive style prizes, but said they would not respond themselves. However, all small groups responded warmly, including IDC firms, diagnostic firms and SMEs, with one group noting that "A series of pulls along the development path are our No. 1 preference".

Many additionally cautioned that milestone prizes should operate within the IP system, rather than being a substitute for it, this being a key factor in their attractiveness to both seekers and solvers. Given this, it is important to have more detail on the remaining prizes, all of which are part of solutions that propose pooling IP to a greater or lesser degree.

Conclusion

InnoCentive style milestone prizes are a highly cost-effective way to encourage small firms to generate innovative solutions to basic research questions and technical problems up to the point of clinical development; however maximum buy-in from the private sector is likely to be obtained by managing prizes within the IP system. Prize design is crucial to generating high DC-impact.

6.4.4 End-Prizes (cash)

Cash end-prizes propose providing a large lump sum at the end of the development process as a reward for product development.

They can in theory be applied to any disease area, although in practice they are mostly considered for cases when the market is insufficient. The prize can be awarded as a pure reward for innovation, allowing the IP-holder to retains rights to their product, or as a 'fee' to purchase the IP from the developer to allow free exploitation by the prize-giver. In theory, the end-prize is meant to reward the entire development process from discovery through to registration, however, as seen below, an end-stage 'pull' is likely insufficient for most products.

Although the notion of cash end-prizes has been generally discussed, only one such proposal was submitted to the EWG, the Prize Fund for development of a low cost Rapid Diagnostic Test for TB (TB-RDT). The TB-RDT proposal is rather complex, involving a $100 million prize fund, which is used to fund a $90 million end-prize for development of a TB RDT, as well as an open information reward and a range of interim prizes. The developer must give over their IP to an open licencing pool administered by a TB Licencing Agency in order to receive the prize; the Licencing Agency can then issue non-exclusive licences to multiple developers to make the test available at low-price to DC markets. There are various other aspects including either a price ceiling or a market penetration test; and a prize for the "best contributions" to the science and know-how needed to develop new TB diagnostic. At least half of the "best contributions" prize money would also be set-aside for research teams working in DCs.

Performance

The TB-RDT proposal performs very well on DC impact, since the product profile is designed to best suit DC needs, and the licencing approach encourages low-cost manufacture and distribution; DC researchers are also prioritized, and the proposal requires hand-over of both IP rights and technical know-how to generic manufacturers, many of whom will be in DCs. However, the complexity of the proposal and the requirement for groups to administer the fund, administer the licences, assess market penetration and administer the various prizes and grants mean it scores very poorly on operational efficiency and feasibility.

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
Prize fund for development of low cost RDT for TB	▪ ▪ ▪		?
Simplified version of end prize (cash)	▪ ▪ ▪	*	???

* More information about the actual operational model would be needed to assess this

We have therefore also assessed a prototype simple cash end-prize i.e. a prize to purchase or reward an innovation, without the associated interim prizes, market penetration test etc. This also performed well on DC impact, assuming the product profile was designed to meet DC needs and that the prize was for purchase of the IP to allow free exploitation, rather than simply a reward for innovation. However, these simpler end-prizes would be expected to perform far better on operational efficiency and feasibility, as with InnoCentive-style milestone prizes.

Financial aspects and Acceptability

Financial and acceptability aspects are discussed together for end-prizes, since prizes only work if they are correctly sized for their target developers.

Developers believed prizes would only work in two cases: either the prize had to equal the commercial value (either of the market or of selling the IP) OR the prize had to be supplemented with push funding to reduce R&D costs and thus allow of a smaller return. Most believed prizes were unsuitable for drug and vaccine R&D since this would require the developer to assume all risk and cost over a period of perhaps 7-15 years: "Prizes as the main pull at the end don't de-risk the development process". In these cases, the final prize would then need to be very large, and probably too large for donors to contemplate. However, diagnostics were seen as a suitable target given their short development time (3-5 years) and lower cost ($5-10 million). In this context, the TB-RDT appears to be over-priced at $90 million.

Small firms and IDC companies were very clear that end-prizes simply do not work for them due to their need for early and ongoing cash; while large companies were unlikely to respond although they could see that a market-sized prize might work for others. The only group that responded positively was diagnostic firms, in particular large firms (smaller firms would possibly still need additional interim prizes or push funding to be able to reach the end-prize). Some public funders have already expressed interest in funding "smaller prizes directed to specific uses".

Conclusion

End-prizes are likely only suitable for diagnostic development, where prizes sufficiently large to reward developers are within reach of public funders. The DC health impact of

the prize would be optimized by IP-buyout prizes rather than prizes purely as a reward for innovation.

6.4.5 Purchase or procurement agreements

Purchase or procurement agreements are contracts between a purchaser (often a government, regional or multilateral group) and product developers, which set out the price at which a product will be purchased and/or the volume of product that will be supplied. The majority of agreements apply to generic products, and are designed to secure bulk price discounts and security of supply, but they do not stimulate R&D.
A more recent innovation is purchase agreements for novel products or products still in development. These proposals are more relevant to this report since they not only secure patient access but can also incentivize or reward R&D. Purchase funds for novel products appear more suited to stimulating late development and manufacture of products that are already in the pipeline, including conducting the necessary DC trials and plant construction for large-scale production, but work less well for incentivising basic research, discovery or early development work (the "pull" effect has limited reach-through to earlier R&D stages - see developer comments below).
Both approaches are, however, considered below as both include elements of potential interest. Examples, from the most simple to the most complex, include:

- Minimum Volume Guarantee (Access RH), which aggregates demand for generic reproductive health products in the form of upfront purchase commitments that result in lower prices, which are passed on to clients

- Minimum Volume Guarantee (MVG) for a novel product: The drug company, GlaxoSmithKline, has signed a long-term price and volume agreement with the Government of Brazil for its novel pneumonia vaccine. This stipulates a higher initial price and lower tail price over an 8-year period, and includes provisions for technology transfer so that Brazil can make the vaccine cheaply itself once the contract expires, as well as applying the technology to other domestically-produced vaccines

- Affordable Medicines Facility - malaria (AMFm) uses pooled demand to negotiate lower prices on anti-malarials (Artemisinin Combination Therapies or ACTs), including novel ACTs, and additionally underwrites costs to patients in least developed countries[120]

- Advance Market Commitment (AMC) pilot, whereby donors commit to price and volume purchase contracts with companies for pneumonia vaccines that meet public health requirements. Developers are assured of higher initial prices (with the patient price subsidized by donors), in return for a lower unsubsidized tail

[120] The AMFm also includes a fund to subsidise prices to patients: this is not discussed further here as it is not pertinent to R&D.

price. Negotiations can be complex since they require advance definition of the desired product profile and contracts are locked in before the vaccine is made.

Performance

Performance of purchase agreements for novel products varies significantly depending on the design of each agreement. The AMC performs least well, due to its failure to preferentially incentivise low cost-of-good products and thus low prices, and its weak technology transfer stimulus; it is also operationally complex and scored low on political feasibility as it would be extremely difficult to scale up for broad use. As regards the GSK-Brazil agreement, we can only reliably draw conclusions from some of its aspects. As with the AMC, the GSK-Brazil approach does not incentivise or reward low cost-of-goods products. However, it has a high technology transfer component, is operationally simple and is easily scaled up to other countries and diseases since it is based on standard commercial agreements. Likely DC impact is, however, difficult to estimate since this agreement was tailored to Brazil's higher purchasing power as an upper Middle Income Country but would presumably be structured at levels far closer to AMC prices for other LIDCs. The AMFm has the highest rating of all, since it uses bulk procurement to secure lowest price, and also requires participating countries to ensure access to even the poorest populations as part of their national product roll-out plan: this is a condition of receiving the subsidised product.

The Access RH model is also included to show: a) the limitations on DC impact for agreements that only cover generics; and b) the high operational efficiency and feasibility of the MVG model (almost the same as the AMC despite its substantial data gaps).

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
Affordable Medicines Facility - malaria (AMFm)	▪ ▪	▪ ▪ ▪	
Advance Market Commitment (AMC)	▪	▪ ▪	?
Access for Reproductive Health (RH) products / Minimum Volume Guarantee (MVG)	▪	▪ ▪	??
GSK & Brazil Minimum Volume Guarantee (MVG) for a novel product	*	▪ ▪ ▪	?

* This is a one-off agreement for a middle-income country so full DC impact is not reflected here

All purchase commitments for novel DC products struggle to achieve financing, with donors and recipients historically accepting a long wait for cheaper generic versions. From a purely financial perspective, the easiest option is for straight purchase contracts between developers and DC countries who can afford their product (likely MICs such as Brazil), where purchase costs can be offset against savings on treatment and hospitalisation. Where this is not possible (most LIDCs), donors will need to provide the necessary purchase funds as GAVI and the GFATM currently do for a range of products. The sums required would be very large and this option is therefore likely only viable for a few priority products, in particular vaccines for high-mortality DC diseases. A globally pooled model with tiered pricing between MICs and LIDCs may also be an option.

	REVENUE STREAM (AND WHETHER SECURE)	FUNDING FOR MANUFACTURE AND DISTRIBUTION	SCOPE
MVG	**N/A:** Efficiency so no revenue needed (pools existing demand). If no existing purchases, then N/A **Yes** for developer (purchase contract)	**No funding needed**, as existing purchases are pooled. Savings of US$3-11m in first 3 years, giving a return on investment of 0.6 – 2.4. Est. start-up costs $5m for the first 3 years, then self-sustaining through user fees.	Reproductive health products (oral contraceptive/ devices)
AMC	**No** for funder **Yes** for developer (purchase commitment)	**Yes**: US$1.5bn/10years for ~200 million doses annually shared amongst the contracted vaccine manufacturers (likely <10); subsidised for LMICs Will require higher sums for future AMCs (if novel products). Start up costs relatively high.	Vaccines for pneumococcal disease
AMFm	**No** for funder **Yes** for developer	**Yes**: Estimated that co-payment on ACTs for pilot phase will cost ~US$212m for 11 DCs. Operational costs of ~US$6.6m per annum	ACT
GSK Brazil purchase agreement	**Yes** funding is mandatory **N/A** – diversity of funders	**Yes:** Euro 1.5bn for 104 million doses over 8 years for Brazil (an MIC) Includes vaccine technology transfer to allow cheaper manufacture after the 8 years expire	Vaccines for pneumococcal disease

Acceptability

Developers gave purchase commitments the highest ranking of all the proposals reviewed, with a unanimous top rating by large and small companies, IDC firms, diagnostic companies and PDPs. All developers felt that purchase commitments – or rather, demonstrated government willingness to purchase products – was the best advance signal of demand they could have, and would incentivize them to conduct R&D. Developers noted that purchase funds for novel products would not stimulate the whole R&D process (which would likely require additional early push funding), but rather had the effect of "steering existing R&D towards the needs of DCs", providing the final added incentive needed. Of the various types of purchase funds, AMCs were least well received, being viewed unfavorably by small firms, while large companies also expressed mixed views, noting that: "We're trying to persuade governments to do a purchase fund, not an AMC".

Funders, however, have shown a marked preference for the AMC approach for vaccines; although they have also supported drug purchase funds such as the AMFm.

Conclusion

Purchase funds for novel products are a vital factor in stimulating increased R&D and providing large-scale access to new products; they are also well suited to steering existing programs towards DC needs, for example, R&D programs for Type I diseases that would otherwise focus on Western product profiles and on production capacity to meet Western needs. However, purchase agreements have limited ability to negotiate decreased price of new products, particularly if there is no competition from similar products. Standard purchase contracts are preferred to AMCs. However, standard contracts should achieve better outcomes by pooling demand to leverage and tier price negotiations, and by early signals to developers as to the desired DC-friendly (and DC price-friendly) profile that would encourage donors to put up purchase funds for the final product. In other words, using the purchase fund pull to actively direct R&D, rather than simply to purchase what developers have already made.

6.5 EFFICIENCY PROPOSALS

The following two proposals reduce R&D costs across the board, thus reducing overall future R&D funding needs and expedite access to new products by developing world patients:

- Regulatory harmonization (DC-focused)
- Pre-competitive R&D platforms

6.5.1 Regulatory harmonization (DC-focused)

A large proportion of the cost of developing and marketing a new product relates to regulatory requirements to establish that the product is safe, effective and of high quality before it is administered to patients in large numbers. Costs are further pushed up by differing regulatory requirements from country to country, with each regulator requiring its own set of information as the basis for national approval and use.[121] Regulatory harmonization aims to improve this process, by aligning requirements of some or many developing countries.

An additional 'quasi-regulatory' stage is in place courtesy of WHO processes aimed at assessing registered products for their suitability for DC use. WHO programmes include Drug Prequalification, Vaccine Prequalification, the WHO Pesticides Evaluation Scheme (WHOPES), work to test diagnostics for field use in DCs, and the WHO Essential Drugs List, which acts as a guide to DCs on which pharmaceuticals are most suitable and necessary for local use. These processes are vital, since regulatory approvals are based

[121] In the West, these differences have been partly addressed by agreement on a Common Technical Document (CTD) structure agreed by Europe, Japan, the US and the research-based pharmaceutical industry.

on national needs, not on suitability for other settings including resource-poor settings with limited pharmacovigilance resources and less well-controlled use. However, WHO processes are not always aligned with the work of other regulatory bodies, with the result that assessments are often repeated by WHO; and WHO reviews can be slow due to limited resources and to their parallel DC capacity-building function. The result can be very long delays in new products being given the WHO seal of approval for use in DC markets. WHO integration or recognition of approvals by rigorous regulatory authorities elsewhere, to the extent possible, would greatly expedite product access for DC patients.
These efficiencies (i.e. harmonization of DC regulation and better integration of WHO processes with those of rigorous regulators elsewhere) would save money rather than requiring money; and their benefits would be very broad, applying to products for all diseases that affect the developing world.
Developing country regulatory harmonisation has begun in some regions, but progress is slow. For instance, in Africa, early steps have been taken by the African Union and by various Regional Economic Communities (RECs). These range from acknowledging the value of a harmonised regulatory dossier by the Economic Community of West African States (ECOWAS), through harmonization of standards and practices for Quality Assurance by the East African Community (EAC), to a pharmaceutical business plan that aims for full regulatory harmonisation in the Southern African Development Community (SADC) over the period 2007-2013. A formal African Drug Registration Harmonisation consortium has also been formed, led by NEPAD, the Pan African Parliament (PAP), the Bill & Melinda Gates Foundation, DFID, the Clinton Foundation and the WHO, which supports African RECs and organisations to develop high-level plans that will be used to attract donor support for the harmonization process.
There has also been some level of integration between WHO reviews and those of other regulators, for instance WHO Drug Prequalification and the US FDA have a confidentiality arrangement that allows the exchange of review and inspections reports, so that products can be quickly added to the WHO Drug Prequalification approved list; however this does not extend to other major regulators such as the European Medicines Agency (EMEA).

Performance

DC regulatory harmonization is likely to have a very high DC impact, since the single act of harmonization facilitates more rapid registration of many products (both generic and brand) in many countries, and may lead to product registration in countries that would otherwise not have had access to that product at all. It is likely to increase patient access since developers are more likely to register products for sale in multiple DC markets if the costs and difficulty of doing so are decreased; and it may have a broader impact if lower development costs translate into lower prices for developing countries across the board (although this is far from a certainty).

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
Developing Country regulatory alignment	▪ ▪ ▪	▪ ▪	

Harmonisation is feasible, as witnessed by the agreement cited in the footnote above, and is essentially cost-free beyond the resources spent on negotiating agreement. However, it ranks only moderately in terms of operationality. Disparate national legislative frameworks are a substantial obstacle; regional countries may not have sufficiently high levels of trust to move to a harmonized system (it took the European Medicines Agency nearly 40 years); national sovereignty issues raise their heads; and loss of income from regulatory fees can pose difficulties for resource-poor nations. Finally, countries need to strike a balance between regional rationalisation and national regulatory capacity building, since national level regulatory skills will continue to be needed. Better integration of WHO processes with those of other regulators is also likely to be slow.

Acceptability

Product developers consistently rated regulatory efficiencies as a number one priority. Large and small companies and PDPs described them as: "very, very significant in terms of de-risking" and "an enormous help as currently the entire burden is on developers"; while diagnostic groups were even stronger, noting that the slowness and difficulty of the WHO system was now actively deterring companies from conducting R&D of diagnostics for poor countries.

Public and philanthropic funders also expressed strong support, with many already actively involved in supporting regulatory harmonization, in which WHO and its regional offices have also played a key role. By contrast, DC countries were sometimes luke-warm on regulatory harmonization, for the reasons set out above; and agreements between WHO and major regulators have been slow to reach.

Conclusion

Political will to move forward on DC regulatory harmonization and integration would be a major cost-saving and greatly increase DC access to quality products.

6.5.2 Pre-competitive R&D platforms

Development of pre-competitive R&D platforms also delivers high-value efficiencies but, unlike regulatory harmonisation, requires up-front investment. Pre-competitive platforms are tools to increase the efficiency of R&D across many products, for instance development of a new animal model that more accurately predicts the value of a TB vaccine in humans, or of surrogate markers that accurately predict the effect of a HIV drug, without requiring months or years of follow-up. These advances are described as pre-competitive since their findings are available to many developers, rather than being

proprietary to one company. Advances like these can save tens of millions to even hundreds of millions of dollars on R&D of a single product, both by decreasing development time and by allowing low performing leads to be detected and terminated early, before many more millions have been invested in their development.
Examples of pre-competitive platform research include:

- The European Commission's Innovative Medicines Initiative (EC-IMI), co-funded by the European Union and the European Federation of Pharmaceutical Industry Associations (EFPIA), which awards research grants to European public-private collaborations working to develop platform breakthroughs. The focus is on diseases of relevance to Europe, although the second call for proposals includes diagnostics for TB and pneumonia

- PATH, a US-based PDP, develops enabling and platform technologies that are made available to all companies making relevant products for its programmes. For example, new assays and cell cultures are available to all manufacturers of a rotavirus vaccine for DCs; and a consensus animal model is used for all pneumococcal vaccine candidates.

Pre-competitive platform advances feed into many products in a given area, but may not translate to other disease areas.

Performance

The DC health impact of pre-competitive R&D platforms depends on their design and targeting. Thus, the EC-IMI platform may deliver high DC impact, however researchers may also choose to focus on commercially relevant aspects that may be less relevant to DCs, for example, high-tech rather than low-tech TB diagnostic solutions. The EC-IMI is operational but complex, taking years to put in place: grant partnerships must include at least two SMEs or universities and two EFPIA industry members; public funds go exclusively to the public sector and SMEs; and the grant process is intensive, with only 10% of applicants being successful (compared, for instance, to around one-third under the US SBIR grant scheme). While cumbersome, this approach has the merit of pairing blue-skies academic and SME innovators with application-focused industry groups, an approach that has been shown to improve outcomes[122].
Pre-competitive platforms that focus specifically on DC needs and that prioritise projects that best address these are likely to have a higher DC impact, as the PATH programme demonstrates. However, we did not have enough data on current DC-focused platform work among various organizations (including PDPs and academic institutions) to evaluate the operational performance of this smaller in-house approach.

[122] Moran M, Ropars AL, Guzman J, Diaz J and Garrison C (2005) The new landscape of neglected disease drug development. *London School of Economics and The Wellcome Trust*. September 2005.

MECHANISM	DEVELOPING COUNTRY IMPACT	OPERATIONAL & FEASIBILITY	DATA GAPS
European Commission -Innovative Medicines Initiative (EC-IMI)		▪ ▪	?
Program for Appropriate Technology for Health (PATH) - type model	▪ ▪ ▪	*	???

* More information about the actual operational model would be needed to assess this

We do not have budget data for the PATH programme; however EC-IMI investments are significant. It has a 5-year budget of €2 billion (50:50 EU: EFPIA), with 15 projects receiving an average €16.5 million each in the first round of calls in 2008. Of the 2008 total, €110 million came from the EU for the support of public partners in the consortia (universities and research organisations) as well as SMEs, patient groups and organizations, and regulatory bodies; and a further €136 million was provided as in-kind from EFPIA partners for their role in the projects.

Acceptability

Both companies and PDPs ranked investment into pre-competitive platforms as a top priority, noting for instance that "ways to reduce the cost of, and simplify, R&D is a real gap", and that "surrogate marker work is incredibly important to accelerate R&D". Industry interest is underlined by their willingness to co-fund the EC-IMI platform.
Philanthropic funders were also strongly supportive: "We really like these as they mitigate risk all the way along", with this being borne out by their willingness to fund PATH's platform work, as well as that of others (e.g. TB Alliance work on mouse models). Public funders outside the EC were, however, less enthusiastic, with one noting that pre-competitive platform R&D was "interesting and valuable but not something we would support ourselves". This position is borne out by 2008 G-FINDER data, which shows that only 0.2% of global public funding for neglected disease R&D went into platform development.

Conclusions

Investment into pre-competitive R&D platforms targeted at DC-relevant products can deliver substantial cost-savings for all development programmes in that disease area. However, platform R&D for DC targets tends to be poorly supported due to public-good/ free-rider issues. Political will in this area would make a substantial difference to expediting R&D and reducing costs.

6.6 PROMISING PROPOSALS

Five further proposals are not included above either because it is not clear how effectively they would scale-up into broad-based solutions and/or because they have design weaknesses in some areas. All nevertheless had innovative elements that were so promising that we believe they should be further examined with a view to either amendment (if possible) and review for implementation, or integration of their high-performing elements into other proposals.

Open source

Open source works on the basis that collaborations in biology allow interested parties to contribute knowledge/possible solutions (e.g. posting raw scientific data) to a biomedical problem. Collaborators forgo patents as the research outputs are placed in the public domain, although arrangements can differ. For instance, the key idea behind Sage Bionetworks (below) is to make Merck's previously proprietary data accessible to all interested parties without any IP strings attached. Versions have already been implemented including by the Indian Government, and by organizations such as Synaptic Leap, Sage Bionetworks http://sagebase.org/index.html; and the Tropical Disease Initiative's 'open access' research site (http://www.tropicaldisease.org).
While it is not clear whether many developers would use this approach, the concept nevertheless scored sufficiently highly across the board to warrant further exploration. As an efficiency, this also offers a low-cost solution.

Patent pools (UNITAID model)

Patent pools along the lines of the UNITAID model have promise. The UNITAID approach is based on creation of "upstream" and "downstream" patent pools, initially focusing on Fixed Dose Combination (FDC) antiretrovirals (ARVs) for the treatment of HIV/AIDS. The "upstream" patent pool aims at facilitating creation of DC-suitable adult and paediatric FDCs (e.g. once daily, heat stable). The "downstream" pool is designed to lower the cost of existing HIV drugs by facilitating production of generic copies. Patents in these areas are voluntarily submitted to the patent pool by companies, researchers or academics. Manufacturers can then obtain a licence to any patent in the pool and use it to create new or cheaper products. A small royalty is payable to the patentee for use of the patent.
The UNITAID patent pool model scored well for operational efficiency and feasibility despite substantial data gaps; and very well on developing-country impact. However, as it is based on voluntary intellectual property (IP) donation, questions remained as to the quantity and quality of IP that patent-holders would choose to donate, particularly outside HIV/AIDS. For the pool to work well it requires a minimum critical mass, and it is not clear whether this will be achieved on a voluntary basis across many diseases. As an

efficiency, the patent-pool model is low-cost; and it is highly recommended for further exploration of its scalability to other disease areas.

Health Impact Fund (HIF)

HIF is a voluntary system offering financial payments to developers of new drugs, which are then sold globally within an administered low price bracket. Instead of the patent returns offered by the regular market, the fund offers payments based on the incremental therapeutic impact of the drug or vaccine, calculated annually based on Quality-Adjusted-Life-Years (QALYs) gained. In return, the company forgoes the opportunity to earn profits on sales of the product during the reward period and must agree to offer a royalty-free open license to allow generic manufacture of the product simultaneously with its own sales. At an approximate cost of US$6bn annually, the HIF would need to be financed by an international fund supported by donors.

This proposal has significant difficulties: developers need to fund R&D upfront, which is difficult or impossible for most, especially if final profits are limited; the methodology of assessing health impact is not agreed and open to dispute; there is a high degree of uncertainty as to the exact pay-out to an individual developer; and control of the 'market' by a central committee is cumbersome and very expensive (costing around $600 million per year). Finally, health impact statistics are likely to be most reliable for high-profit commercial diseases, where developers would likely choose the IP system over the HIF; and least reliable for low-profit neglected diseases where the HIF would theoretically be more attractive.

The HIF is nevertheless deserving of further consideration for specific innovative aspects that could perhaps be captured in other ways. In particular, it creates markets where none previously existed and it ties financial rewards to health impact.

Priority Review Voucher (PRV)

The PRV offers 'priority regulatory review' of a commercial product in return for US registration of a neglected-disease (ND) drug. Priority review allows a company to bring their product to market faster, which translates into many hundreds of millions of dollars of additional sales for a blockbuster product. It has been estimated that receiving priority review could be worth US$322m on average to developers, based on a reduction in the review time from 19.4 to 6.4 months for a drug[iii] . The vouchers are tradable.

However, the PRV has major design issues and could deliver substantially better value if these were addressed. There is no requirement for the ND product to be suitable for DC use; developers only need to conduct first U.S. registration, thus firms can trigger the voucher by registering products in the US that have already been used in other countries for many years (as was the case with the first product to receive a PRV); and there is no link between award of the voucher and actual uptake of the ND product in developing countries (i.e. the firm does not need to register or sell the product in DCs in order to receive the voucher).

The PRV may be worth further consideration due to its attractiveness to SMEs: it may be one of the more potent pulls to encourage these firms into the field, including IDC firms. However, this would only be the case on the strong proviso that the PRV be re-designed to address the flaws noted above in order to deliver far better value for money for both the funders (Western patients) and the recipients (DC patients).

Orphan Drug Legislation (ODL)

Several countries have implemented ODL to stimulate development of products for rare diseases, including the US, European Union (EU), Japan and Australia[123]. ODL incentivizes developers to make products for low-profit markets by offering a package of push incentives (tax credits, regulatory fee waivers and priority review) and pull incentives ranging from 7 years of domestic market exclusivity in the US to 10 years in domestic market exclusivity in Europe. The pull element is by far the strongest incentive for developers, and the key to the success of ODL.

Although ODL is primarily designed to encourage R&D for rare diseases of the West, it is also used for neglected disease products for DCs. However, in the latter context it performs far less well since the domestic market pull is generally tiny, as neglected diseases barely exist in these Western markets. A further issue is that ODL does not require regulators to review the orphan product for DC suitability, only for domestic suitability.

Orphan is nevertheless included here it may provide a more attractive incentive if the disparate market pulls could be aggregated. Some degree of market aggregation already exists with ODL, for instance Australia and the US have linked orphan recognition, so that a product that receives ODL status in the US automatically receives ODL status in Australia. If Orphan Drug approval in one jurisdiction could automatically trigger orphan approval in most other jurisdictions – and possibly also WHO Prequalification and/or EDL listing – the aggregate neglected disease market pull of ODL would be substantially increased. Specific requirements for DC-sensitive regulatory review would also need to be incorporated for reciprocally-approved ND orphan products.

6.7 GAPS

Collectively, the allocation proposals presented above (excluding promising proposals, whose mettle has yet to be tested) cover R&D for all the DC-relevant disease areas and developer groups (see Table below), however there is one area where <u>all</u> groups may not be mobilized. This is discovery and early development activity for Type II and III diseases that is conducted independently by large companies outside PDP partnerships. It is possible that large companies may self-fund early discovery work - many already do - however development up to Phase II represents significant costs, which it is unlikely a company would want to bear alone. In areas where there are no PDPs active, large companies have no suitable incentives, since they are unlikely to respond to milestone

[123] Rare diseases are defined as diseases with a prevalence of less than 200,000 cases in the US and less than 5 per 10, 000 inhabitants in Europe

prizes or to be sufficiently motivated by the promise of support for trial costs and a low-price purchase fund.

This gap may be partially covered by the FRIND proposal, which covers drug development activity by both PDP and industry for a range of neglected diseases; or one could rely on SME activity in response to incentives (or even consider a new PDP in key areas in order to take advantage of larger scale PDP funding solutions). These decisions need to be weighed up as part of the in-depth review described below (see Next Steps).

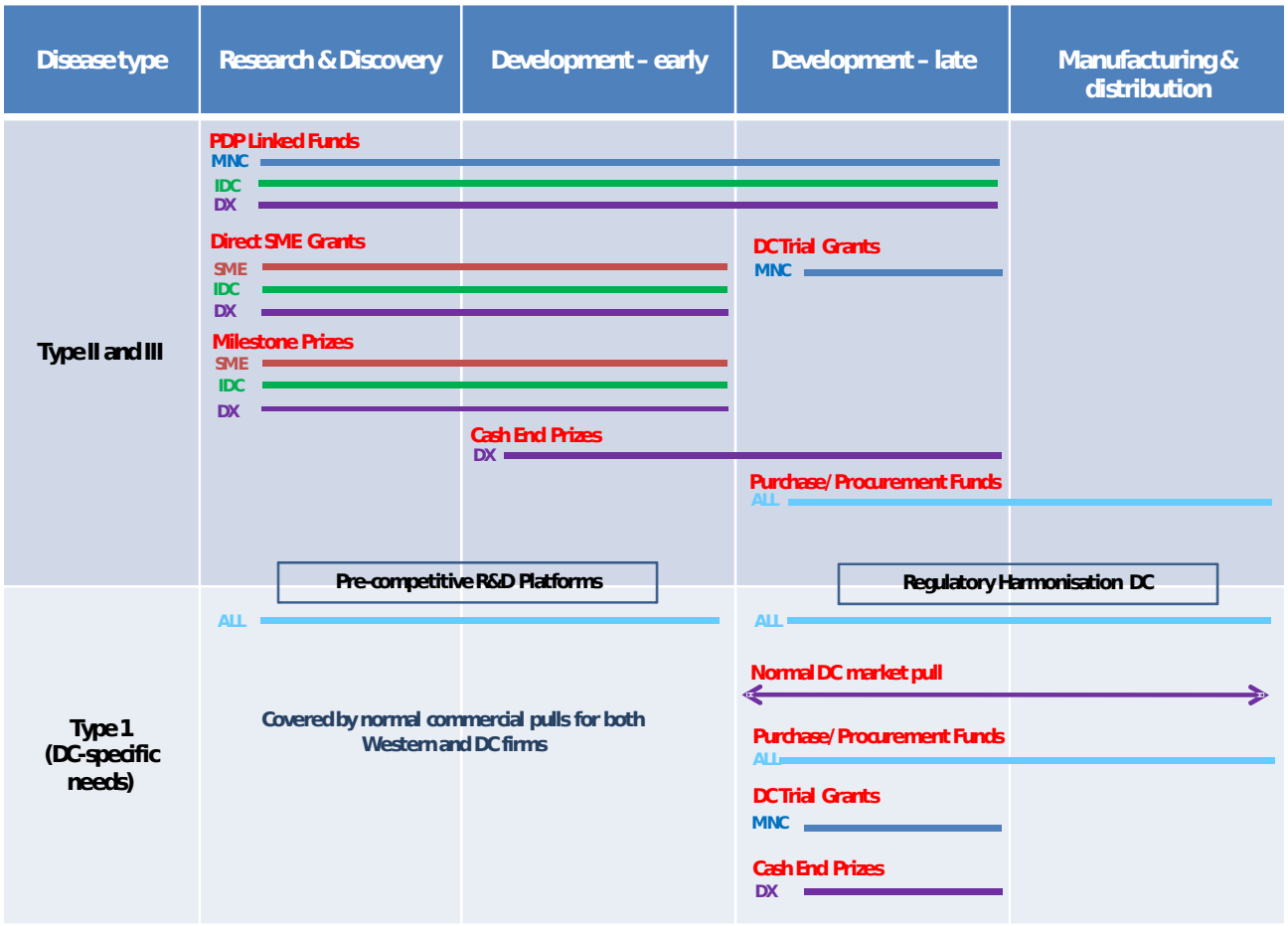
A larger issue is that, in order to perform optimally, additional measures are needed that fall outside the R&D arena:

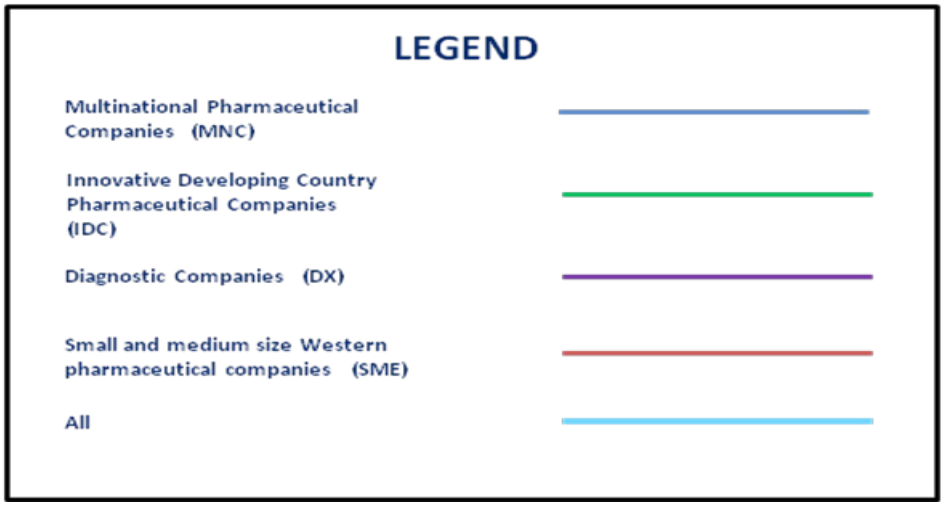
- Coordination of funding outside PDPs (e.g. SME grants, DC clinical trial grants: Funding routed through the proposed PDP funding mechanisms automatically provides a level of funding coordination and project prioritization. However, this does not exist for other funding routes, leaving donors faced, for example, with a series of choices on who to provide grants to and which prizes to put in place. In order for these proposals to work easily for donors, they will require a mechanism to coordinate funding to "non-PDP" areas (although, as noted, this may be resolved by further work on FRIND-based solutions to provide broader coverage)

- Prioritising prizes and purchase funds: Coordination of milestone prizes is likely less important, given their smaller size, however end-prizes and particularly purchase funds require a far greater financial commitment. Funders and developing countries will therefore need to carefully decide which disease priorities matter most and are most feasible in terms of product development, in order to determine where to best apply the first prizes and purchase funds.

One further issue causes us deep concern. The driver behind the CIPIH, the IGWG and now the EWG was the need to secure earlier access to medical breakthroughs for developing world patients: it was considered untenable that these patients should have to wait for patents to expire before they had access to affordable treatments. At the same time, it was clear that patents were the key to funding the R&D that creates these new products. Our suite of proposals addresses this issue fairly well for Type II and III products, where linkage of PDP-funding mechanisms, cash end-prizes and purchase funds collectively provides broad access to suitable low-cost products. Proposals for funding independent industry activity outside these routes are also expected to perform well <u>if</u> they are carefully designed to ensure that substantial injections of public funds are adequately reflected in lower priced end-products.

Coverage of Developing Country R&D





However, we were disappointed and troubled to find that, on analysis, none of the proposals aimed at securing early, low-cost patient access to products for Type I diseases performed well – indeed, most performed exceptionally poorly. We have sought to fill this void as best we could with the materials at hand, including the use of public subsidies for clinical trials (which would need to be tied to lower LIDC prices); the use of end-

prizes that allow IP-handover; and the use of purchase funds, which would ideally focus on suitable products for DCs. The rapid growth of IDC capacity to develop and supply Type I (and Type II) medicines will also, we believe, go some way towards addressing these needs. However, the larger problem of access to Type I products registered and used in the West remains unresolved. This is now increasingly pressing as the waiver on TRIPS implementation, which allows LIDCs to delay protection of patent monopolies, will expire in seven years.

6.8 CONCLUSIONS AND NEXT STEPS

We recommend implementation of the following approaches as best suited to maximizing R&D targeted at developing world needs, provided the provisos set out above are adhered to:

- Fundraising
    - A new indirect tax (a consumer based tax)
    - One or more voluntary business and consumer contributions
    - Taxation of repatriated pharmaceutical profits
    - New donor funds for health R&D
- Fund allocation
    - Product Development Partnership (PDP)- linked funding
    - Direct grants to small companies and grants for DC trials
    - Milestone Prizes
    - End-Prizes (cash)
    - Purchase or procurement agreements
- Efficiencies
    - Regulatory harmonization (DC-focused)
    - Pre-competitive R&D platforms

These fundraising mechanisms, depending on choice of proposals within them, could raise an additional $US4.6 to US4.9 billion per annum for health R&D for the developing world. The proposed allocation and efficiency mechanisms would allocate these funds efficiently, and in a manner that provided coverage of Type II and III diseases, and was well suited to maximizing developer activity. If the provisos noted are taken into account, these allocation mechanisms are also expected to provide good public health and capacity building results for the developing world. We note that these funds could be substantially expanded if donors divert current financial support from low-performing approaches (see Annexe 1) to the higher-performing approaches identified here.

Some of the recommended approaches are either already in place, or the general approach is in place to act as a framework, host or model for a developing-country specific version of the mechanism (e.g. PDPs; grant schemes; milestone prize vehicles; purchase or procurement funds hosted by GAVI, GFATM and others; regulatory harmonization and integration initiatives; and isolated pre-competitive platform initiatives within individual

organisations). Other proposals would require implementation, including mechanisms to fund PDPs and cash end prizes.

However, unlike many lower-performing proposals that were reviewed, none of the recommended mechanisms have a revenue stream, with all currently relying on donor contributions and philanthropy. The financing mechanisms proposed in this report are, however, well suited to address these funding deficits. We are therefore relatively confident that the above-proposed financing and allocation mechanisms will, if implemented, provide a sustainable solution to the needs of DC patients for new Type II and III disease products.

Type I disease products do not fare so well. As noted, the recommended mechanisms cover DC-relevant adaptations of Type I products fairly well, but there were no effective proposals to address gaps in DC access to patented Type I products.

Next steps

If policy-makers accept our broad conclusions, we recommend rapid transition to a "working phase" that would focus on the following key activities:

1. Conduct an In-depth review of proposals within both the recommended and promising approaches. This review should result in selection of the best performing proposal in each category (e.g. the best PDP-funding mechanism; the best direct grant approach etc) or – even better – in development of new solutions that combine the best features of each

2. Set up a funder group to test the acceptability of some or all of the final proposals for implementation

3. Begin matching revenue streams to allocation mechanisms. As an example, the broad-based high volume consumer tax (e.g. a digital tax) would be well-sized to support Purchase Funds for new products – and consumers may willingly contribute a tiny amount each of their monthly phone or internet bill for the purchase of meningitis or TB vaccines for infants in the developing world. Likewise, a tax on pharmaceutical industry profits in DCs might be readily linked to PDP-funding proposals, providing large infusions of cash to the proposed central PDP funds, which would then be available back to companies partnering with those PDPs. We suggest a formal process involving donors also be set up to conduct this process

4. Commence discussion on a mechanism to coordinate funding allocated by proposals outside the PDP model (e.g. SME grants, DC clinical trial grants)

5. Determine which mechanisms best suit which disease areas, and prioritise their implementation by disease and product. For example, purchase funds are most likely to be immediately needed for diseases with portfolios in late-development e.g. TB or meningitis vaccines; grants to subsidise DC clinical trials will be most

suitable for disease areas with products moving into large-scale trials in the next few years etc

Finally, we recommend additional work in two areas that were not covered by any of the proposals (or in some cases, were not covered by any adequately-performing proposals). The first is developing country access to Type I products: this should be a top priority. While it is possible that solutions to improving access to medicines for Type I diseases may come from combining elements of the recommended proposals or promising approaches noted above, it seems more likely that a truly durable solution will only come from new, more creative and realistic proposals. Secondly – and an area that may well provide solutions to the foregoing problem – the role of the IDC commercial sector in R&D for DCs should (and we believe must) be a policy priority going forwards.

APPENDIX 1: LOW PERFORMING PROPOSALS

The lowest-performing proposals overall are listed below. We believe these do not merit further consideration.

- Transferable Intellectual Property Rights
- Green IP
- Removal of data exclusivity
- Biomedical R&D Treaty
- Large end-stage prizes (impact- based rewards)
- Neglected Disease tax breaks for companies

The remaining proposals on the EWG's Inventory of Proposals were either too specific to be scaleable or performed insufficiently well to merit further consideration (*see Inventory*).

Pekar N, editor (2001) The Economics of TB Drug Development. New York: Global Alliance for TB Drug Development. Available: http://www.tballiance.org/downloads/publications/TBA_Economics_Report.pdf

Serdobova I, Kieny MP (2006) Assembling a Global Vaccine Development Pipeline for Infectious Diseases in the Developing World. Am J Public Health 22 (9): 1554—1559. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1551949

Ridley DB, Grabowski HG, Moe JL (2006) *Developing Drugs for Developing Countries*, Health Affairs 25 (2) pp 313-324.

Appendix 2
Methodology to evaluate health R&D financial proposals

Evaluation Framework and Inventory

An inventory of 90+ health R&D financing proposals was initially compiled from the following sources:

- Submissions to the EWG public hearing in March-April 2009
- Submissions from EWG members
- Literature searches of major databases, and grey literature
- Proposals from related Working Groups, Commissions and projects:
    - The Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH)
    - The Taskforce on International Innovative Financing for Health Systems, co-chaired by the UK Prime Minister and the President of the World Bank[iv]
    - The Brookings Institute analysis of evaluation tools: "Innovative Financing for Global Health: Tools for Analyzing the Options"[v].

This initial inventory was reviewed for completeness and supplemented with proposals submitted to the second public hearing organised by WHO, which took place from the 17th of August to the 5th of September 2009.

These 90+ proposals, defined the scope of what was evaluated. The proposals were included in an evaluation framework that grouped them into two main categories, depending on whether the proposed mechanism was solely intended to raise funds or whether it also had provisions to allocate these funds to R&D activities.

Fundraising proposals were sub-grouped according to the source of funding (e.g. government, consumers) and type of funding (e.g. frontloading, taxes), while allocation proposals were sub-grouped according to their stated R&D target including disease type (I, II, III, all), product type (drug, vaccine, diagnostic, all), research type (building health R&D in developing countries, basic research, product development (early and late), manufacturing and distribution) and principal actors (public, private, academic, Product Development Partnerships, multinational companies, generic manufacturers, small companies). The evaluation framework's main structure was based on research type, and this also provided the basis for the structure of the report.

Evaluation tool

An evaluation tool was developed, setting out high-level criteria against which to assess proposals. The initial tool was refined based on stakeholder feedback from the second public hearing. The final tool included three high-level criteria divided into twelve sub-criteria (and close to 100 detailed criteria) as set out in the table below.

These detailed criteria were subsequently used to conduct a comparative analysis and screening of mechanisms.

Developing country impact	o Health impact, including whether it incentivises R&D for DC health priorities and DC use, has measures to ensure safety, quality and efficacy and encourages innovation. o Access: price, registration/ distribution, IP approach, including whether the cost-of-goods is in line with DC requirements, maximises both affordability and access, fosters generic manufacturers or increases competition and increases distribution. o Capacity building, including whether DC capacity is encouraged, whether DC regulators and/or manufacturers are involved. o Technology transfer
Operational efficiency and feasibility	o Risk management, including whether funding arrangements are mandatory, there is a diversity of funders, the funding stream for recipients is certain, spreads risk for investors, and (for manufacturing and distribution proposals only) mitigates against stock outs o Technical feasibility, including whether the mechanism requires changes to legal, regulatory or administrative systems and whether the mechanism can be operationalised quickly by using existing entities or structures o Long-term functioning, including whether the mechanism provides clear rules on funding allocations to allow long term planning by principal groups, whether the mechanism is able to be adapted in light of real life experience, and whether it could be politically sustainable o Accountability, governance and transparency, including whether the mechanism has a sound governance structure, includes all appropriate groups (including DCs), whether there is a dispute resolution mechanism, the mechanism operates transparently, including having an accountability system and roles and responsibilities documented, and whether participating groups are treated equitably and fairly

	o Interactions with other proposals
Financial aspects	o Revenue stream and size o Costs o Quality of funding for the allocation proposals including additionality; certainty of revenue; reliability and applicability of mechanisms; absence of inefficient conditions; and additional benefits e.g, lower R&D time and cost. While for the fundraising proposals it was based on the degree to which the mechanism has a degree of certainty over revenue forecasts, has a potentially wide scope geographically, is free from inefficient conditions and distortionary tax effects, and it has spill-over benefits to the global good and development agenda.

Screening

Each proposal was independently screened against the evaluation tool by 2-6 evaluators, to determine how well it met each of the up-to-100 criteria. The team of evaluators had a diverse skill-set, and included IP, financing, R&D, regulation and DC public health experts. The objective and scope of the proposal determined which set of evaluators screened it. Marked discrepancies in screening results were resolved through further research and discussion amongst evaluators. In the instances where a criterion was not applicable to the proposal, the proposal was not screened or scored against that criterion.

For DC impact and operations and feasibility the top ranking proposals are represented in the table by a score of three, middle ranking by a score of two, with low scoring proposal on one or zero. Only top scoring proposals were considered as suitable for further consideration. The exception to this is efficiency proposals, which were considered as suitable for further consideration with an operations and feasibility score of two or over: this is because efficiency proposals, by definition, require change in existing systems and are therefore more difficult to operationalise, particularly across legislatures. Financial aspects were analysed and tabled separately.

While every effort was made to answer each question for each proposal, there were instances where there was no data available for a proposal against a particular criterion, and as such this was recorded as ‘no data’, as it could not be given a positive score. These proposals have been identified as needing more work and are marked as having data gaps in the table at the front of each section of the comparative analysis. These ‘no data’ results need to be read in conjunction with the DC impact and operations and feasibility results. Thus, where there was a high proportion of no data results the score could potentially be improved if more data was made available. This led to a group of proposals being flagged as ‘promising proposals requiring further work’.

Determining acceptability - key criteria

To work in the real world proposals need to be acceptable to both funders and to those equipped with the skills and tools to develop the desired products. Therefore, in a parallel process, a wide range of public, philanthropic, industry and civil society groups were asked to nominate which criteria were most important to them in an R&D financing proposal, with feedback being submitted through the WHO website and with follow-up interviews conducted where necessary. In particular, groups were asked to nominate those criteria that were essential or highly important for them. Funders and product developers were additionally asked which proposals were most and least likely to encourage them to fund or conduct R&D to generate new products for the developing world. These responses were then sorted into groups: public funders, philanthropic funders, large companies, small companies, PDPs, developing country industry, civil society.

The responses of each group were analysed to determine which factors were most important to them. This, in turn, determined how high the 'bar' should be set for each criterion. For example, DC impact was very important to almost all funders; while operational efficiency and feasibility were almost unanimously nominated as the most important feature by developers; however no groups believed that value for money was the most important driving principle.

Short listing of proposals

In order to shortlist the proposals, cut-off points were set, below which a proposal was not included for further consideration. In response to feedback on the criteria, we set a high cut-off point for DC impact and operational efficiency and feasibility, but only a moderately high cut-off point on value for money. Responses from funders and product developers were then used to further shortlist proposals i.e. to select proposals that were both high scoring and acceptable to funders and principal actors – the most effective proposals; and low scoring and not acceptable – the least effective proposals.

Although DC impact and operational/ feasibility issues were given equal importance, we note for readers that some components of a mechanism are easier to address than others. For instance, it is relatively easy to re-target a proposal to give a better DC health impact – e.g. by fine-tuning the list of diseases, by providing a tighter product profile that suits DC needs. However, it is very difficult to change the fundamentals of how a proposal operates. For this reason, readers should place particular emphasis on proposals that perform well operationally, and that can be re-targeted for better DC health outcomes.

Fund raising proposals, on the whole, do not have an allocation component i.e. they raise money but this money could be spent on virtually any object, thus fundraising proposals were not assessed for DC impact, but only for operational and financial aspects.

Taskforce on Innovative Financing for Health Systems (2009). Raising and Channeling Funds. Working Group 2 report. Final Draft (3 June 2009). Available: http://www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf Accessed 17 July 2009

De Ferranti, David et al. (2008). Innovative Financing for Global Health. Tools for Analyzing the Options. Washington DC: Brookings.

Available: http://www.brookings.edu/~/media/Files/rc/papers/2008/08_global_health_de_ferranti/08_global_health_de_ferranti.pdf Accessed 17 July 2009

[i] Pekar N, editor (2001) The Economics of TB Drug Development. New York: Global Alliance for TB Drug Development. Available: http://www.tballiance.org/downloads/publications/TBA_Economics_Report.pdf

[ii] Serdobova I, Kieny MP (2006) Assembling a Global Vaccine Development Pipeline for Infectious Diseases in the Developing World. Am J Public Health 22 (9): 1554—1559. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1551949

[iii] Ridley DB, Grabowski HG, Moe JL (2006) *Developing Drugs for Developing Countries*, Health Affairs 25 (2) pp 313-324.

[iv] Taskforce on Innovative Financing for Health Systems (2009). Raising and Channeling Funds. Working Group 2 report. Final Draft (3 June 2009). Available: http://www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf Accessed 17 July 2009

[v] De Ferranti, David et al. (2008). Innovative Financing for Global Health. Tools for Analyzing the Options. Washington DC: Brookings. Available: http://www.brookings.edu/~/media/Files/rc/papers/2008/08_global_health_de_ferranti/08_global_health_de_ferranti.pdf Accessed 17 July 2009