Stakeholder Views Regarding a Health Impact Fund (HIF), to Incentivise Pharmaceutical Innovation Relevant to Diseases of Poverty

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The HIF scheme, aims to create an alternative (Patent-2), to the existing Intellectual Property Rights (IPR) regime for rewarding pharmaceutical innovations through monopoly patents. Innovators would choose between the traditional IPR approach and the Patent-2 system to recoup innovation costs. Under Patent-2, reward would be based on the positive impact of the innovation on health globally. A two stage, international, expert stakeholder Delphi survey (N=25) was conducted to identify stakeholder requirements for acceptance and implementation of Patent-2. Broad stakeholder support for the scheme was identified. Some practical issues were identified which require resolution. A larger survey (N=84 international stakeholders) was used to validate these findings. Results broadly corroborated the conclusions of the Delphi survey.

INTRODUCTION

Despite recognition of the need to amend the current system of IPR in order to deliver reasonably priced health care to patients around the world[1], the implementation of concrete alternatives has been hampered by pragmatic difficulties to action any change. However, reform of the existing patent system for pharmaceuticals may be achievable through application of a potential two-tiered patent system, involving the traditional IPR patent model together with an alternative "Patent-2" approach.[2,3] This alternative approach would enable innovators to opt to register their patented product under the "Patent-2" system which involves renouncing any veto powers over the manufacture of the patented medicine worldwide in exchange for title, during the lifetime of the patent, to a stream of reward payments proportioned to the product's global health impact, facilitating the medicine being sold at minimum cost so maximising its potential impact on the global burden of disease. Patent-2 holders would be rewarded, from a global, publically-funded Health Impact Fund (HIF) in proportion to the impact of their invention on the global burden of disease (GBD)[1,4]. However, as this approach may not be acceptable to all stakeholders, the aim of the research reported here was to ascertain potential stakeholder and end-user opinions including their priorities for the outcomes (and associated impact measures) of an HIF scheme, together with identification of potential implementation barriers, and thoughts on how these might be overcome.

THE HIF PROPOSAL

Discussion of the weaknesses of the current system of funding innovation in the pharmaceutical sector is provided by Hollis (2008)[5]. Of particular relevance to the issue of neglected diseases and diseases of poverty is the contention that many innovations which would be socially valuable would provide inadequate profits through a traditional

patent system to make investment in R&D profitable for the patentee. In addition, the existing patent system encourages the patentee to charge a price which would simultaneously make the pharmaceutical unaffordable to those for whom it could be beneficial. Hollis (2008)[5] further argues that the costs of litigation associated with extension of existing patents further hinder innovation processes as they dis-incentivise investment in further pharmaceutical development and innovation. In contrast, a Health Impact Fund[6] (HIF) would incentivise the development of new medicines with large measurable health impacts, (for example, an effective treatment significantly reducing diseases of poverty such as Tuberculosis, HIV/AIDS or Malaria). The incentive is independent of the ability of the end user to pay, and facilitates access at low prices. Payments from an HIF (which would be funded by national governments, international bodies, industry and charitable funds) would be contingent on impact, measured, for example, in QALYS (quality-adjusted life years). Criticisms of the HIF have focused on practical issues, particularly relating to designing and implementing methods to assess the comparative cost-effectiveness of novel pharmaceuticals, the risk of pharmaceutical companies exaggerating the health impact of a new drug in order to increase payments, international disparity in funding (where public funding of the rewards for invention coming from taxpayers in developed countries, while most of the benefits could accrue to people in developing countries), and difficulties associated with obtaining political support without broad international cooperation[7] Stakeholder "buy-in" across all sectors is therefore a prerequisite of effective implementation of an HIF, where "stakeholders" include the pharmaceutical industry, national governments, intergovernmental organizations, representatives of civic society, medical agencies, charities, and funding bodies.

STUDY 1: THE DELPHI SURVEY

Delphi[8,9,10] is an iterative technique used for the systematic measuring and aiding of forecasting activities and decision making, and has been applied across a variety of disciplines. Delphi is recognised as being an effective procedure when reliable consensus of opinion needs to be obtained from diverse stakeholder groups, and involves sequential collection of two or more rounds of questionnaire data interspersed with controlled and anonymous opinion feedback. Often there is an exploratory round, in which key issues are identified. At the end of the process, the 'group's' position is indicated by the average response to the particular questions, although the extent of agreement/disagreement is also noted The advantage of Delphi over single round questionnaires is that it allows the provision of anonymous feedback, often but not always in a statistically summarised form, although sometimes as quotes from participants. This allows participants to revise opinions in light of the views of other relevant stakeholders. This may provide the basis of greater consensus across the group, as views and opinions are made transparent[11].

Delphi has proven to be a useful method for eliciting international expert opinion within the domain of governance, for example, relating to food policy[12], or development of research policy and agenda setting for future research activities[13]. Given the aims of the HIF research, international stakeholder inclusion in the Delphi study was essential. The inclusion of international expertise demands a methodology that makes it feasible to consult with disparate experts and Delphi methodology is highly appropriate to such

objectives, particularly given the need to include geographically dispersed experts with potentially a broad range of views regarding their priorities for an HIF, and where lack of consensus may arise across the stakeholder group[14].

Methods

Potential experts were identified through collaboration and discussion with project consortium members. Thus personal contacts were utilised, an approach proven to be effective in recruiting potential participants to international Delphi surveys in previous research[12]. Experts were identified from the community of relevant international policy actors, end-users and other stakeholders, pharmaceutical industry actors, academia and both public and private funding bodies, utilising both personal contacts and cascade methodology. The aim was to obtain a broad spread of representation across stakeholder groups, particularly individuals who were influential in their field.

In an initial round of consultation, a semi-structured questionnaire was developed[15]. An invitation to experts to participate in the survey, an explanation of the Delphi process, and a summary of the HIF scheme was also prepared and circulated by email to the 65 identified experts, stakeholders and end-users during June 2009. Participants were also provided with web links to key documents relating to Patent 2 and the HIF approach[16].The purpose of round 1 was to enable participants to comment on the proposed HIF approach, consider its potential acceptability to different stakeholders, identify potential barriers to successful implementation of the scheme, suggest ways in which the scheme might require modification, consider critical success factors relevant to policy development and valorisation, and suggest possible mechanisms and timescales for implementation. The initial invitation made clear that the Delphi methodology used was an iterative process that would require commitment to at least two rounds of responses. The anticipated outcome and analysis of this first round semi-structured questionnaire was to provide qualitative information relevant to policy implementation and obtain expert stakeholder input to the development of a second quantitative questionnaire. The results of round 1 were analysed to identify whether any consensus views had emerged. Minority consensus was classified as 50-79% agreement with 80% or more agreement being classified as a majority consensus.

The second quantitative questionnaire was circulated by email to those participants who had replied to the first questionnaire. Round 2 focused on ranking the barriers and critical success factors identified in round 1. A statistical summary of first round responses (mean group response) was included in the second round, in order to provide feedback to participants regarding anonymous group responses to individual items. Participants were also informed of those responses for which consensus views had emerged. Views on which consensus was achieved in round 1 were not considered for further discussion in round 2.

Delphi round 1 Materials and Results

All questions were developed following consultation with the Innova-P2 project consortium. A copy of the questionnaire and invitation to participants is provided in Annex 1. The key questions asked in round 1 were as follows:

- Is there broad stakeholder and end-user support for the HIF?
- What are the most important barriers to treating diseases of poverty and neglected diseases?
- Are any refinements to the HIF required to address these barriers (including pragmatic issues related to implementation of the scheme)?
- Are the estimated resources needed and assessment measures used appropriate in terms of implementation?

A combination of qualitative and quantitative questions was applied to solicit expert and stakeholder opinion regarding these issues. The profiles of participants who responded to round 1 questionnaire are provided in Table 1. Of the initial participants invited, (65 in total) 24 responded, resulting in a round 1 response rate of 39%. Of the participants involved in round 1, all but 1 responded to the second round questionnaire. The round 1 Delphi survey was conducted in June 2009.

Table 1: Professional affiliations of experts involved in round 2 of the Delphi Questionnaire

Type of organization	**Country of professional affiliation (n).**
Pharmaceutical companies and providers	Denmark (1) France (1) United Kingdom (1)
International organizations	International (1)
National government	The Netherlands (1)
Health services	United Kingdom (1)
NGOs	International (1)
Academics	Belgium (1) China (5) Kenya (1) Netherlands (1) United Kingdom (2)
Other Stakeholders and end-users	Denmark (2) Netherlands (2) United Kingdom (2)

Participants with industrial affiliations, and from developing, (as opposed to emerging) economies were slightly under-represented (Table 1). Other key stakeholder and end-user groups (representatives of regulatory and ethical bodies, IPR lawyers, patient groups, for example), did not choose to participate, although such individuals were included in the original database. This lack of participation needs to be considered in interpretation of the results. In contrast, researchers from academic institutions were over-represented. It is possible that relevant opinions from representatives of these groups might be reflected by the international and NGO participants, but this cannot be assumed to be the case. Inspection of self-reported occupational titles indicated that the majority of participants were relatively senior within their organizations. Women were

under-represented (83% of the sample were male) in terms of participants who responded.

Consensus opinions identified in round 1

Agreement of more than 80% was assumed to indicate reasonable consensus across the sample.[11,12] The results indicated that participants agreed on the following items:

- There was a need to adopt "special measures" regarding the treatment of neglected diseases.
- The HIF would provide a greater incentive for the pharmaceutical industry to develop tools to fight diseases of poverty.
- An HIF scheme would encourage commercial pharmaceutical companies to collaborate with publicly funded research initiatives.
- Pharmaceutical interventions should be eligible for an HIF payment.
- Health system innovations should be eligible for a HIF payment.

Seventy-four percent of participants agreed or agreed slightly, and 17% had no opinion that "in addition to national Governments, other donors, such as private foundations, will be willing to fund an HIF scheme", again suggesting that reasonable consensus existed across the participants. However, almost 60% of participants were unable to estimate whether the proposed size of the fund (US$6bn) was an appropriate sum for an HIF scheme. The remaining participants provided a wide range of estimates, and indicated that they were uncertain of the accuracy of these estimates. This suggests that a convincing economic analysis of the financial resources required will be essential if institutional and industrial "buy-in" to the HIF scheme is to occur.

Delphi round 2: Open-ended responses from round 1.

Round 2 questions were developed from the round 1 responses, in particular from the qualitative responses of participants. A copy of the Round 2 questionnaire is provided in Annex 2. The survey ran between December 2009 and January 2010. Two researchers involved in the study separately coded these open-ended responses from round 1, developing a coding scheme grounded in the data available. Following development of the coding scheme, participant responses were subsequently recoded using the scheme. Where disagreement regarding coding of responses occurred, the researchers discussed the appropriate code for a particular response until agreement was reached. The categories identified were then used to develop quantitative responses for inclusion in round 2. These are summarised in table 2, and focused on "Barriers to effectively treating neglected diseases of diseases of poverty", "Incentives for the private sector to invest in treating or curing neglected diseases", and "Barriers to successful implementation of an HIF scheme". Participants were asked to rate the importance of items in each category on a five point scale, (anchored by 1 ="not important at all" to 5="extremely important").

Barriers to effectively treating neglected diseases of diseases of poverty

A range of potential barriers were identified in round 1. In round 2, participants were asked to rate the extent to which they perceived each potential barrier to be important or unimportant to the treatment of neglected diseases (table 2)**.**

Table 2: Relative Importance of Potential Barriers to Treatment of Neglected Diseases and HIF

Issue	**Mean score (SE) N obtained across stakeholder sample in 2nd round of Delphi survey (n=25) ***	**Mean score (SE) N obtained across stakeholder sample in quantitative survey***
Barriers to effectively treating neglected diseases of diseases of poverty		
Current intellectual property rights systems	*3.1 (0.2)*	*4.3 (0.5)* ***78***
Lack of cohesion between different international funding initiatives	*3.3 (0.2)*	*4.5 (0.1)* ***79***
Poor sanitation	*3.5 (0.2)*	*4.5 (0. 1)* ***79***
Lack of diagnostic tools	*3.6 (0.2)*	*4.5 (0.1)* ***79***
Treatments take too long, shorter treatment regimes needed	*3.7 (0.4)*	*4.2 (0.1)* ***79***
Lack of political will (national)	*3.9 (0,2)*	*4.5 (0.1)* ***79***
Lack of treatments	*4.0 (0.3)*	*3.9 (0.1)* ***79***
Local health care infrastructure inadequate	*4.0 (0.2)*	*4.7 (0.1)* ***79***
Lack of priority spending on healthcare in the developing world economies	*4.0 (0,3)*	*4.6 (0.1)* ***79***
Lack of incentives for pharmaceutical companies to develop treatments	*4.1 (0.2)*	*4.5 (0.1)* ***79***
Cost of medicines (individuals cannot afford them)	*4.1 (0.2)*	*4.7 (0.1)* ***79***
National governments input into health care	*4.2 (0.2)*	*4.6 (0.1)* ***78***
Poor access to medicine	*4.3 (0.2)*	*4.7 (0.1)* ***79***
Lack of political will (international)	*4.3 (0.3)*	*4.8 (0.1)* ***79***
Incentives for the private sector to invest in treating or curing neglected diseases		
Facilitating Private Public Partnerships	*1.7 (0.2)*	*4.6 (0.1)* ***79***
Creation of new markets for pharmaceutical products	*1.8 (0.2)*	*4.4 (0.1)* ***79***
Create the potential for the industry to make profits	*1.9 (0.4)*	*4.5 (0.1)* ***79***
Economic compensation from international	*1.9 (0.2)*	*4.3 (0.1)* ***79***

governments and organizations.		
Ensuring respect for intellectual Property Rights	*1.9 (0.2)*	*4.0 (0.1)* ***79***
Encouragement and promotion by international governmental bodies	*2.1 (0.1)*	*4.3 (0.7)* ***79***
Compulsory corporate social responsibility	*2.5 (0.4)*	*3.5 (0.2)* ***78***
Voluntary corporate social responsibility	*2.9 (0.3)*	*3.6 (0.2)* ***78***
International governmental regulation/ resources allocation	*3.4 (0.5)*	*4.2 (0.2) 78*
Barriers to successful implementation of an HIF scheme **		
Developing country governments will not "buy in" to the scheme	*3.2 (0.3)*	3.17 (0.2) **77**
Lack of cohesion between (inter)national development policies and (inter)national research	*3.3 (0.2)*	4.3 (0.1) **77**
Uncertainty about the potential risks, costs and benefits to industry	*3.4 (0.3)*	4.2 (0.1) **76**
The HIF scheme does not deal with information and education of the healthcare chain (including patients and communities)	*3.4 (0.4)*	3.4 (0.1) **77**
Uncertainty about resources required to operationalise an HIF	*3.4 (0.2)*	4.4 (0.1) **76**
The "patent problem" is not adequately resolved	*3.4 (0.5)*	3.8 (0.2) **77**
Uncertainty about the potential size of financial incentives for industry	*3.5 (0.2)*	4.2 (0.2) **77**
Problems with interactions between donor organizations and industry	*3.5 (0.4)*	3.9 (0.2) **77**
Methods for effectively measuring impact are not available	*3.6 (0.3)*	3.7 (0.2) **77**
Difficulties in raising funding from international organizations	*3.8 (0.3)*	4.3 (0.1) **77**
Difficulties in raising funding from national governments	*3.8 (0.3)*	4.5 (0.1) **77**
The HIF scheme does not deal with diagnosis methods and facilities available locally	*3.9 (0.4)*	4.3 (0.1) **76**
The HIF scheme does not deal with drug distribution systems to remote areas	*3.9 (0.4)*	4.5 (0.1) **75**
Lack of cohesion between (inter)national development policies and (inter)national research agendas	*3.9 (0.3)*	4.3 (0.1) **77**
Developed country governments "buying in" to the scheme	*4.3 (0.1)*	3.6 (0.1)**77**
The HIF scheme does not deal with available healthcare personnel locally	*4.3 (0.5)*	4.4 (0.1) **76**
Industry will not "buy in" to the scheme	*4.4 (0.4)*	*4.1 (0.1) 77*
Lack of adequate funding at the start of the scheme	*4.4 (0.3)*	*4.4 (0.1) 77*
The HIF scheme does not deal with "end of pipe"	*4.9 (0.6)*	*4.4 (0.1)* ***75***

problems		

*Participants were asked to indicate the extent to which they agreed or disagreed that each of the items identified in round 1 of the Delphi survey (italic) contributed to the main question indicated in the Bold header on a 5 point scale, anchored by 1=agree totally, 5=disagree totally.
** Note reversed "direction" of scales

All the potential barriers were rated as at least slightly important (table 2). The barriers rated as being most important included *lack of political will* (national and international), *the cost of medicines*, *local infrastructure problems*, and *lack of innovation in the pharmaceutical sector targeting diseases of poverty*. Of these, perceived *lack of cohesion between different national funding initiatives* is worth mentioning, as this relates to the development of more efficient and harmonised strategies utilising existing resources, rather than the allocation of new resources to the problem of neglected diseases.

Incentives for the private sector to invest in treating or curing neglected diseases

Issues identified in round 1 as relevant to incentivising the private sector to invest in treating or curing neglected diseases are summarised in Table 2**,** *Incentives for the private sector*. In round 2 agreement with the relevance of all of the issues identified in round 1 was, on average, above the mid-point of the rating scale. The highest importance ratings were associated with *international government regulation* (tied to resource allocation), and *corporate social responsibility* (either voluntary or compulsory). Greatest agreement focused on *profitability* (including, for example, *the development of new markets, respect for intellectual property rights,* and *industry compensation*). Participants also agreed that the potential to *develop effective public–private partnerships* would incentivise industry to direct pharmaceutical innovation activities to the treatment of neglected diseases.

Barriers to successful implementation of an HIF scheme

In round 1, participants were asked to provide qualitative responses to identify potential barriers to successful implementation of an HIF scheme. The different barriers are summarised in table 2. In round 2 all of the barriers were rated as being important barriers to implementing the scheme. The most important barrier related to "*end-of-pipe*" delivery of pharmaceuticals. "Buy-in" (for example, by stakeholders, including industry, and developing country governments) was also regarded as potentially problematic, as was having sufficient resources allocated at the start-up of the scheme.

Measuring the impact of an HIF scheme

Health impact is the basis for payments from the scheme. At present, QALYS have been identified as the potential metric by which health impact could be measured following health interventions. In round 1 of the Delphi, participants were asked to suggest alternative measures which could be used to metricise health impact. Most participants had problems in identifying appropriate metrics, although the following were

mentioned. "New measurements specific to the context of developing countries", "Morbidity" (depending on the disease)", "Percentage of treatable diseases currently untreated", "Mortality (depending on the disease)", Relapse (depending on the disease), "Consumer uptake of pharmaceutical products", "Socio-economic potential (of country) improved or restored", "QALYS", "DALYS", and "Preference-based measures (used in conjunction with QALYS)". In round 2 of the Delphi, participants were asked to rate the extent to which they agreed or disagreed that each of the measures identified would represent an appropriate metric for assessing health impact. Of all the alternatives, the need to develop new metrics "specific to the needs of developing countries" was rated most positively, although many participants responded that they had no opinion regarding this issue, suggesting considerable uncertainty regarding this issue across the stakeholder group. The ability to effectively metricise health impact is an essential element of the scheme, insomuch as pharmaceutical payments from the scheme are contingent on measurable impact. The (lack of) specialist knowledge required to test and validate appropriate metrics of health impact may also have resulted in participant uncertainties in responding. It is important to investigate whether using multiple measures (including developing country specific measures) and triangulating the results is regarded as the most appropriate approach by stakeholders. This may be particularly relevant if the HIF is to include pharmaceutical delivery in developed, as well as developing countries, as Health Impact Measures may not be equally sensitive in different socio-cultural and health service provision contexts. Despite this, common metrics must be included in an assessment battery to enable comparative analysis between the developed and developing world.

Other issues relevant to the implementation of an HIF scheme

In round 1, participants were asked to identify other issues relevant to the implementation of an HIF scheme, and these were coded as before by two researchers. In round 2 of the Delphi, (table 2), the highest level of agreement was obtained regarding the need to develop an "inclusive governance structure for an HIF scheme," involving all major stakeholders, the "need to focus on diseases other than Malaria, HIV and tuberculosis," and the need to "develop local capacity and capability in health care". Participants also agreed that there was a need to pilot and further refine an HIF scheme before it could be "rolled out".

In the first round, considerable disagreement was identified regarding the extent to which participants perceived that "current IPR systems acted as a disincentive for developing treatments or cures for diseases of poverty." The question was again asked in the second round, (participants rating their agreement or disagreement with the statement on five point scales anchored by "agree completely" to "disagree completely"), and participants were asked to explain their answers using open-ended responses. Around 26% indicated agreement and 43% disagreement with the statement, the rest neither agreeing nor disagreeing, or indicating that they had no opinion regarding this issue. The groups did not differ in opinion based on whether they worked in a particular sector with each view being held by stakeholders from different sectors. Inspection of the qualitative responses indicated a wide range of potential reasons for this lack of consensus, varying from the need for IPR to incentivise innovation, through to overestimation of the role of IPR in treatment development.

For example:

> *"'Not patentable' products do not get developed because the financial incentives do not exist"*
>
> *Director of policy, health organization, UK.*

> *"I think the influence of IPR is slightly overestimated…it is possible to respect IPR and develop more treatments for neglected diseases"*
>
> *Academic, the Netherlands*

The extent to which protection of IPR acts as a potential barrier to the treatment of neglected diseases has not been resolved by the Delphi study.

An HIF scheme would provide an incentive for commercial companies to develop cures not treatments

In the first round, considerable disagreement was identified regarding the extent to which participants perceived that an HIF scheme would provide an incentive for commercial companies to develop cures rather than treatments. The question was again asked in the second round, (with feedback about first round responses). Around 50% of the participants agreed with the statement in the second round, the remainder neither disagreeing or disagreeing, or expressing no opinion. Disagreement tended to be linked to uncertainties associated with the financial mechanisms underlying the scheme.

> *"To be a true incentive for research, a mechanism such as HIF should provide clear visibility on possible financial compensations at a very early stage in the design of an R and D project"*
>
> *Pharmaceutical company, Vice President, France*

Participants who agreed that the scheme would act as an incentive tended in contrast, to present arguments associated with increased certainty of reward mechanisms.

> *"If the health impact is captured well, a medicine that cures AIDS, for example, would be given the same value as 10 or 15 years of chronic AIDS treatment. It would be a lot more convenient for companies to receive a reward for providing one treatment, than to receive exactly the same reward* for *providing treatment during 15 years".*
>
> *Academic researcher, international*

> *"Treatment may be more attractive to commercial companies as they are likely to sell more of a treatment product rather than a cure"*
>
> *Research funder, Director, UK.*

Would an HIF scheme primarily benefit developing, as opposed to developed, countries?

In round 1, considerable disagreement was identified regarding whether the primary beneficiaries of an HIF scheme would be in developing, as opposed to developed, countries. The question was again asked in round 2, with provision of feedback from open ended responses from round 1. In round 2, 77% of participants agreed that the benefits of an HIF scheme would apply primarily to developing countries, and so this was treated as a (marginal) consensus agreement. This change in agreement between the two rounds of Delphi is significant and is attributed to the impact in round two of feedback from round 1, which argued convincingly for the funding of the HIF to be primarily applicable to innovation in developing countries and demonstrates the utility of the Delphi approach in expert consultation.

STUDY 2 – QUANTITATIVE SURVEY

A final quantitative survey was carried out, based on the outcome of the two-round Delphi study. The Delphi study was effective in identifying and refining those issues that need to be tested in order to see if the development and implementation of an HIF is viable including certain changes of focus from the scheme as originally devised such as its applicability to health system innovations and developing countries. The purpose of the quantitative study was to validate the results from the Delphi study in a larger sample of high-level experts across a broader range of countries and organizations, who may not have been in a position to commit the time to participate in the qualitative Delphi rounds.

This final survey was conducted using Survey Monkey™ in January 2011. A total of 697 potential participants were sent a personalized email invitation to participate in the survey. The letter of invitation included a brief explanation of the Health Impact Fund, a link to the online survey and links to other documents which provided more in depth information on the HIF concept, using the same materials as for the Delphi study. The questionnaire itself was identical to the Delphi survey round 2 for the items included. Not all responses are reported here for reasons of brevity, and the focus of the results section will be on quantitative items relating to "barriers to fighting neglected diseases or diseases of poverty", "incentives for the private sector to invest in treating or curing neglected diseases", and "barriers to successful implementation of an HIF scheme." A copy of the invitation letter, accompanying documents and questionnaire are provided in Annex 3.

Results of Study 2

The survey sought to draw on the views of key actors in the area of global health, together with those having high level experience and expertise in the field. Six hundred and ninety-seven prospective participants received personal invitations and of these 84 (12%) responded by completing the questionnaire. While low, this response rate is appropriate to validate the results of the Delphi, and is not unusual for expert surveys of this type[10]. A good gender balance was achieved with 44.7% of the participants being female and 55.3% male. 27 Countries and the European Commission were represented and of the 84 participants, 30% were at President, CEO or director level in their organization, 21% at professorial or senior academic level, 20% were Departmental

Heads or Senior Advisors, 9% were at managerial level and 4% at Ministerial or UN Ambassador level. Thus 84% of participants indicated they had a high level of responsibility or expertise in areas highly relevant to the HIF (Table 3).

Table 3: Professional affiliations of participants in quantitative survey by sector

Stakeholder Sector	**Number of Respondents**
Academic	29
Development Agency	4
Health Insurance	1
International Organization	20
IPR (intellectual property right) Law	1
National Government	4
NGO (Non-governmental oranizations)	13
Patient group	2
PDP (product development partnerships)	4
Pharmaceutical Industry	2
Regulatory and Ethics	1
Not identified	3

Academics, international organizations and NGOs were overrepresented relative to other sectors. Sixty-two percent of participants were in the 46-65-age range, reflecting the more senior levels at which most respondents were employed within their organizations.

Survey results

There was a high level of support for the HIF in principle, although there was consistent agreement that there are many important barriers to be overcome. There was also high level of agreement that an HIF should be piloted, suggesting that, although there was strong support for the scheme among stakeholder groups, the details of the scheme need to be tested and further refined.

Table 4: High Levels of Agreement

High Levels of Agreement that:	"Special Measures" should be adopted to tackle neglected diseases	An HIF would facilitate the formation of Public Private Partnerships	An HIF should be piloted	Pharmaceutical inventions should be eligible for HIF payments
Agree %	97	92	90	79
High levels of agreement that:	Health system innovations should be eligible for HIF payments	An HIF would incentivize the industry to develop tools to fight diseases of poverty	An HIF should take distribution systems and whole pipeline delivery into account in impact measurement.	An HIF would incentivize industry to develop cures rather than treatments
Agree %	78	77	75	66

However, there was disagreement or uncertainty on a number of points.

Table 5: Areas of Disagreement

Areas of disagreement	Agree %	Disagree %	No opinion %
An HIF should be available for diseases in developed as well as developing countries	42	46	10
Believe their organization would support an HIF	49	16	35
Would industry "buy in" to the scheme	42	16	42

The participants were asked to rate the extent to which they agreed that the different barriers to fighting neglected diseases or diseases of poverty identified in the Delphi study were important (scales as for the Delphi survey). The results are summarized in Table 2. As for the Delphi study, average agreement for all of the barriers was greater than the midpoint of the scale. This lends credence to the robustness of the Delphi process in identifying important barriers. Amongst the most important were lack of political will to deal with the issue, poor access to medicines, cost of medicines, inadequate local healthcare infrastructure, and lack of national government spending on

healthcare in developing countries. Of relevance to the proposal for an HIF is the finding that lack of treatments (i.e. treatments did not exist) was considered an important barrier. Although it ranked last in importance of 14 barriers in the stakeholder survey, given that all barriers were, on average, rated as being important, it arguably makes little sense to pay too much attention to ranking or prioritizing, and further significance testing was not applied. Levels of agreement with the types of incentives available to industry identified in the Delphi study were also high (Table 2).

Participants also answered questions focused on perceived barriers to implementation of the health impact fund, again indicating the extent to which they agreed of disagreed with barriers identified in the Delphi survey (Table 2). Again there were reasonable levels of agreement between the issues identified by the Delphi process and the levels of agreement in the survey regarding their relevance. The most important barriers to the success of an HIF are perceived as relating either to uncertainty about adequate funding provision for an HIF and the HIF not dealing with 'end of pipe' issues. This was supported by some of the comments provided in the free comments section. For example

> *"The need to address healthcare systems in developing countries, especially the need to increase healthcare and equity of access to services and social support are essential. The availability of "cheap" drugs cannot be expected to drive healthcare allocations by governments."*
>
> *President – NGO*

> *"The absence of infrastructure to deliver care far outweighs barriers of cost to appropriate technology for the setting".*
>
> *CEO - International Organization*

Although establishing effective impact measures did not have the highest level of agreement in the quantitative study it emerged as an important concern in the free comment section. For example,

> *"The greatest challenge will be measuring 'health impact'. For those populations which are the most important target for the HIF, the available systems for measuring health status are the weakest in the world and therefore the problem of measuring a change in that status is enormous. Unless this is explicitly and very adequately addressed, it will be difficult to convince the main constituencies - donors, recipient countries and, most of all, the private sector - of the viability of the scheme."*
>
> *NGO participant*

> *"I know you have considered the difficulty in measuring health impact. DALYs seem a problematic choice, particularly because of all the subjectivity involved in weighing disability, and the problem with the value of life at different stages. On the other hand, even*

accepting it, data is not available for every country, so results would be biased."

Academic participant

In addition, concerns were raised about how incentivization would in practice, relate to health impact assessment.

"Incentives are critically important. It is difficult to get the balance right, in terms of incentive levels and conditions that need to be met to receive incentives."

Manager, International Organization

DISCUSSION

There was participant agreement regarding the need for an HIF fund, and consensus that such an approach would facilitate the treatment of neglected diseases. However, some issues needed to be addressed if the final implementation was to be successful. In particular, participants were uncertain as to whether the size of the fund, and the health impact measure(s) to be used as the basis for payments from the fund, were appropriate. This is not surprising as many people not directly involved in pharmaceutical research will have little idea of the magnitude of research costs. However a realistic size for the fund needs to be further thought through and tested. It is also essential to pilot the utility of existing and other metrics, such as Quality Adjusted Life Years (QALYs) or Health Adjusted Life Years (HALYs) type approaches or country specific metrics, in order that a system of impact measures fit appropriate to the scheme be developed. In addition, participants indicated that various barriers (in particular related to stakeholder "buy-in") needed to be overcome if the fund was to be implemented successfully. Concerns related to the focus of the HIF were also identified. For example, participants indicated that the focus of the HIF should extend beyond the "big three" (HIV, malaria, and tuberculosis). It may therefore be more appropriate for on a particular disease of developing countries (such as schistosomiasis or leprosy) which already has a treatment available in developed countries but which is not readily accessible in the developing world and for which an impact assessment might be readily developed. It may then be more appropriate, following such pilot studies, to roll-out the scheme to one or more of the "big three" diseases, and extend to other areas of health. The results also suggest that innovations in pharmaceutical development alone are unlikely to significantly reduce disease incidence, particularly in developing countries, unless they are linked to "end of pipe" measures such as capacity building and further innovation in local health delivery infrastructures. A question then arises as to whether the latter should also be eligible for reward payments in an HIF. Concerns were also raised as to whether the scheme might potentially divert funding from other related research, While the majority of respondents were of the opinion that an HIF would have a positive effect on the efforts of international organizations through collaboration and coordination, and addressing the issue of affordability and supply of medicines for the developing world, some did express concern that an HIF might be an additional demand on a finite funding "pot" and as a result detract from existing programmes funded by

international and national bodies, and other funders. Further work on a cost-benefit analysis may be needed in this regard.

Several issues have been highlighted that merit further discussion. Delivery of pharmaceuticals to end-users in developing countries, the development of efficacious local health service infrastructures, and the development of "political will" (both local and international) are also important elements in optimising health outcomes. However the focus under the current IPR system is on rewarding research delivering the development of new pharmaceutical treatments rather than research on the development and innovation of existing health related-structures and services. Against this, however, in terms of overall impact on population health in developing countries, it is well-established[17] that in most cases improvements in health care delivery is likely to have a bigger effect than the implementation of a new pharmaceutical product. For example, in many developing countries only a minority of the population have access to modern healthcare treatment. In addition, limitations in the capacity of medical staff available to provide health services may mean that by no means all patients receive either the correct diagnosis or an effective management of their treatment. These factors all affect any attempt at reduction of disease burden and reduce the overall impact of any new pharmaceutical intervention. For example, supposing a pharmaceutical company develops a new product for a disease where the original intervention was effective in 50% of the cases treated while the new product is 90% effective, this will not lead to the disease incidence being reduced by a health impact of 80%. Even assuming there is no shortage of product available, if only 35% of the population have access to medical care and only 65% of those receive a correct diagnosis, and therefore the new product, and if the treatment is only managed effectively for 75% of the patients, then there will only be an improvement in population health (impact) of around 7% over the old product. However if at the same time the pharmaceutical company could also improve capacity for diagnosis and management to say 75% and 85% respectively then the health impact for the same product would increase to around 12% over the old product. Improving population access to health care would have an even more dramatic effect on health impact. Combining development of a new pharmaceutical product with a reduction of exposure to the disease would also increase impact significantly; a good example of this has been the provision of bed-nets alongside malaria treatment or prevention. The results of the Delphi survey confirm this view by suggesting that the development of an effective health impact measure is likely to register optimal improvements in health if both novel pharmaceutical development and local health service, and infrastructures issues are considered. However, including both in the proposed HIF may result in a scheme which is too complex and difficult to implement.

Some limitations of the Delphi study need to be mentioned. The first relates to the representativeness of participants in terms of geographical and institutional affiliation. By no means all countries in the world were represented and participants from developing countries and industry were under-represented. Also, although invited, no IPR lawyers or individuals from regulatory bodies and patient groups chose to participate. While their contribution may have brought some additional perspectives it is unlikely that this would have made a significant difference to the consistency of views expressed on many of the key issues by participating stakeholders across a wide range of interests. It should be made clear that the Delphi study asked for individual comments and people responded as individuals, giving their own opinions as experts but not

necessarily the opinions of their organization and so did not act as national or organizational representatives. The key results of the Delphi study were assessed through the quantitative survey, and no major discrepancies or differences between the Delphi results (which focused on identifying the key issues) and the quantitative survey were found. This suggests that the Delphi process was a good predictor of stakeholder concerns associated with the HIF, and this indeed has been supported in other policy areas (see for example, Frewer et al,2011). Furthermore, while the gender balance for the Delphi study was predominantly male (85%), that of the quantitative survey was much more equitable with almost 45% female participants. However as the outcome of both studies was very similar it suggests as expected, that the gender of experts has little or no effect on their opinion in this area. In addition, the quantitative survey could not be said to be representative of all interested stakeholders, as the number of countries and sectors represented was not inclusive. Despite this, it is arguable that the high level of agreement with the key issues presented, suggests that these factors will be important. Furthermore, although the original experts for the first round of Delphi were recruited in 2009, results from the study continued to be gathered until 2011. Much has been written both for and against the HIF concept and the Delphi study itself may have had some impact on developing opinions by bringing the scheme to the attention of the high level experts who participated in the study. There does appear to be growing support for at least pilot studies of a HIF scheme from entities such as The Global Fund, international organizations such as WHO, and some national political entities, particularly in Germany and Canada[18,19].

Given the general level of support for the HIF scheme, it is necessary to translate the results of this study into concrete and actionable policy recommendations. The following are clearly important in this respect.

PILOT STUDIES

Pilot studies are needed to test the validity of all the barriers identified and whether these can be overcome. There also remains lack of clarity as to the impact assessment measures that would be most appropriate. As there is some support for the possibility of country or disease specific impact assessment metrics, more than one pilot study would be needed to assess different measures. As a consequence, a series of pilot studies should be developed and costed.

Practical financial support should be secured from key stakeholders to fund the pilot studies to test the concept. Potential funders could include the European Commission's DG DEV and DG RTD, USAID, The Global Fund, UNDP/WHO, National development aid funders e.g. DFID, BMZ etc., and the pharmaceutical industry. It is suggested that, because of the high level of industrial commitment required to successfully implement the HIF scheme, the involvement of at least two or more pharmaceutical companies at the pilot stage would be essential, would encourage the necessary industry "buy-in" to the scheme, and ensure that its objectives align with industry objectives.

DEVELOPMENT OF A ROAD MAP

Results from the pilot studies could give rise to a Road Map (perhaps in conjunction with the Global Fund and WHO) demonstrating how the HIF would be implemented

and how the potential barriers would be overcome. This road map could be used to demonstrate the potential advantages of the scheme to all interested stakeholders, as well as provide evidence of the practical applicability of the scheme regarding its future operationalization.

CLARIFICATION OF THE CURRENT HIF SCHEME

The current proposal for an HIF scheme does not distinguish between diseases of poverty and chronic diseases of the developed world, nor does it envisage HIF rewards being allocated to health system innovations but focuses instead on pharmaceutical innovation. However, because of the high level of stakeholder support for an HIF to take into account health system and other end-of-pipe issues, it is essential for the HIF to clarify whether it sees its objective primarily to develop a mechanism for encouraging the pharmaceutical industry to develop products for neglected diseases or whether it's primary objective is to reduce the global burden of disease. These two objectives are very different and where the focus of an HIF lies will determine not only the scheme infrastructure, the nature of the pilot studies and the practical operationalization of the scheme but will also impact on the level of support from different stakeholder sectors. Thus it will be essential for any HIF scheme that is to be implemented to be clear on its focus and whether it will make any distinction between rewarding health impacts on diseases of poverty and diseases of the developed world. For diseases of the developing world, the biggest health impacts are likely to result from health system innovation leading to better prevention and better delivery of medicines rather than simply the discovery of new pharmaceutical products. The most significant health impacts will be achieved by health system and pharmaceutical innovations working together. The HIF scheme must therefore be clear on whether and to what extent health system innovations, either alone or in conjunction with pharmaceutical innovation will be eligible for HIF rewards and impact metrics must be developed that are able to take account of this.

CONCLUSIONS

The results of the two studies suggest that there is considerable stakeholder and end-user support for an HIF scheme in principle, although some practical difficulties will require resolution prior to implementation of an HIF. These include the focus of the scheme (in terms of diseases included, size of the scheme, appropriate and effective metricization of health impacts, and whether the HIF should include other health interventions over and above pharmaceutical developments). Potential diversion of funding from other initiatives was also perceived as problematic, and would need to be considered through an effective international harmonization of funding practices. Most people agree that an HIF would incentivise industry to greater involvement in fighting neglected diseases and diseases of poverty, and increase collaboration with the public sector. There is strong support for an HIF to be piloted and this is also regarded as a precondition to full implementation in order to validate and refine operationalization of the HIF scheme. Despite this overall support, there remain serious concerns about potential barriers to successful implementation of an HIF. Therefore practical support

and funding to implement an HIF may not be forthcoming unless policy-makers, funders and industry can be convinced that these barriers can be overcome.

ANNEXES
ANNEX1 - Copy of invitation to participate in Delphi study and Questionnaire for Round 1

ANNEX 2 – Copy of questionnaire for Delphi study Round 2

ANNEX 3 – Copy of invitation to participate in Quantitative Survey and copy of Quantitative Survey questionnaire

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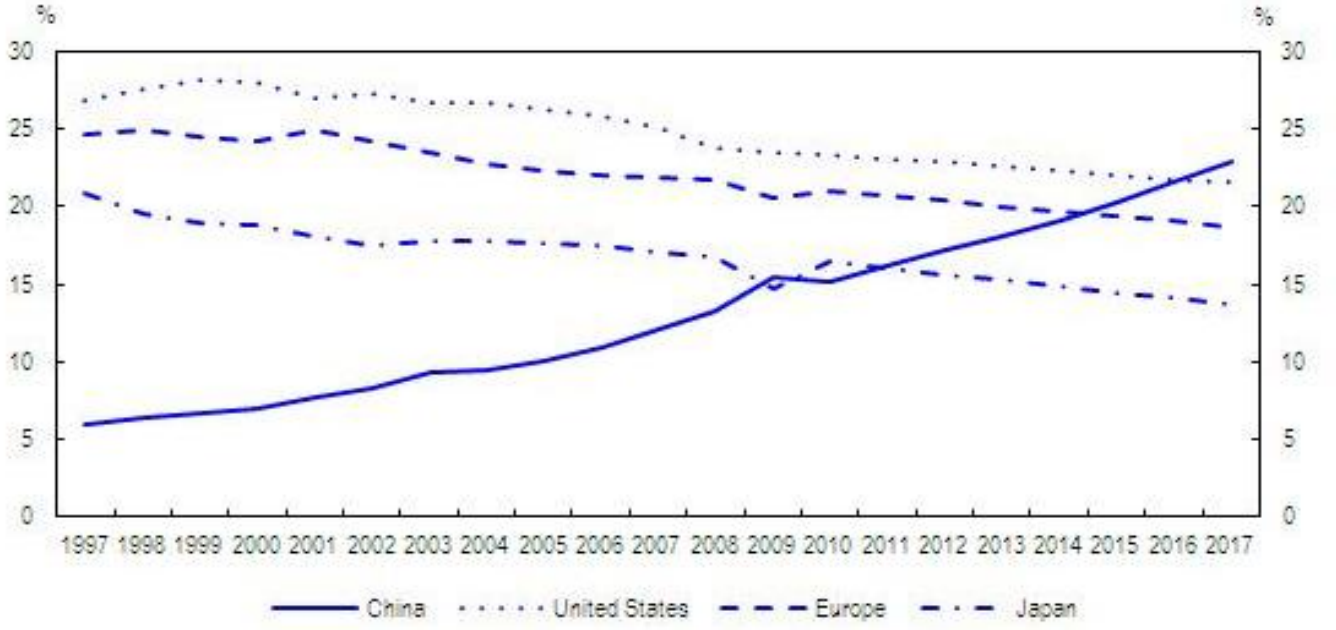
Figure 1: Shares in world manufacturing value-added at constant 2000 market prices, comparison of China, United States, Europe, and Japan



Source: World Development Indicators; OECD estimates for 2009 and later.

FIGURE 2: CHINESE HEALTH SYSTEM FOR DISEASE CONTROL

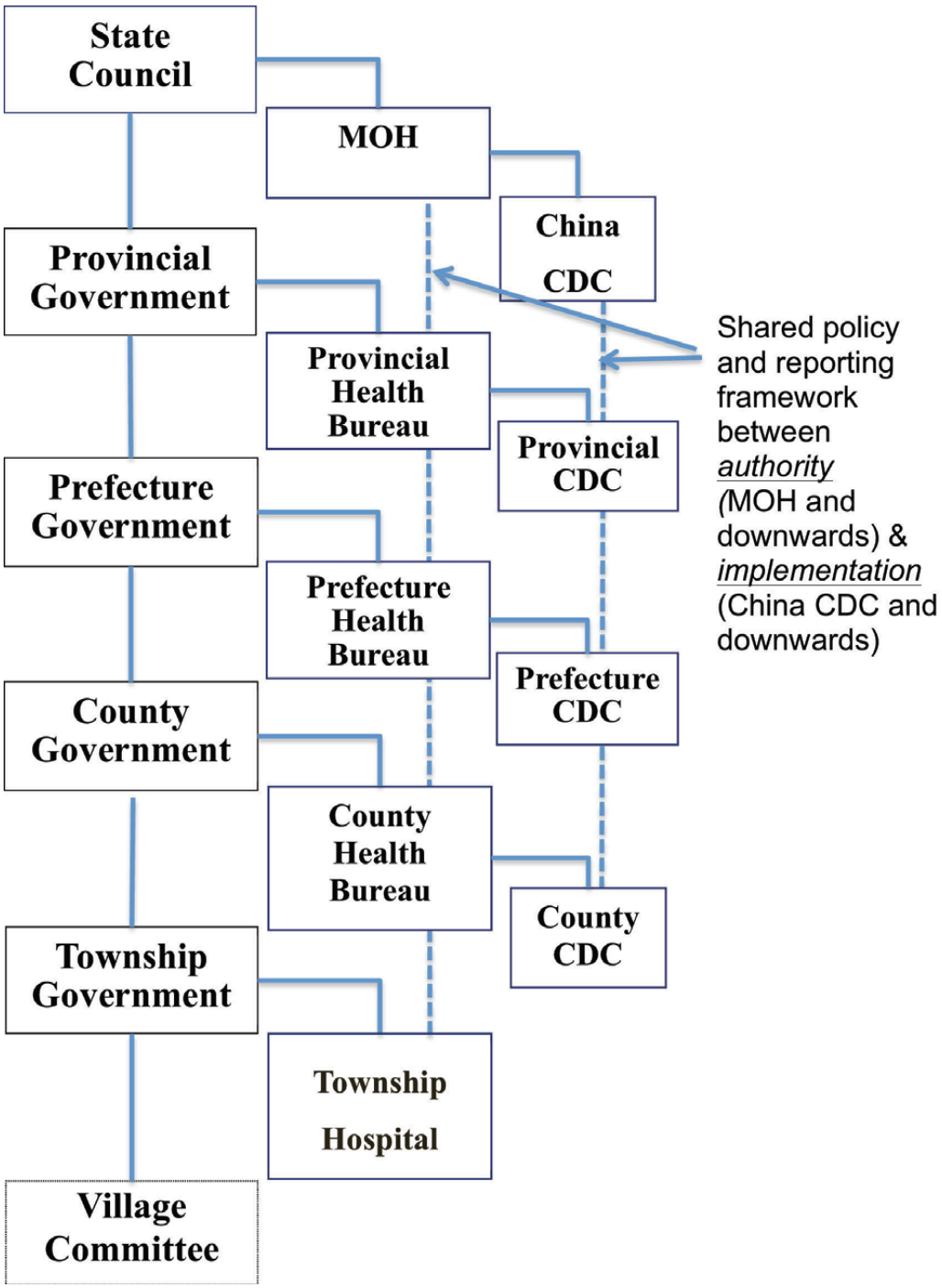


FIGURE 3: CHINESE MEDICAL TEAMS SENT TO AFRICAN NATIONS, YEAR, SENDING CHINESE PROVINCE, RECEIVING AFRICAN COUNTRY (1963-1989)

1963	Hubei Province	Algeria
1964	Jiangsu Province	Zanzibar
1965	Jilin Province	Somalia
1966	Liaoning Province	North Yemen
1967	Tianjin	Congo
1968	Zhejiang Province	Mali
1968	Shandong Province	Tanzania
1968	Heilongjiang Province	Mauritania
1968	Beijing	Guinea
1970	Anhui Province	South Yemen
1971	Shaanxi Province	Sudan
1971	Guangdon nea	Equatorial Guina
1973	Hunan Province	Sierra Leone
1973	Jiangxi Province	Tunisia
1973	Hebei Province	Democratic Republic of Congo (former Zaire)
1974	Henan Province	Ethiopia
1974	Shanxi Province	Togo
1975	Shanxi Province	Cameroon
1975	Fujian Province	Senegal
1975	Gansu Province	Madagascar
1975	Shanghai	Morocco
1976	Guangxi Province	Niger
1976	Sichuan Province	Mozambique
1976	Sichuan Province	Sao Tome and Principe
1976	Beijing	Burkina Faso
1976	Guizhou Province	Guinea-Bissau
1976	Liaoning Province	Kuwait
1977	Tianjin	plus canopy
1977	Guangdong Province	Gambia
1978	Ningxia autonomous reg	Benin
1978	Henan Province	Zambia
1978	Zhejiang Province	Central Africa Republic
1981	Fujian Province	Botswana
1981	Shanxi Province	Djibouti
1982	Inner Mongolia Autonor	Rwanda
1983	Yunnan Province	Uganda
1983	Beijing	Libya
1984	Sichuan Province	Cape Verde
1984	Heilongjiang Province	Liberia
1985	Hunan Province	Zimbabwe
1985	Shandong Province	Seychelles
1986	Qinghai Province	Burundi
1989	Jiangxi Province	Chad

Source: X. Ping, "Chinese medical teams," *Xinhua (Chinese news service)* 2005.

Link: http://news.xinhuanet.com/ziliao/2009-04/13/content_11178783.htm

FIGURE 4: OFFICIAL DEVELOPMENT ASSISTANCE FROM ALL DONORS TO AFRICA IN U.S.$1960-2011[4]

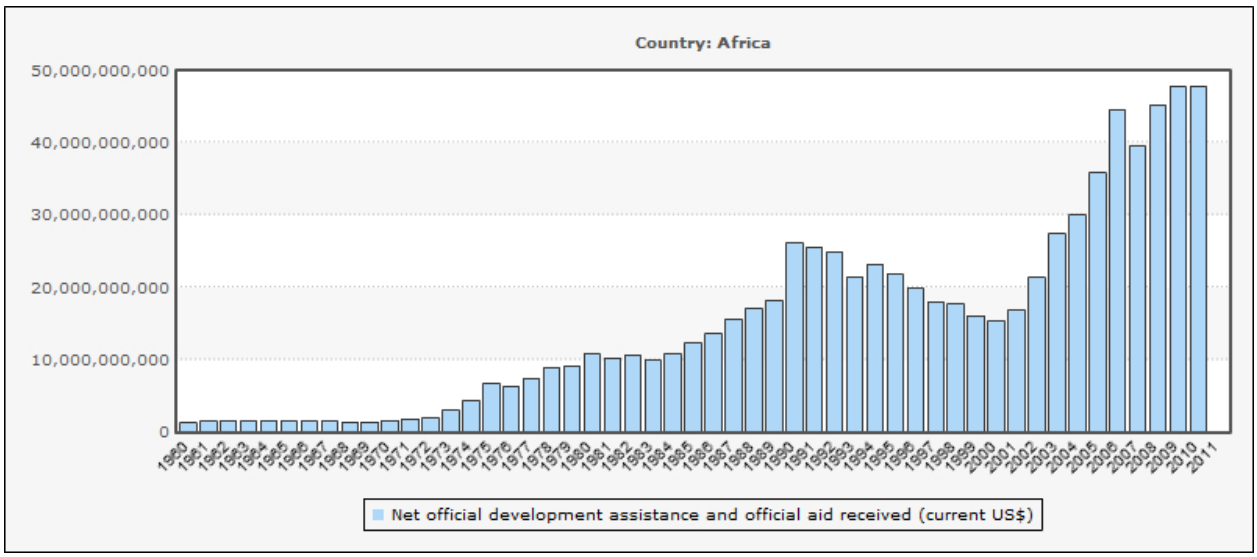


FIGURE 5: OFFICIAL DEVELOPMENT ASSISTANCE TO AFRICA FOR HEALTH FROM ALL DONORS, COMPARED WITH U.S. ASSISTANCE TO AFRICA, 1960-2010[4]

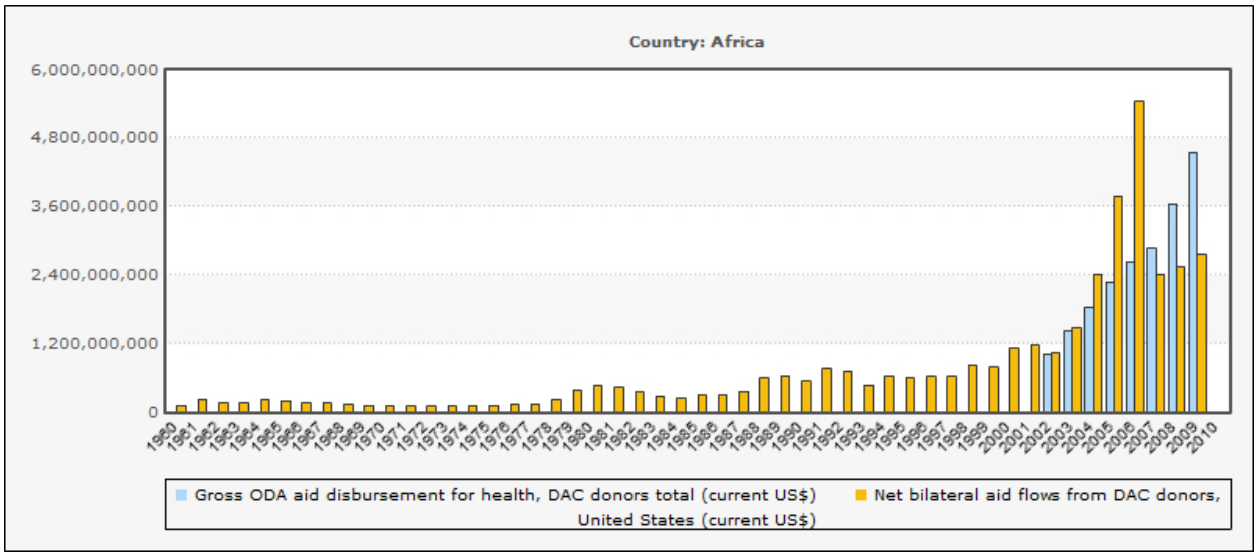
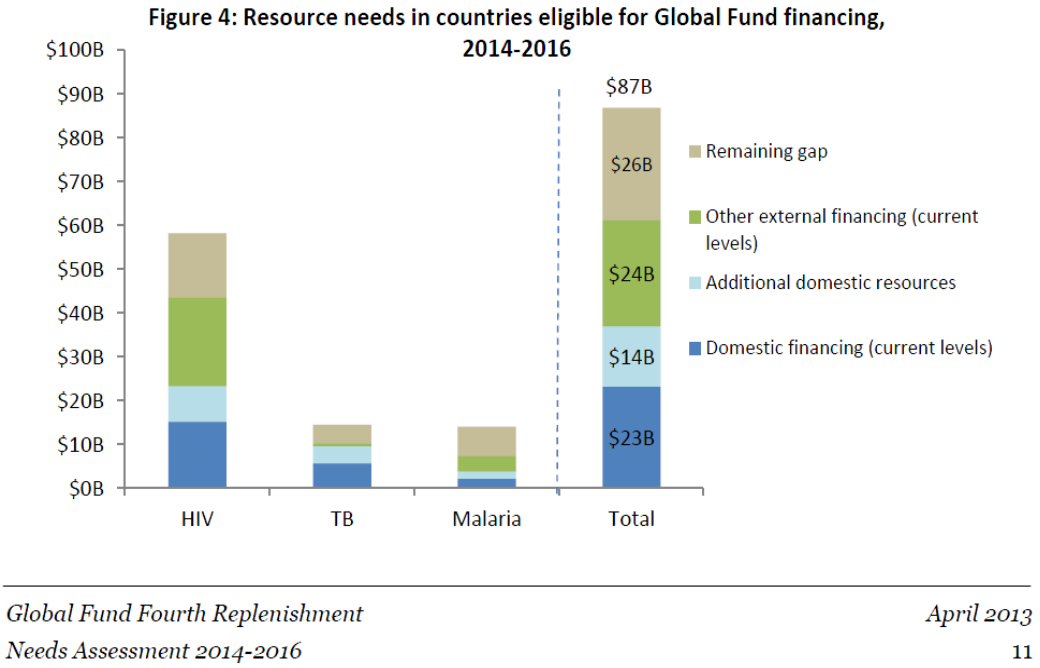


Figure 6: Resource needs in countries eligible for Global Fund financing 2014-2016



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