Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:

Antibiotics Innovation Funding Mechanism (AIFM).

2.* Submitted by:

Knowledge Ecology International

3.* Target disease or health condition:
(Focus on type II and III diseases and special R&D needs of developing countries in type I diseases where there is an identified health technology gap.)

This proposal focuses on addressing antibiotic resistance, which is a critical threat that affects the treatment of type I, II and III diseases.[1]

Cases of infections from antibiotic-resistant strains of bacteria are growing and resistant bacteria are causing significantly decreased efficacy in the newest generations of antibiotics. Infections caused by bacteria are widely prevalent illnesses and include tuberculosis, meningitis, cholera, and typhoid fever, many of which are widespread in developing countries. As access to antibiotics has improved in developing countries, new challenges have arisen as resistance to those antibiotics is increasing. In a 2010 book on antimicrobial resistance in developing countries, Sosa *et al.* highlighted the challenges faced by developing countries (as contrasted with developed countries) regarding antibiotic resistance,

> "Growing resistance to antimicrobial agents began to take away more and more of the cures that the agents had brought. It then proved to be much more resource-intensive to keep patients from becoming infected with and failing treatment for drug-resistant bacteria than it had been to deliver the drugs that had caused the problem. Resource-limited countries that had managed to make antimicrobials available to their infected patients could not afford to do all the things that were then needed to manage the antimicrobial resistance that resulted."[2]

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[1] Center for Disease Control and Prevention. "Antibiotic Resistance Threats in the United States, 2013." US Department of Health and Human Services. September 2013. World Health Organization. "Antimicrobial Resistance." Fact Sheet No.194. May 2013. http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed 25 Oct 2013. Sosa, A., Byurugaba, D., Amabile-Cuevas, C., Hsueh, P., Kariuki, S. and I. Okeke. *Antimicrobial Resistance in Developing Countries.* New York: Springer. 2010.

[2] Sosa, A., Byurugaba, D., Amabile-Cuevas, C., Hsueh, P., Kariuki, S. and I. Okeke. *Antimicrobial Resistance in Developing Countries.* New York: Springer. 2010. Pg. v.

4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)

Development of new antibiotic drugs.

5.* Project summary: *(Approximately 500 words)*

Introduction

There is a high level of awareness of the exigent need to develop new antibiotic drugs, and also the fact that antibiotic drugs present unique challenges for both innovation and use, including in particular the need to reconcile developer incentives with the conservation of the resource.[3]

The proposed project would test a new open innovation business model for the development of antibiotic drugs. The project would have two stages of implementation. The first stage would involve the creation of a new governance structure, initial funding commitments, and the adoption of initial policies and norms, and the use of grants and innovation inducement prizes to stimulate innovation. The second stage would involve the implementation of a new fee or tax on the use of antibiotic drugs, with the revenue from the fee or tax used to partly or completely fund the grants and innovation inducement prizes, and to discourage low value uses of antibiotic drugs that generate significant negative externalities.

Taken together, the project would replace the current system of temporary monopolies as the reward for the development of new drugs, with a new system with the following features:

- The creation of new financial innovation incentives that are de-linked from drug prices.
- The elimination of perverse incentives for drug developers to promote inappropriate or low value use of drugs, particularly where there are significant negative impacts on the conservation of the antibiotic resources.
- The creation of economic incentives to induce the open sharing of knowledge, data, materials, and technology relevant to the development of new products.
- The competitive production of generic supplies of products at affordable prices.
- The transfer of technology to drug manufacturers in developing countries.
- Opportunities for researchers, institutions and both small and large businesses to participate as suppliers of innovations, in both developed and developing countries.
- A sustainable system of financing for open source development of new antibiotics.

[3] An appendix briefly compares the AIFM to other proposals to stimulate innovation and conservation of antibiotic drugs, including (1) longer or infinite patent terms, (2) transferable (wild card) patent extensions, and (3) recent proposals for special prize type subsidies designed to induce both innovation and changes in company marketing practices.

Mechanics

An Antibiotics Innovation Funding Mechanism (AIFM) is created. In Stage 1, the AIFM provides a combination of grants and innovation inducement prizes. (Elaborated in answer to question 7).

Among the innovation inducement prizes are (1) end product prizes, (2) interim results prizes, and (3) open source dividend prizes that reward the open sharing of knowledge, data, materials, and technology relevant to the development of new antibiotic drugs.

The AIFM would operate under policies that condition grant and prize money to the licensing of rights in inventions, data, and other intellectual property. These rights would be managed according to policies set out by the public sector entities providing funding for the grants and prizes (See answer to question 15).

In Stage 2, the AIFM would be engaged in the development of multilateral norm setting as regards the levels of funding for the innovation grants and prizes, the implementation of a system of fees or taxes on the use of antibiotic drugs, and the norms and objectives as regards the conservation of antibiotic drugs. (See answer to question 17).

Context

Antibiotics present an unusual innovation challenge. There is a consistent need for new drugs, but also a need to limit access to the drugs, in order to avoid resistance.[4] The use of an antibiotic can often be modeled as a resource that declines in efficacy with use. This negative externality (use generating future drug resistance) has a global dimension. As a consequence, there is a global public interest in restricting the use of antibiotic drugs, particularly when the drug is not necessary, when an older antibiotic drug is effective, or when the drug is otherwise used

[4] See: Antibiotic Resistance Threats In The United States, 2013, CDC, and *The evolving threat of antimicrobial resistance: options for action,* World Health Organization, 2012. Also, see: A. de J. Sosa et al. (eds.), *Antimicrobial Resistance in Developing Countries*, Springer, 2010. DOI 10.1007/978-0-387-89370-9. In Chapter 5 of the Springer publication, Carlos Franco-Paredes and Jose Ignacio Santos-Preciado have an article titled:"The Introduction of Antimicrobial Agents in Resource-Constrained Countries: Impact on the Emergence of Resistance," They write "While it is recognized that the burden of antimicrobial resistance represents a significant threat to the health-care costs and clinical outcomes of infectious diseases in resource-rich countries, the impact on resource-poor countries has been shown to be devastating. The issue is that limited resources become scarcer and therefore control strategies to prevent and treat infections become ineffective. Indeed, many of the infectious diseases that are potentially treatable with newly introduced antimicrobials are themselves frequently considered poverty-promoting conditions because they hamper economic and social human development. Moreover, the association of poverty with poor sanitation and hygiene, unsafe water, overcrowding, poor housing, and lack of environmental sustainability programs converges to facilitate transmission and spread of resistant infectious organisms. Therefore, in many of these developing-country settings, infectious diseases have become a double threat due to the already existent burden of the infectious disease concomitant with the synergistic emergence and spread of drug-resistant microbial strains." (citations omitted).

inappropriately, such as when the drug has a low private value, but generates significant negative externalities.

Proposals to discourage excessive, inappropriate or low value uses of antibiotics include a rich set of recommendations to drug companies, farmers, patients, doctors and others who collectively influence the decisions to use or not use particular antibiotic drugs, as well as many different proposals to change the mechanisms for rewarding, subsidizing and otherwise enhancing research and development efforts. Some proposals involve extending or making stronger the monopoly rights in antibiotic drugs, including, for example, longer or even infinite patent terms for antibiotic drugs, relaxing antitrust rules to permit more collusion among manufacturers, or extending patent-like protections to places and times where patents do not exist.

While stronger and more durable monopolies can be used to increase the rewards for drug developers, and the higher prices will discourage some low value or inappropriate uses of drugs, such strategies also have high costs, including the risk of expanding rather than decreasing the incentives for inappropriate marketing and promotion of products, and a barrier for persons who have low incomes -- a result that is ethically objectionable. High prices for antibiotic drugs also impose burdens on consumers and health reimbursement agencies.

Measures not related to drug prices play an import role in regulating the marketing, promotion and use of antibiotic drugs. These non-price efforts to regulate are more effective when not undermined by inappropriate and socially harmful promotion and market efforts by drug developers.

Some drug companies and public health groups[5] have expressed interest in the use of innovation inducement prizes as a complement to or a substitute for patent incentives. For example, from a 2011 article in the *WHO Bulletin*:[6]

> This delinking of research costs and drug pricing is something that industry may be

[5] James Love, Prizes, not prices, to stimulate antibiotic R&D, SciDev.net. March 26, 2008.

> "For antibiotics, a reward system of cash prizes could value new products using economic models similar to those used to value stock options, inventories and other financial instruments. A new antibiotic would be valued not only for its use during the patent term, but as part of an ongoing portfolio of products needed for new diseases, conditions or resistance problems that are expected to emerge over time. Prizes can be paid even in cases where current consumption is zero, or close to zero, as long as the new product enhances the security and sustainability of the treatment programme. These pricing models need not be highly complex. A large but simple cash bonus for the registration with the US Food and Drug Administration (FDA) of a new antibiotic that has a useful drug resistance profile, coupled with competitive generic production, would create better economic incentives for rational management of an antibiotic than a 20-year marketing monopoly that is valuable only if converted into product sales at high prices. It is possible to do better than this, of course, but even such a simple starting point would offer improvements over the status quo."

[6] "Race against time to develop new antibiotics, " Bulletin of the World Health Organization 2011;89:88–89. doi:10.2471/BLT.11.030211, http://www.who.int/bulletin/volumes/89/2/11-030211/en/

prepared to accept, according to Richard Bergström, director-general of LIF, the trade association for the research-based pharmaceutical industry in Sweden.

"Incentives that separate the financial return from the use of a product are the only way to change this behaviour," said Bergström at a conference held at Uppsala University in September 2010. "Intelligent pull incentives, such as advance commitments and prizes, provide financial rewards to the developer that are not based on the volume of use of the novel antibiotic. With the right set-up, pharma companies will have no incentive to drive use. Maybe they will not do any promotion at all. Use would be agreed with public policy-makers, purchasers and national health systems."

Bergström called for a "global compact" similar to the one used for the United Nations programme for good governance and sustainable development enshrined in Millennium Development Goal 7. This agreement "could focus on the agreed and gradual introduction – and responsible marketing and use of – new agents".

"A global compact would require that not only industry but also governments, physicians and pharmacists join forces to preserve the new medicines that our children and grandchildren need," said Bergström. "No single tool will solve the problem. What is really needed is a collection of incentives that address the multiple obstacles to success."

Bergström, now the Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA), described the antibiotics problem as a combination of the need to stimulate innovation in new products, and to regulate and limit their use.

Prize Design

The use of innovation inducement prizes to stimulate R&D for new drugs, vaccines or diagnostics has been widely discussed,[7] but antibiotics pose unique health challenges, and require somewhat different challenges for the prize designs, particularly for end product prizes, where nearer term utilization may be negatively correlated with the life cycle value of the drug . The technical issues in prize design are important and interesting, but are not discussed in detail in this template. The proposal does provide for a consultation on prize designs in Stage 1 of the project.

[7] For KEI views, see, for example, James Love and Tim Hubbard, "Prizes for Innovation of New Medicines and Vaccines," Annals of Health Law, Vol. 18, No 2, (2009 pages 155-186. James Love and Tim Hubbard. "The Big Idea: Prizes to Stimulate R&D for New Medicines," Chicago-Kent Law Review, Volume 82, Number 3 (2007). For a large number of cites, see: Annotated Bibliography of Articles and Books on Innovation Prizes, http://keionline.org/prizes/cites. There is really an extensive and growing literature regarding innovation inducement prizes, and an explosion of experiments in a wide range of fields. A few that are rarely cited but are interesting were Stan Finkelstein, M.D. and Peter Temin, Reasonable Rx: Solving the Drug Price Crisis, Financial Times Press (2008), and Burton Weisbrod. "Solving The Drug Dilemma." Washington Post Op-ed. August 23, 2003.

Funding

As noted above, a new Antibiotic Innovation Funding Mechanism (AIFM) would be set up, and initially resourced at whatever level was available from governments willing to become donors. Donors would have the flexibility to fund grants, and/or the innovation inducement prizes, including prizes that would reward upstream innovations and interim results, as well as end product prices. In Stage 2 of the project, a system of user fees or taxes would be evaluated, as a system of sustainable funding.

For prizes with high standards to qualify, donors could commit funding contingent upon a successful project (a pure pay-for-success commitment), buy insurance that would pay off in the event of a successful project (in some cases a less expensive obligation), or otherwise put money in escrow, to be returned if no one is able to achieve the standard during the period of the prize offer.

Governance

The governance of the AIFM would be, at a high level, through a committee of donors, voting either by membership, or some modified system, such as half by membership and half in proportion to (the square) of their contributions. The committee of donors would contract with a third party to provide a secretariat, and with various parties that could manage different aspects of the operations, such as the licensing of intellectual property (see answers to question 15), or the management of portfolios of grants or prizes. (See answers to questions 7 & 17).

Delinkage of R&D costs and product prices

All funds allocated for grants or cash prizes would be conditioned upon licenses to use all patents, know-how, data and other intellectual property rights, in the field of use of antibiotics for humans and animals. As noted above and elaborated in the answers to question 15, the AIFM would operate under policies that condition grant and prize money to the licensing of rights in inventions, data, and other intellectual property, according to policies set out by the public sector entities funding the grants and prizes (See answers to question 15).

The types of innovation inducement prizes would include rewards for the successful development of end products (end product prizes), as well as prizes for achieving well defined upstream milestones, and an open source dividend, to reward persons who openly share knowledge, data, materials and technology that prove useful in end products. The amount of funding for each type of prize as well as the grant programs would be determined both by the preferences of the donors and the entity administering the AIFM.

Global regulation of conservation

The broader compact that Bergström referred to above suggests the development of more effective global efforts to regulate antibiotic use, in order to conserve the resource. In this regard, one can imagine regimes involving varying degrees of decentralized implementation of higher level norms and obligations.

In the field of fisheries, wildlife and other industries with negative conservation externalities, regulatory standards for utilization are sometimes implemented at high levels, such as periodically adjusted geographic quotas for fishing harvests or carbon emissions, or at the firm level, such as for CAFE standards[8] to discourage the use of gasoline.

With a regional or firm based quotas on utilization, the methods of managing the resources within the quota constraints can be decentralized, an approach that may be preferred in a world with significant differences in national regulatory traditions and capacity. For carbon emissions and other pollution externalities, economists have proposed systems that would permit secondary markets for emission rights, providing economic incentives to reduce use below quotas, and to also permit higher value uses that exceed quotas. In the context of pharmaceutical drugs, such systems would be potentially ethically problematic, if high income consumers were able to acquire such use rights from lower income consumers. One modification would be to limit the selling of quota rights to countries of similar or lower incomes. Countries could also be allowed to exceed quotas, subject to payment of conservation taxes, and the money from the conservation tax could be used to strengthen regulatory systems, to improve access to medicines for lower income consumers, and/or to expand funding of the AIFM.

6.* Public health need that the proposed project aims to address:
(Explain the public health need in terms of burden of disease; prevalence; incidence; fatality rate; geographical spread; current interventions and their limitations; and what proposed new technology would change in terms of disease prevention, control, diagnosis, treatment etc. If detailed information is not possible at present then please provide some basic level information) *(Approximately 400 words)*

The proposed project aims to address the escalating threat of antibiotic resistant infections. Although cases of antibiotic resistance are increasing globally, the burden is particularly heavy in resource-poor settings. Developing countries lack the resources that richer countries have in hospitals (where resistant-bacteria infections are most prevalent), and do not have the wealth of disposable items and sanitation staff essential in limiting the spread of infections in a hospital setting. Furthermore, resource-poor nations have the double burden of infections from diseases prevalent in high income countries as well as infections from diseases not as prevalent in affluent nations such as typhoid, malaria, and cholera.[9] Thus, there is more valid use of antibiotics in developing countries as well as inadvertent misuse of antibiotics from diagnosis complications, both of which bolster the growth of antibiotic resistant bacteria. In reference to the world regional differences in the threat of antibiotic resistant bacteria, Dr. Pravin Amin, an intensivist in Bombay Hospital was quoted saying:

[8] The Corporate Average Fuel Economy (CAFE) standard, which is set by the US Department of Transportation. The CAFE is a sales-weighted harmonic mean of fuel economy, for the manufacturer's fleet of passenger cars. Manufacturers pay fines if they do not meet the standard.
[9] Sosa et al. 2010. Pg. vi.

> "The antibiotic-resistance problem is worse here in comparison to the West. In the past few years, we have seen a rapid rise in antibiotic resistance. Earlier, the bacteria that showed 90% sensitivity to antibiotics are now showing just 20-30% sensitivity.'"[10]

As put succinctly by Sosa *et al.*, "Africa bears the greatest infectious disease burden, and with it considerable burden from antimicrobial resistance."[11] Those infected with resistant pathogens face life-threatening illnesses, as the second-line drugs to combat antibiotic resistant infections are both expensive and largely unavailable in most of Africa. Additionally, drug resistance has been particularly notable for infections associated with HIV, malaria, tuberculosis, respiratory pathogens, and sexually transmitted bacteria, which are all highly prevalent in the region.[12] For example, over two-thirds of outbreaks of cholera in the last decade have occurred in Africa, and furthermore, evidence has suggested that the emergence of resistance in the *V. cholerae* strain has increased mortality in the recent African outbreaks.[13]

In the west Pacific area, antibiotic resistance in cases of *Streptococcus pneumoniae* has the highest reported resistance rate in the world.[14] Other cases of resistant infections associated with *Haemophilius influenzae* and non-typhoid *Salmonella* species have seen marked increases in Asia over the last decades and community-aquired methicillian-resistant *Staphylococcus aureus* (CAMRSA) has been noted, a marker of the spread of MRSA which was previously predominantly only acquired in hospital settings.[15] Additionally, cases of extensively drug resistant tuberculosis (XDR-TB) have become a global threat, with many new cases arising in Asia. XDR-TB is defined as multi-drug resistant TB (which is already resistant to riframpicin and isoniazid) that is resistant to fluroquinolone and at least one of three injectable second line drugs.[16]

According to Sosa et al., "Antimicrobial resistance in Latin America and the Caribbean is widespread and is a limitation for proper treatment of both community- and hospital-acquired infections."[17] Furthermore, hospital-acquired cases of infections have seen high rates of resistance to antibiotics, particularly in instances of MRSA, ESBL-*producing* Enterobacteriaceae, carbapenem-resistant *Pseudomonas aerginosa* and *Acinetobacter baumannii*.[18] Nosocomial MRSA, which is multi-drug resistant, is a growing problem in the Latin America and Caribbean region, with Argentina (51%), Brazil (54%), and Bolivia (55%) showing some of the highest rates of resistance to hospital-acquired MRSA.[19] Cases of CAMRSA have also rapidly expanded, following the report of the first case in Latin America in Brazil in 2003.[20]

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[10] Pal, Somita. "*US view on antibiotic-resistance scares Mumbai doctors*." DNA India. 30 Oct 2013. http://www.dnaindia.com/health/report-us-view-on-antibiotic-resistance-scares-mumbai-doctors-1911075. Accessed 30 Oct 2013.
[11] Sosa, A., Byurugaba, D., Amabile-Cuevas, C., Hsueh, P., Kariuki, S. and I. Okeke. *Antimicrobial Resistance in Developing Countries.* New York: Springer. 2010.
[12] Sosa et al. 2010. Pg. 301.
[13] Sosa et al. 2010. Pg. 302.
[14] Sosa et al. 2010. Pg. 315.
[15] Sosa et al. 2010. Pg. 317-319.
[16] World Health Organization. "Global Tuberculosis Report 2013." World Health Organization. 2013. Pg. 49.
[17] Sosa et al. 2010. Pg. 331.
[18] Sosa et al. 2010. Pg. 331.
[19] Sosa et al. 2010. Pg. 334.
[20] Sosa et al. 2010. Pg. 335.

A significant area of concern for drug resistance is in cases of tuberculosis. In the 2013 Global Tuberculosis Report, the World Health Organization identifies 22 high-burden countries including the Russian Federation. From 1994-2010, the Russian Federation and several Eastern European countries had the highest rates of multi-drug resistant TB (MDR-TB) among new TB cases in the world, greatly exceeding those in Africa, Latin America, and North America.[21] According to a 2013 report published by the WHO, "Eastern European and especially central Asian countries continue to have the highest levels of MDR-TB." Some of the highest rates of MDR-TB in new cases of TB include Azerbaijan (22.3%), Belarus (34.8%), Estonia (19.7%), and Kyrgyzstan (26.4%) while in previously treated cases, rates of MDR-TB exceeded 50%, with those same countries reporting rates of 55.8%, 68.6%, 50%, and 68.4%. respectively[22] In the Russian Federation, although the average percentage of cases with MDR-TB is not greater than 50%, the percentage in several sub-national regions was significantly higher, for example the Ulyanovsk Oblast in Russia reported a 74% rate of cases of MDR-TB in 2011.[23]

As a means of combating the spread of antibiotic-resistant infections, the US Center for Disease Control and Prevention outlines a four step plan, the most critical of which is the development of new antibiotic drugs. The other three actions, preventing infections, tracking cases of resistant infections, and improving antibiotic stewardship, are important steps to take to counter the spread of these infections, however, antibiotic resistance naturally occurs as bacteria grow and evolve.[24] This means that antibiotic resistance can be slowed by these measures, but never completely stopped. Thus, there is a pressing need to support the development of new antibiotic drugs that can fight infections which are resistant to older generations of drugs.

In April 2013 the Infectious Disease Society of America (IDSA) provided a grim landscape[25] of the arsenal of antibiotics in the pipeline noting that,

> The IDSA report tracks a steady decline in new antibiotics, from a high of 16 new compounds approved from 1983 to 1987 to only 2 approved since 2008: ceftaroline fosamil and telavancin. Of the 14 systemic antibacterial drugs approved since 1998, only 4 introduced a novel mechanism of action.
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> "Antibiotics are not economically the most viable of drugs," Dr. Boucher said. "Most drug companies and sponsors want to make drugs patients will take for the rest of their life, drugs for hypercholesterolemia and obesity. Antibiotics, by design, are used for a short period of time and often are priced in a reasonable way, to meet a public health need."

The graph below, from a report published by the CDC in 2013, shows the decline in antibacterial

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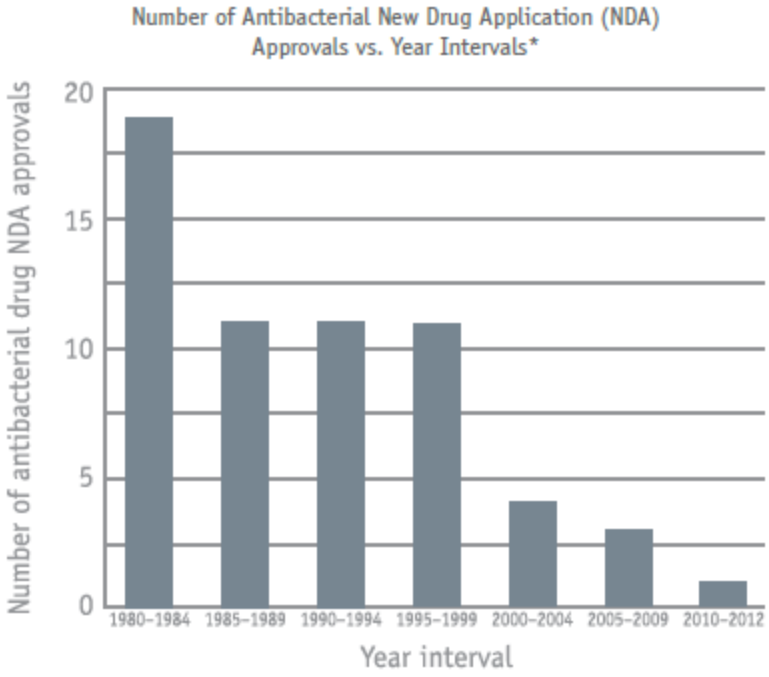
[21] World Health Organization. "Percentage of new tuberculosis cases with MDR-TB." Antimicrobial Resistance Factsheet No. 194. May 2013. http://www.who.int/mediacentre/factsheets/amr_mdr_tb_map.jpg. Accessed 25 Oct 2013.
[22] World Health Organization. "Global Tuberculosis Report 2013." World Health Organization. 2013. Pg. 48.
[23] World Health Organization. "Global Tuberculosis Report 2013." World Health Organization. 2013. Pg. 48.
[24] Center for Disease Control and Prevention. "Antibiotic Resistance Threats in the United States, 2013." US Department of Health and Human Services. September 2013. Pg. 31.
[25] Laidman, Jenni. "*Despite Growing Crisis, Few New Antibiotics are in Pipeline*." Medscape Medical News. 22 April 2013. http://www.medscape.com/viewarticle/802891. Accessed 30 Oct 2013.

new drug application approvals since the 1980s.[26]



*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents.
Data courtesy of FDA' s Center for Drug Evaluation and Research (CDER).

7.* Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate?

(This is a very important part to be filled. The idea of these demonstrations projects is "to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken" (WHA66.22). 66th WHA considered these demonstration projects as part of the efforts to "take forward action in relation to monitoring, coordination and financing for health research and development". The assembly decided to identify such projects that: "(address identified research and development gaps related to discovery, development and/or delivery, including promising product pipelines, for diseases that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken; (b) utilize collaborative approaches, including open-knowledge approaches, for research and development coordination; (c) promote the de-linkage of the cost of research and development from product price; and (d) propose and foster financing mechanisms including innovative, sustainable and pooled funding; (2) The demonstration projects should provide evidence for long-term sustainable solutions.") *(Approximately 300 words)*

[26] Center for Disease Control and Prevention. "Antibiotic Resistance Threats in the United States, 2013." US Department of Health and Human Services. September 2013. Pg. 44.

The most innovative aspects of the project as regards financing innovation and coordination of R&D would be the creation of a financing mechanism that offered different kinds of innovation inducement prizes, each tied to access expanding licensing of intellectual property rights, and eventually (stage 2) a financing mechanism using fees or taxes on the use of antibiotic drugs to jointly finance innovation and enhance conservation of the resource.

The types of innovation prize would include:

1. **Interim results** prizes to reward solving specific technical challenges, such as those listed in the Nature Open Innovation Pavilion.

2. **End product prizes** as an inducement both to develop commercial products and also to induce the licensing of the intellectual property rights.

3. **Open Source Dividend** prizes to induce sharing knowledge, data, materials and know-how with drug researchers and developers.

The Licensing of Innovations is discussed in more detail in the answer to question 15. In general, grants or cash prizes would only be available to persons who license relevant intellectual property including patents, data, regulatory test data and know-how, at least in a field of use for antibiotic drugs.

Unlike some proposals to create centralized systems, the AIFM would provide a role for decentralized decision making and management, including through the use of **Competitive Intermediaries** to manage grants and interim results prizes. One challenge for innovation inducement prizes is to place a value on an interim result that may or may not prove useful in the development of a new drug, and/or to create the appropriate end-points for the interim challenge. A system of competitive intermediaries seeks to mitigate criticisms of specific decisions by creating a system whereby donors can choose to fund more than one intermediary to manage such prizes. Over time, the benefits of each intermediaries' decisions become apparent to donors.

The project is designed to introduce in its second stage a sustainable funding mechanism based upon user fees or taxes on the use of antibiotic drugs. The funding mechanism is designed to pay for the grants and prizes, and discourage certain low value uses of antibiotic drugs. This mechanism is discussed in more detail in the answer to question 17.

8.* Evidence of market failure/research landscape:
(Explain why there has been no investment in this technology or why investment has not resulted in access to the health care product.) *(Approximately 200 words)*

There are several types of market failures associated with antibiotic drugs. The challenge in designing economic incentives is to recognize and address several market failures.

On the one hand, companies are asked to invest in a product for which the primary incentive is a grant of a market monopoly. On the other hand, health authorities want to limit the use of the product, in some cases severely, including during its early product life, which coincides with the term of a patent, when the developer has the largest incentive to encourage use. The inconsistency between the nature of the current R&D incentive, which encourages promotion of use, and the social objectives concerning conservation and limits on uses, cannot be resolved without a **change in the business model for R&D**. The demonstration project seeks to directly address this market failure.

There are other market failures relating to R&D which the AIFM seeks to address. One is that the patent system is not well designed to reward **re-purposed drugs**, because the new use may not have meaningful patent protection, when the earlier use is no longer subject to patent protection. Another important market failure particularly relevant to the lack of innovation for antibiotic drugs is that researchers have the wrong **incentives to share (or not share) knowledge, data, materials and technologies.**

A third market failure is that some interim R&D results may be useful for drug development, but predictably will not by themselves result in a commercial product or even a patented invention. The systems of grants and innovation inducement prizes have the advantage of being able to provide subsidies or rewards for all of these types of R&D activities, including to induce open sharing of knowledge, materials, data and technologies, to re-purpose drugs, and to stimulate R&D that achieves benchmarks and other **useful interim results**.

The current R&D incentives are designed in such a way that new products that are protected by patents are very expensive, while older products off patent are often very inexpensive. The AIFM would permit affordable generic production of the products, reducing inequalities of access that are caused by high prices. If a broad based user fee or tax was implemented on generic antibiotic products, the prices for generics would increase, by an amount that was relatively small in percentage or absolute terms. The fees or taxes could potentially be scaled to discourage certain low value uses of antibiotics, such as excessive use in certain agricultural settings, and would also compensate to some degree the negative externalities of the uses of the products.

An antibiotic user fee, as well as the price premium that is paid when there is a patent monopoly, can be evaluated as a tax like instruments, from the point of view of the consumer. It is useful to note that in economics literature, as a general rule, the dead-weight loss to society increases with the square of the tax rate. For this reason, low tax rates on a broader base of economic activity is generally considered more efficient than the converse.

The current systems of monopoly for new products and generic production of off-patent products creates a very high effective tax on a small number of new products. By providing a broader base, more products and uses are subject to the tax, but at a lower percentage rate,

which is more efficient as regards distortions in uses. Tax fees or taxes can also be more deliberately designed to achieve conservation and social objectives. (See also discussion in answer to question 17).

9. The scientific and technical feasibility:

(Describe the scientific and technical basis for the proposed technology in terms of the state of the art e.g. candidate molecules; biomarkers; pipeline; previous efforts, if any, to develop same or similar technology etc. Include some risk analysis) (Approximately 500 words)

The development of new antibiotic drugs is certainly feasible. The challenge will be to obtain sufficient funding to have both have an impact on innovation, and to induce open licensing of innovations. There may be some legal challenges with the implementation of large innovation inducement prizes, when linked to open licensing of inventions, including, for example, the provisions in the EU's proposed rules for the use of prizes in the Horizon 2020 R&D budget.

It is sometimes argued that prizes "won't work" as an incentive to develop new drugs, as if there is something magical about the grant of a patent enforced monopoly that "will work" and prizes somehow are lacking this magical property. On one level, this is like saying, investors don't care about money, all they like are monopolies. We know that is not true, because we observe companies buying and selling intellectual property rights, products, subsidiaries and even whole companies, when the price is right. On the other hand, it is very likely true that small cash prizes will not induce large cash investments. For inducement prizes to stimulate large investments, the inducement prizes themselves have to be large, a point echoed by a 2010 WHO report titled: *Policies and incentives for promoting innovation in antibiotic research*, which stated:[27]

> "The pull effect produced by a prize-based incentive is dependent on an appropriate calculation of the reward (see Box 6.9 for discussion). If the magnitude of the prize is sufficiently large, sales can be decoupled from the recouping of R&D costs. In this case, monetary prizes can help prevent the overmarketing and subsequent overconsumption of an antibiotic product that is ultimately developed."

The authors of the WHO/EURO report raise some technical concerns about the use of prizes, such as their comment that "the separation of sales from the amount of compensation the developer receives implies that continued product quality has no bearing on the magnitude of the reward."[28] This would be true for some prize designs, but not others. In the Sanders bill approach, which has been an influential model for drug development rewards, the amount of the

[27] Elias Mossialos, Chantal M Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama, David Brogan. Policies and incentives for promoting innovation in antibiotic research. World Health Organization 2010, on behalf of the European Observatory on Health Systems and Policies. Page 149.
[28] Ibid.

end product prize is not determined on a single date, but rather is a series of payouts over a 10 or 15 year period, every year reassessing the evidence concerning the health benefits of the product, which in turn are defined as improvements in health outcomes, when benchmarked against older alternatives. There would be some modifications to this approach for an end product prize involving antibiotics, because there would be more interest in modeling a longer life cycle for the product, and taking into account the dynamic nature of negative externalities as regards resistance, and possibly considering also other factors, such as the option value of the product, for possible future health crises that are unknown, but possible.

The Sander's approach to end product prizes[29] is not bound legally to a particular valuation or measurement approach. While QALY's have been presented by some as an important element of the valuation[30] of prizes or prize type mechanisms, there is nothing that suggests that other approaches would not be more useful in particular sets of circumstances, and certainly when one examines the evaluations of drug reimbursement decisions by governments or insurance companies, one sees a wide range of approaches considered as regards the measurement of benefits. It is worth noting that one aspect of the Sanders bill approach that is highly appealing is that the amount of the rewards themselves are set dynamically, through a competition. What is important to keep in mind is the highly stochastic process that produces innovations in the first place, sometimes entirely unanticipated, and often far from the mark as regards the initial predictions of efficacy, safety or profitability. What is most important is that drug developers see the reward system as transparent and fair, reasonably related to the health result one is trying to achieve, and robustly funded. Investors are used to taking risks on payouts, so long as on average, the system produces sufficient rewards.

When looking at the evidence base for a particular prize reward, there is also the question of: "compared to what?" It certainly would be difficult to claim that the patent system produces rational prices for medical inventions.

The current system of mechanisms to fund R&D for new drugs is mature and receives extensive support from intellectual property and drug reimbursement regimes. The development of national and global norms and mechanisms to fund innovation as a public good is less mature, and that presents challenges.

10. Reasons for proposing:

(Provide details if any priority setting and/or selection criteria that has underpinned the consideration to take up this area of technology for development.) *(Approximately 200 words)*

[29] See as described in "the Big Idea", Supra.

[30] See Chapter 10 of William Fisher and Talha Syed. Drugs, Law, and the Health Crisis in the Developing World. Stanford University Press. 2010. Also, Aidan Hollis. "The Health Impact Fund: A Useful Supplement to the Patent System?". *Public Health Ethics* 1(2), (2008) pp 124-133. Oxford University Press.

The world is facing a crisis associated with a lack of innovation and the excessive and inappropriate use of antibiotic drugs. We believe it is important to create a new system of supporting R&D for antibiotic drug development that does not create incentives for drug developers to promote excessive use of products, and which can create a more open system of innovation, including broader upstream sharing of knowledge and other R&D inputs. We are also concerned that some proposals to address the innovation challenges for antibiotics are designed to expand monopolies and high prices for new drugs, unnecessarily creating inequalities of access between high and low income persons, and/or involve expensive new outlays on antibiotic drugs, creating new burdens on consumers and reimbursement systems, without providing significant benefits as regards innovation or conservation. This proposal is an effort to present a system that taken together, addresses concerns about innovation and conservation in a manner that is cost effective and fair, and which challenges policy makers to think differently about the system that is currently designed and functioning poorly.

11. Who could potentially develop the technology/carry out the research?
(Provide known details: individual researcher? Group of researchers? Research/coordination organization including PDPs? Group of research organizations working together? Combination of these; What would be the process of selection of developers?) *(Approximately 100 words)*

The use of grants and innovation inducement prizes will provide subsidies and incentives that would be open to researchers around the world, in both for profit and non-profit settings. The AIFM can include various degrees of regional or national implementation of elements of the financing, including for example decentralization of the management of grant programs in order to ensure that researchers, institutions and businesses in developing countries play an important role as suppliers of innovation. The design of the innovation prizes would certainly provide opportunities for individuals and small businesses and non-profit institutions to compete for every type of prize, from the end product prizes to the open source dividend and the interim results prizes. Prize rewards or grants could be designed in ways to creative incentives for research teams that collaborate across borders, and/or have partners in developing countries, an approach that has been used by the European Union in elements of its Framework program.

12. Who could potentially manufacture the final product?
Multinational company? Local production? Joint venture? How the decision will be made about the producer? *(Approximately 100 words)*

With disclosure of know-how and open licensing of intellectual property, local production, small business production serving regional or global markets, joint ventures or large multinational manufacturing are all possible. Licensing obligations to providing technology transfer and capacity building in developing countries or regions are one of the policies to be determined.

13. What could be the role of WHO, if any, in this demonstration project to bring this

venture to fruition? *(Approximately 200 words)*

The WHO could play an important leadership role in convening meetings to consider possible global norms for the conservation of antibiotics. The WHO could provide the secretariat for the AIFM, in a fashion similar to the UNITAID.

14. Please outline a timeframe and projected milestones for the project covering the first 5 years. This should also highlight the immediate actions that need to be taken? *(Approximately 200 words)*

Stage 1

Create a governance structure, open bank accounts, negotiate contracts with WHO (or some other entity) to provide secretariat services, and with the Medicines Patent Pool (or some other entity) to manage the licenses.

First round of voluntary financial commitments.

Adopt initial policies on licensing, conservation objectives, innovation priorities.

Adopt policy on use of competitive intermediaries to manage grants and interim prizes.

Offer and later award initial grants.

Consultation with experts and stakeholders on innovation inducement prize designs.

Design initial prizes, including both end product prize, open source dividend, and at least one interim results prize.

Stage 2

Create the user fee or tax on antibiotic drugs.

Identify global revenue targets.

Identify conservation objectives.

Make recommendations and share best practices as regards norms for scaling fees and taxes to achieve conservation and other social objectives, particularly as regards low value uses of drugs with significant negative externalities, and differential prices to accommodate differences of incomes between and within countries.

15. What is the intellectual property (IP) landscape relative to this project? Is there any IP, e.g. patents that need to be licensed in to be able to develop and market the product in developing countries? How would IP and related intellectual assets, including knowhow, proposed to be managed in this project? *(Approximately 400 words)*

There are challenges as regards patent thickets in some areas relevant to the development of new antibiotics. In some cases, government agencies, such as the U.S. Center for Disease Control (CDC), National Institutes of Health (NIH) or Department of Defense (DoD) have rights in patents that can be exercised by or for the United States government, anywhere the world, including for purposes of development of new antibiotic drugs. Governments everywhere have the authority to grant compulsory licenses to use patents under several different provisions contained in the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights , including Articles 30, 31 and 44, as well as under the LDC exceptions as regards the granting of patents.

As regards the management of IP, the demonstration project would require the licensing of patents, data, know-how, and other intellectual property rights, as a condition for receiving the grant or prize funding. These licenses would at a minimum cover a field of use that included the development, manufacturer and sale of antibiotic drugs. The policies as regards the licensing of the intellectual property would be determined by the governments funding the AIFM. In general, this should include broad rights to expand access to knowledge and know-how, to facilitate research and development activities, and to enable the competitive manufacturer of affordable generic products of good quality. Governments participating in the program would either manage the licenses themselves, or contract with an entity such as the Medicines Patent Pool (MPP). Among the policy issues to be resolved by the donors would be any requirements for manufacturing in developing countries, or in particular regions, ownership, licensing and rights to use follow-on inventions, and possible payment of fees to accomplish the joint and compatible goals to financing the innovation fund and encouraging conservation of the antibiotic resources.

16.* What would be the strategy to ensure access to the product once it is developed?
(Access is an important dimension of these demonstration projects, it is important for the projects to begin with the end in mind, explain how this project would deliver the technologies to the needy patients i.e. price and affordability; modes of supply; storage; prescription; dispensing; and compliance; WHO will develop guiding principles for ensuring access to any products coming out of the demonstration projects) (Approximately 400 words)

The licensing of intellectual property associated with research grants, contracts and innovation prizes is designed to enable more competition and lower prices for new products.

In stage 2 of the project, there would be a business model change. There would be a switch from a system of very high prices on new products and low prices on generic products to a system where the base price for all product is a low generic commodity, but supplemented by a fee or tax on the use of the antibiotic drug, to discourage low value uses and finance the innovation grants and prizes.

17. How could the project be financed paying particular attention to the need to

demonstrate new and innovative forms of financing? Also provide an estimated cost of the project. ***(Approximately 200 words)***

As a demonstration project with a relatively short time horizon, the initial funding would be based upon the voluntary contributions from governments and other donors who share an interest, capacity and inclination to commit resources for the development of new antibiotic drugs, using the open innovation approach and novel pull mechanisms such as innovation inducement prizes with strong public interest licensing conditions. In the longer run, the financing model would be more sustainable, and potentially more useful in achieving conservation objectives.

At least since Clem Tisdell[31], scholars and policy analysts have proposed an obvious intervention to discourage low value uses of biologic drugs – imposing taxes on the consumption of the products. A theoretically well designed tax designed to correct market prices so the private costs match the social costs of the consumption is sometimes referred to as a Pigouvian tax. A well known and widely cited economist, Arthur C. Pigou proposed using taxes to discourage actions which caused negative externalities – precisely the situation when drug use leads to decreases in future efficacy of the drug.

The grant of a monopoly leads to high prices, and by raising prices, acts in some ways that are similar to a tax on consumption. But a private monopoly does not seek to scale the "tax" to address treatment objectives, and more important, the private monopoly keeps the money. If consumption is taxed by governments, the money can be used for something else, including to fund the AIFM. The high prices charged by holders of patent monopolies are only imposed on new drugs, in the time and places where patents are in effect. But taxes on antibiotic use can applied to both new and old drugs, and in times and places where patents do not exist. With a broader base, the same amount of money can be raised with less dead-weight loss, and the taxes or user fees can be scaled in useful ways. For example, as noted by Eric Kades[32] and others, taxes can be lower in developing countries, and higher in higher income countries, because a smaller tax will have a larger impact with low income consumers. Taxes could be scaled differently for agriculture than for human use, and differently for different types of uses, and even scaled for individual drugs, given differential regulatory objectives as regards use.

A proposal to introduce a user fee for antibiotic use was made by the Infectious Disease Society of America (IDSA) in 2011, as part of a wider set of recommendations to stimulate innovation while reducing use of antibiotic drugs. The IDSA proposal was to create an Antibiotic Innovation

[31] Clem Tisdell, Exploitation of Techniques That Decline in Effectiveness With Use, 37 Public Finance /Finances Publique 428 (1982).

[32] Eric Kades, "Preserving a Precious Resource: Rationalizing the Use of Antibiotics," (2005) 99 Northwestern University Law Review,. 615 2004-2005. Page 626. Available at Faculty Publications. Paper 52. http://scholarship.law.wm.edu/facpubs/52. An earlier version of the paper is available a s Eric A. Kades, Plagues, Policy, & Patents: Addressing Overuse of Antibiotics, William & Mary Law School Working Paper No. 2003-Kades-1, March 11, 2003.

and Conservation (AIC) fee.[33] The IDSA proposed that 75 percent of the fee be used to fund R&D for new antibiotic drugs, and 25 percent be used to fund "antimicrobial stewardship."

In some ways the tax on antibiotic use would be similar to the funding mechanism for UNITAID, a commitment by governments to fund programs for HIV/TB and Malaria from fees on airline tickets. For antibiotics, the tax is particularly appealing, because it can be used to achieve conservation goals, and the benefits of the tax are returned to the drug manufacturers in the form of new R&D subsidies, and to the consumers in the form of lower prices on the new products developed as open source products.

An initial goal of 1 percent of the global antibiotics market, would provide more than $400 million per year in grants and innovation inducement prizes. At 2 percent, the size of the AIFM would be large relative to the innovation tasks. With a switch to a delinkage approach as regards R&D costs and drug prices, the net costs to taxpayers, consumers and reimbursement entities would be favorable, and one can imagine even larger percentages being considered, with each increase leading to more innovation, less monopoly power for new drugs, and better conservation of older drugs. Since the money from the taxes would be used to fund R&D for new products, researchers and businesses involved in the supply of innovation would favor robust funding levels, as would patient groups that were alarmed by the lack of innovation.

The UNITAID experience shows the benefits of a decentralized and flexible approach as regards the collection of the revenue. Not every member of UNITAID uses a tax on airline tickets to meet its obligations to UNITAID. Decisions about how to collect the taxes or user fees on antibiotic uses could be implemented at the national level, within broad guidelines, and a combination of dialogue and sharing of best practices, by both finance and public health officials.

The notion that taxes, user fees or royalties can be imposed on an activity for the purpose of

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[33] IDSA Policy Paper, CID 2011:52 (Supl 5). From page S407 of the report: "With respect to public monies, IDSA proposes creation of an Antimicrobial Innovation and Conservation (AIC) Fee. The AIC Fee would be a flat fee (e.g., $3 per daily dose, inflated by the consumer price index annually) charged against the wholesale purchase of every daily dose unit of antibiotics (both branded and generic) in the US, including for human, animal and plant agriculture, and aquaculture use. The fee would be paid by the dispensing entity (e.g., pharmacy, animal feed mill, aquaculture company, etc.) at the time of wholesale purchase from the supplier. The rationale for such a fee is that effective antibiotics represent a ''shared societal benefit,'' and every antibiotic manufacturer, prescriber, and user must share the responsibility to maintain this benefit. Antibiotic resistance resulting from antibiotic use (both appropriate and inappropriate) is an example of the ''tragedy of the commons''. A prescription may help the individual patient, plant, or animal, but such use also causes collective erosion of the benefit (effectiveness of antibiotics) for society as a whole. Analogously, use of highways by a vehicle has a cost to all users. Tolls (and differential rates) are means to have users pay their fair share of societal costs for establishing and maintaining a shared benefit. Because of the emergence of resistance, use of antibiotics differs from use of all other drugs that affect only the individual patients taking them. Hence, an AIC Fee would be charged to maintain the ''shared societal benefit'' of effective antibiotic therapy. Obviously, safeguards need to be incorporated into the AIC Fee structure to ensure that any costs passed on to consumers will not negatively impact vulnerable populations' access to these important drugs."

ensuring investments in the R&D is not new, and has been implemented in diverse settings. Examples include the 1982 decision by the National Cancer Institute to require Bristol-Myers to contribute approximately $40 million to third parties for cancer research, in return for extending the monopoly on the cancer drug cisplatin. Bristol-Myers Squibb later proposed a similar system be implemented to extend the term of test data protection for Taxol, another cancer drug. Brazil requires oil companies to invest in energy related R&D projects, and Colombia is using royalties from mining to invest in R&D projects. Some corporate trade associations and agricultural cartels use dues or revenues to fund R&D projects that benefit members. Some standards associations, such as the World Wide Web Consortium (W3C) use dues to participate in decision making to offset what are essentially costs associated with an R&D activity producing technologies that are available royalty free to everyone. The W3C members appreciate that in some cases, having R&D produced as a public good makes it more valuable both to society and to the firm. There is a parallel in the AIFM. To the extent that the grants and innovation inducement prizes expand royalty free access to knowledge, know-how, materials, data and technology, a drug developer can spend less money acquiring these assets, and still make claims on other prizes, including the lucrative end product prizes.

18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination? *(Approximately 200 words)*

The WHO could play an important role in convening, coordinating and even providing the secretariat for the AIFM, similar to the role it played in the creation of UNITAID.

The governance itself would be led by the governments that are willing to support the project financially. As UNITAID has shown, this can include diverse membership, and mobilize significant budgets.

There are different roles, responsibility and tasks, and the governance system should provide for structures that deal with scientific and financial issues, in addition to other policy making activities, such as setting norms for licensing, considering the appropriate degree of decentralization for managing and designing innovation grants and prizes, collecting revenue or achieving conservation objectives.

19. Have any donor agencies/governments already indicated interest in supporting the project? ***(Approximately 200 words)***

No. Several are obviously on record expressing alarm at the problem, and note the need to address both the innovation and the conservation challenges.