PROPOSAL FOR DEMONSTRATION PROJECTS

*1. Title of Project:

Establishing a Drug Discovery Platform for Sourcing Novel Classes of Antibiotics as Public Goods

*2. Submitted by:

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*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)

The target health condition would be the spectrum of infectious diseases caused by drug-resistant bacterial pathogens. These include respiratory infections, diarrheal diseases, gonorrhea and tuberculosis, all of which have disproportionate burden of disease in low- and middle-income countries.

*4. The suggested health technology that project seeks to develop:

(e.g., medicine; diagnostic test; medical device; vaccine etc.)

Novel classes of antibiotic drugs for the treatment of drug-resistant bacterial infections

*5. Project summary

This innovation demonstration project proposes to establish a drug discovery platform for sourcing novel classes of antibiotics as public goods. Drug resistance has eroded the effectiveness of first-line therapy for bacterial infections, from pneumonia and meningitis to
gonorrhea and neonatal sepsis, and puts at risk the miracles of modern day medicine, from organ transplants to cancer chemotherapy. This infectious disease burden disproportionately falls in low- and middle-income countries, but the risk to future treatment of non-communicable disease is growing. Resistant bacterial pathogens respect no political borders and represent a significant global risk, according to the World Economic Forum. Worse yet, the R&D pipeline for novel antibiotics has faltered, with only two new classes of antibiotics since the 1960s.\(^1\) Antibiotics that cure a patient in a few days just do not stack up well as an R&D investment priority against drugs, like those lowering blood pressure or cholesterol, that are taken for a lifetime. Both therapeutic competition and efforts to restrict the use of novel antibiotics also limit the appeal of pursuing antibiotic innovation. However, the bottlenecks are not just financial, but also scientific.

Enriching a public compound library, particularly with natural product sources, would provide an innovation platform for discovering new classes of antibiotics. Over a third of small molecule drugs over the past three decades have originated from natural products, and among antibiotics coming to market between 1982 and 2002, over three-quarters of the drugs derived from natural products.\(^2\) Repleting the antibiotic R&D pipeline would address the scientific bottleneck that has stymied the pharmaceutical industry, which has reported very low yields from high-throughput screening of their proprietary compound libraries. With the low-hanging fruit having been picked, low- and middle-income countries possess a biodiversity of natural product sources that may replete these compound libraries, a wealth of traditional knowledge, and growing capacity in medicinal chemistry.

By shaping the conditions under which these compounds are made available, various R&D pathways for innovation might be tested, for example: 1) milestone prizes for creating promising, druggable leads for novel antibiotics; 2) non-exclusive licensing to publicly funded product development partnerships for generic production and scale up limited to rational use, thereby ensuring conservation of the effectiveness of antibiotics produced; or 3) open source, online collaboration platform for sharing annotation data in a research commons, with a click-wrap license ensuring that the intellectual property generated belongs to the community contributing to the repository.

Importantly, the project has the potential to demonstrate the importance of delinkage – divorcing a manufacturer’s returns on investment from price and quantity (or revenues) of that product. From the drug discovery platform, a range of approaches for managing intellectual property, publicly financing the R&D, and scaling the project could be piloted. This proposal would fill an important gap: addressing a scientific bottleneck, lowering the barrier for researchers from academic institutions and small firms to tackle this challenge, and enabling low- and middle-income country research institutions a role in bringing potentially life-saving antibiotics forward.

*6. Public health need that the proposed project aims to address:
Over 80 years after the discovery of penicillin, bacterial diseases still contribute significantly to the global burden of disease. Despite the gains in global life expectancy over the past four decades, that burden of disease has become complicated by growing drug resistance, notably among some of the most common childhood infections, including neonatal sepsis, pneumonia and meningitis. Pneumonia is also the most common cause for adults being hospitalized in sub-Saharan Africa – 4 million episodes – and accounts for 200,000 deaths a year. These infections disproportionately affect those in low- and middle-income countries, with 99% of child deaths from pneumonia in these settings. Nearly a quarter of *Streptococcus pneumonia* strains are reportedly resistant to three classes of antibiotics.

Across Africa and Asia, the resistance of bacillary dysentery to ciprofloxacin – the treatment recommended by WHO – in children has risen from negligible to 30% in a decade. Drug resistance to gonorrhea has risen in waves – first to fluoroquinolones, then to cefixime, and more recently to azithromycin. As a study in a tertiary hospital in Tanzania suggests, gram-negative sepsis in children had a mortality rate twice that of malarial infection.

Antibiotic resistance also puts at risk the miracles of modern day medicine, from cancer chemotherapy to organ transplants. As the spread of NDM-1 bacteria – a gene that produces an enzyme that results in resistance to penicillins, cephalosporins and carbapenems – and other antibiotic-resistant strains illustrate, political borders have not contained the globalization of these pathogens. Reportedly, NDM-1 infections spread across the globe, from South Asia to Europe, North America, Africa and Australia within a short period of time since the enzyme was first reported in 2009.

While a protective vaccine exists for some of these conditions, many must rely on antibiotic treatment. In 2008, of the more than 22,000 children less than 5 years old enrolled in the WHO Invasive Bacterial Diseases Surveillance system, only 14% of the children with likely bacterial meningitis had disease against which a protective vaccine would have helped, and nearly a quarter of those hospitalized with this diagnosis subsequently died. Vaccination coverage rates are also lower in Sub-Saharan Africa.

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

Enriching a public compound library, particularly with natural product sources, would open the door to discovery of classes of antibiotics with novel mechanisms of action. Between 1982 and 2002, 70 of the 90 antibiotics reaching market came from natural product sources, and a
majority of all classes of antibiotics have natural rather than synthetic origin.\textsuperscript{11} Repleting the antibiotic R&D pipeline with potentially new families of compounds addresses the scientific bottleneck that has resulted in such low yields of successful antibiotic leads from high-throughput screening of proprietary compound libraries.\textsuperscript{12} Low- and middle-income countries possess a biodiversity of natural product sources, a wealth of traditional knowledge, and growing capacity in medicinal chemistry.

Harnessing this traditional knowledge involves consideration of community ownership and benefit sharing. Defining material transfer agreements or licensing terms on compounds in such a library provides a strategic opportunity to shape innovation and downstream access. By shaping the conditions under which these compounds are made available, various R&D pathways for innovation might be tested, for example: 1) non-exclusive licensing to publicly funded product development partnerships for generic production and scale up limited to rational use; 2) open source, on-line collaboration platform for sharing annotation data in a research commons, with a click-wrap license ensuring that the intellectual property generated belongs to the community contributing to the repository; and 3) milestone prizes for creating promising, druggable leads for novel antibiotics. Prizes in this precompetitive space might be an exceptionally efficient means of casting a wide net and crowdsourcing potential leads. Prizes could buy out the underlying intellectual property, both patents and preclinical data, and the resulting leads could form a pool of novel antibiotic compounds worthy of further development.

*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.)*

In recent years, only two new classes of antibiotics have come to market,\textsuperscript{13} but equally troubling is the dearth of novel antibiotics in the pipeline. An EMA-ECDC-ReAct study of the antibiotic pipeline identified 90 antibacterial agents in clinical development. Of the 15 drug candidates that could be administered systemically, only four had demonstrated \textit{in vitro} activity against antibiotic-resistant Gram-negative bacteria, and not one of these acted via a novel mechanism of action.\textsuperscript{14} Compared to other lucrative therapeutic categories, the return on investments for antibiotics is relatively low. Antibiotics that cure a patient in a few days just do not stack up well against drugs, like those lowering blood pressure or cholesterol, that are taken for a lifetime. The large number of existing antibiotics already approved may result in a high level of therapeutic competition for newly developed agents. The market life cycle of an antibiotic might well be self-limited by the emergence of drug resistance, thereby curtailing its potential return on investment. Finally, there is a policy tension between drug R&D programs that would favor broad-spectrum antibiotics and large-scale distribution, and public concerns that seek to limit use of these new agents.

9. The scientific and technical feasibility:
The components of the proposed drug discovery platform have strong scientific and technical foundation, but applied to sourcing novel classes of antibiotics, offers catalytic opportunity. These components include: 1) the availability of biorepositories that could contribute these new families of compounds; 2) the identification of promising antibiotics from natural products; 3) strategic management of the intellectual property and benefit sharing; and 4) screening and development of druggable leads.

In a study by investigators from GlaxoSmithKline, it was noted that most corporate compound collections closely conform with the Lipinski rule of five – properties that make a compound more easily druggable as an orally active drug in humans – but antibacterial drugs did not. The differing chemical properties of antibacterials have also been characterized. So the scientific bottleneck may, in part, reflect this mismatch between proprietary compound libraries and potential new families of antibacterial compounds.

In a study reviewing new chemical entities approved as drugs over the past three decades, over a third of small molecule drugs originated from natural products. For antibiotics coming to market between 1982 and 2002, over three-quarters of the drugs derived from natural products. The relative drought in new classes of antibiotics in recent decades suggests the need to enrich compound libraries, particularly with natural products.

The rationale for this initiative is similar to that laid out for the NIH’s Molecular Libraries Initiative, but focused on tapping the rich biodiversity of natural products from low- and middle-income countries for bacterial targets. In making the case for Molecular Libraries Initiative (MLI), the U.S. NIH noted:

For the most part, pharmaceutical and biotechnology companies prefer to focus on the ‘druggable genome’ thought to be more amenable to drug development. The majority of the genome that is currently considered ‘undruggable’ (i.e., unmanipulable by small molecules) is therefore a major focus of the MLI.

Large libraries of small molecules have traditionally been unavailable to academic researchers, but with the advent of combinatorial chemistry and commercial suppliers of high-quality compound libraries, small molecules can now be obtained on a large scale. At the same time, advances in robotics and informatics have made screening and analysis of such large compound libraries possible. Up to a million compounds can now be screened against a target in a single day, three orders of magnitude greater than was possible only a decade ago. Together, these developments make a public-sector small-molecule screening and chemistry initiative such as the MLI possible.
This proposal would fill an important gap: addressing a scientific bottleneck, lowering the barrier for researchers from academic institutions and small firms to tackle this challenge, and enabling low- and middle-income country research constitutions a role in bringing potentially life-saving antibiotics forward.

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.)

In recent years, antibiotic resistance as a priority global health challenge has repeatedly surfaced, from WHO,20 U.S. CDC,21 and the Chennai Declaration in India22 to policy venues as varied as the World Economic Forum23 and G8 Science Ministers meeting.24 Several reasons underlie why antibiotic resistance and the need for novel antibiotics have emerged insistently as a concern of the highest priority. The need for effective antibiotics is the cornerstone not only to treating the burden of infectious disease in low- and middle-income countries, but also makes possible many of the miracles of modern day medicines, from organ transplants to cancer chemotherapy. And the erosion of effective first-line treatment with the emergence of drug-resistant bacterial pathogens has forced a retreat to expensive, second-line treatments for tuberculosis, gonorrhea, and various Gram-negative infections. The spectre of untreatable infections, like Carbapenem-resistant Enterobacteriaceae, also looms while the pipeline for novel antibiotics has faltered.

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?)

This proposal has the potential of engaging a broad range of stakeholders. These include: 1) research institutions from high-, low- and middle-income institutions, such as US-NIH, UK-MRC, India’s Council on Scientific and Industrial Research, the Kenyan Medical Research Institute, Brazil’s Farmanguinhos, or China’s National Center for Drug Screening; 2) research networks like the African Network for Drugs and Diagnostics Innovation and ASEAN-NDI; 3) product development partnerships like the Drugs for Neglected Diseases Initiative, Medicines for Malaria Venture and the Global Alliance for TB Drug Development; and 4) pharmaceutical firms, including those from low- and middle-income countries and small biotechnology companies.

12. Who could potentially manufacture the final product?
Multinational company? Local production? Joint venture? How the decision will be made about the producer?
The proposed drug discovery platform could partner flexibly with a range of potential manufacturers. Much like how the U.S. NIH’s National Center for Advancing Translational Sciences or the European Union’s Innovative Medicines Initiative has done, public funders might support precompetitive research inputs, such as by paying for pharmacodynamic/pharmacokinetic studies or toxicology work, paving the way to first-in-human trials. By derisking the R&D for such products, this approach may broaden the breadth of groups that bring novel antibiotic drug candidates forward. In selecting producers, different pathways might be piloted, each ensuring both affordable access and scaling for rational use of the antibiotic.

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

WHO could serve a convening role in bringing key stakeholders together. Having conducted a 2005 country survey of traditional medicine regulations, pharmacopoeia for herbal products and monographs on herbal products, WHO is well positioned to reach out to this network to identify potential compound libraries and biorepositories that might contribute as stakeholders to this demonstration project. TDR’s efforts in seeding the African Network for Drugs and Diagnostics Innovation and the emerging ASEAN-NDI (ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicines Innovation) may offer other key stakeholders to this convening.

WHO’s Department of Public Health, Innovation and Intellectual Property and the agency’s role in convening intergovernmental negotiations over the Pandemic Influenza Preparedness (PIP) Framework could offer normative guidance in structuring discussions on material transfer agreements and the conditions for humanitarian access licensing of the compounds. In 2008, WHO/TDR entered an arrangement where it would select targets and screens for identifying new drug candidates for a range of infectious tropical diseases, and the National Center for Drug Screening at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, would screen a small molecule library donated by Novo Nordisk for this use. WHO/TDR had developed a Drug Target Database, considered the idea of a TDR Compound Bank, worked on creating networks for screening, medicinal chemistry, drug metabolism and pharmacokinetics, and leveraged industry collaborations with Pfizer, Merck-Serono and Chemtura for enhancing drug discovery efforts for neglected parasitic diseases. Drawing upon these experiences, WHO would be particularly well suited to convene relevant stakeholders and to structure effectively these discussions.

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?
At the outset, a series of strategic convenings could help chart the roadmap forward, identify key stakeholders to involve, and flag obstacles that will require deeper evaluation and discussion. In the first five years, however, the project milestones might include:

- A survey of existing public compound library collections, traditional knowledge biorepositories and potential proprietary collections from which licensing arrangements might be struck;
- A review of existing compound library partnership agreements with public institutions and PDPs, best practices in the licensing of traditional knowledge, and framework for the public sector’s strategic use of intellectual property rights to ensure both benefit sharing and especially affordable access to resulting end-products;
- A legal and policy analysis for structuring a non-profit entity to which licensing agreements might be pooled;
- A scientific roadmap for guiding the optimal pathways for harnessing natural products and prioritizing resources;
- A strategic plan for linking and/or resourcing one or more networks of centers involved in screening, medicinal chemistry, drug metabolism and pharmacokinetics and for handing off promising druggable leads to those positioned to carry out first-in-human trials (e.g., EDCTP or a PDP like DNDi or Global Alliance for TB Drug Development); and
- A business plan for sustainably resourcing these activities over time.

The drug discovery platform for sourcing novel classes of antibiotics can unfold in stages. Some pathways for bringing new drug candidates forward will be facilitated by existing infrastructure, prior experience, and the resources and commitment to contribute towards a global public good.

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 know-how, proposed to be managed in this project?

Much of the work on identifying novel classes of antibiotics might be considered pre-competitive; however, bringing forward a new drug candidate will require a clear plan for handling intellectual property rights. Intellectual property arrangements enter at various steps in the process, including 1) the patenting and licensing of the compound; 2) the material transfer agreement on the compound; 3) R&D tools related to the product (e.g., toxicity testing, biomarkers); and 4) pre-clinical and clinical data.

The compound library for this initiative will have multiple sources. In pooling access rights to these compounds, contributing biorepositories and collections would have to agree to a common minimum standard by which compounds would be made available to interested researchers and commercial firms. Various licensing approaches are possible. From the European Rare Diseases Therapeutic Initiative\textsuperscript{29} to WHO/TDR’s compound library arrangements
with Merck-Serono and Pfizer, these arrangements seem to share some provisions in common: a layer of confidentiality, the option of first refusal, and potential access to proprietary data. A useful framework based on similar principles has been proposed for accessing small molecules of potential commercial value, beyond those for rare or neglected diseases. A second approach is the benefit-sharing system established under the Pandemic Influenza Preparedness Framework. In exchange for gaining access to biological materials made available through the virus-sharing system, the industry pays for half the annual operating costs of the system’s infrastructure. Under the standard material transfer agreement that allows the sharing of these biological materials with vaccine manufacturers, firms primarily from industrialized countries commit to benefit-sharing provisions, such as vaccine donations or vaccine doses discounted to affordable prices. Such an arrangement is supported through tiered pricing of the product between high-income country and LMIC markets.

Relaxing these conditions, an alternative framework might more closely resemble the approach taken by the Indian Council on Scientific and Industrial Research’s Open Source Drug Discovery (OSDD) Initiative. Using a click-wrap license, members of their community contribute to the research commons, but do so with the understanding that the resulting intellectual property remains with the commons. Public funding supports much of this work, and the drug candidates developed through OSDD will be licensed for generic production at close to marginal cost. However, the feasibility of this IP arrangement depends on the level of public financing commitment.

*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)

As life-saving drugs, antibiotics must be affordable to those in need. With growing drug resistance, second-line therapy is often multiples more expensive than first-line treatment. Premium pricing unfortunately not only fails to ration access according to clinical need, but also gives the wrong incentive to drug companies to market an antibiotic for broader indications and wider use. Delinkage of a firm’s return on investment from revenues on a product is key to realigning economic incentives for rational use of antibiotics. Revenues reflect both price and quantity. At the same time, delinkage of a firm’s return on investment from the price of a product can help ensure close-to-marginal cost pricing. To conserve novel antibiotics for those most in need, attention must be paid to both price and quantity.

To meet the twin aims of innovation and access, the demonstration project must also provide adequate return on investment to firms involved in R&D as well as manufacture of the antibiotic. The intervention proposed here helps to derisk the R&D pipeline, thereby lowering the barrier to entry and the upfront R&D costs for bringing a novel antibiotic to market.
Keeping that price low as R&D proceeds will depend on public financing to carry the promising lead to first-in-human trials and through Phase 3 clinical testing. Already parts of that pharmaceutical value chain are publicly financed, from product development partnerships and the EDCTP’s support of clinical trials in low- and middle-income countries to the research infrastructure supported by developing country governments. So handing off novel antibiotic drug candidates to such publicly financed groups will enhance the likelihood that the end-product will remain affordable.

Access concerns should not be limited to the price and supply of the product. In the R&D pipeline, an innovation demonstration project generates data, journal articles, and research tools. All of these also should be made broadly available. Data on shelved products, as well as marketed ones, can prevent the pursuit of blind alleys, anticipate adverse drug reactions in patients, or suggest alternative approaches to optimizing a lead into a druggable compound. Such annotation is invaluable in enriching the value of a compound library collection. The publication of research in open access journals and the non-exclusive or royalty-free licensing of research tools also will contribute to shifting the paradigm of pharmaceutical innovation to meet the needs of those in resource-limited settings.

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.

The project design allows it to be scaled, proportional to available resources. In its simplest conception, the project could be housed as an initiative, similar to TDR’s Target Database and compound library arrangements in a specific product development partnership. As a virtual collaboration, it could grow to require resources similar to the scale of the Medicines Patent Pool seeded by UNITAID and then established as an independent non-profit entity. However, if it were to take on other functions, like acquiring compounds, storing and replenishing the compound collection inventory, or arraying the compounds in sets suitable for high-throughput screening and distributing these compound arrays, then fixed and variable costs, proportional to the size of the collection, would mount. Several other factors will affect the project’s costs, such as 1) the opportunity for initial incubation, 2) the level of in-kind donations and 3) the degree to which the project provides support to enable the development of druggable leads.

While innovative financing is not required for seeding and maintaining this initiative, the project design lends itself to an innovative financing approach. For antibiotics, the reason for delinking return on investment from the sales of the product is compellingly rooted in the biology of drug resistance. An incentive to profit from greater sales of an antibiotic invites overuse and greater drug resistance. Delinkage for antibiotic innovation involves not just divorcing the return on investment from product price, but also volume. Both push and pull mechanisms can help achieve delinkage. Push mechanisms pay for inputs of R&D, and in exchange for such support, can be conditioned to ensure affordable access and scale up for access, but not excess. Pull mechanisms pay for outputs of R&D, but as an upstream intervention, this project could apply
milestone prizes to maintain IP rights as the druggable lead becomes optimized for first-in-human trials. The degree to which antibiotics might be treated as public goods – to be conserved for those in need – depends on the degree of public financing and the public’s insistence on fair returns for that government investment.32

18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination?

The governance and coordination of this project could evolve in stages. The initial stakeholder convenings would benefit from hosting by the WHO. This would also allow a gestational stage when the identification of key biorepositories and compound library collections, drug screening facilities, intellectual property arrangements, potential funders and a business plan for sustainability might be pulled together. Importantly, WHO is well positioned to negotiate the framework for benefit sharing and access to natural products sourced from the biodiverse repositories of member States. As licensing arrangements are struck, this might be best facilitated by creating a non-profit entity. A policy and legal analysis of similar arrangements (from product development partnerships and the Coalition Against Major Diseases to the Biomarkers Consortium, the Medicines Patent Pool and the Critical Path to TB Drug Regimens Initiative) would inform those involved of the best options to ensure efficient and effective operations. This non-profit entity might be able to lower transaction costs for the sharing of promising drug compounds while minimizing liability and antitrust concerns. Representation of key stakeholders, particularly from research institutions and governments of low- and middle-income countries, would ensure collective ownership of the project as a global public good.

19. Have any donor agencies/governments already indicated interest in supporting the project?

Outreach work would need to be done to elicit interest. The G-FINDER provides a portrait of the current funding environment for neglected diseases. The Wellcome Trust, Bill & Melinda Gates Foundation, U.S. National Institutes of Health and the Biomedical Advanced Research and Development Authority, and European Union’s Innovative Medicines Initiative are among the groups that fund in the pharmaceutical R&D space. Other bilateral donors, notably Sweden and the United Kingdom, have raised concerns about the need for antibiotic innovation. Of note, donors focused on the “Big Three” infectious diseases – AIDS, TB and malaria – are already paying attention to a leading bacterial pathogen – tuberculosis. Importantly, India’s Council on Scientific and Industrial Research has already embarked on the Open Source Drug Discovery Initiative that initially focused on drugs to treat tuberculosis, and Japan’s Global Health Innovative Technology Fund has created a Drug Discovery Screening Platform by which five Japanese companies and academic institutions can make available screening libraries to identify novel compounds for treating malaria, tuberculosis, and neglected tropical diseases.
REFERENCES

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