

*1. Title of Project: Building a Diagnostic Innovation Platform to Address Antibiotic Resistance

*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 and tuberculosis, diarrheal diseases including typhoid, sexually transmitted infections, trachoma and rheumatic fever, 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.)

Diagnostic tests for the management of bacterial infections and detection of drug resistance as well as low-quality antibiotics could be build upon a microfluidic platform and offer non-instrumented, disposable point-of-care tests particularly suited for use in low-resource settings.

*5. Project summary (max 500 words)

Fewer than a third of children in low- and middle-income countries receive antibiotics when pneumonia is suspected.¹ The reported rates of neonatal infections are 3-20 times higher in low- and middle-income countries compared to high-income countries, and about 70% of these infections would not be adequately covered by the typical, empiric, first-line therapy of ampicillin and gentamicin.² A study of gram-negative sepsis in Tanzanian children found a mortality rate twice that of malarial infection.³ These findings all underscore the need for improved diagnostics for bacterial infections in low- and middle-income countries.

Novel diagnostics are needed to target treatment for both existing and new antibiotics. This not only will conserve the effectiveness of these treatments, but also avert the unnecessary costs associated with using presumptive or second-line treatment. Such diagnostics could also reduce the costs of clinical trial recruitment. Using the same technology platform, other diagnostics could even test for low-quality antibiotics that contribute to drug resistance. The development

of these diagnostic tests faces therapeutic, financial and structural access barriers.

This proposal for a diagnostic innovation platform to address antibiotic resistance would pool R&D inputs at three key points in the value chain: 1) a specimen bank that serves as a reference against which to test diagnostics; 2) a patent portfolio license bundling key components of the diagnostic platform technology; and 3) a clinical trial network for testing diagnostics. The technology platform discussed here as an exemplar is a microfluidic, paper-based analytic device. Both the paper and patterning for diagnostic purposes have a very low marginal cost. The goal would be to develop a non-instrumented, disposable, point-of-care test particularly well suited for low-resource settings at the base of the pyramid of care. Applying delinkage here, this would make the approach of upfront public funding in exchange for an end-product priced close to marginal cost very attractive.

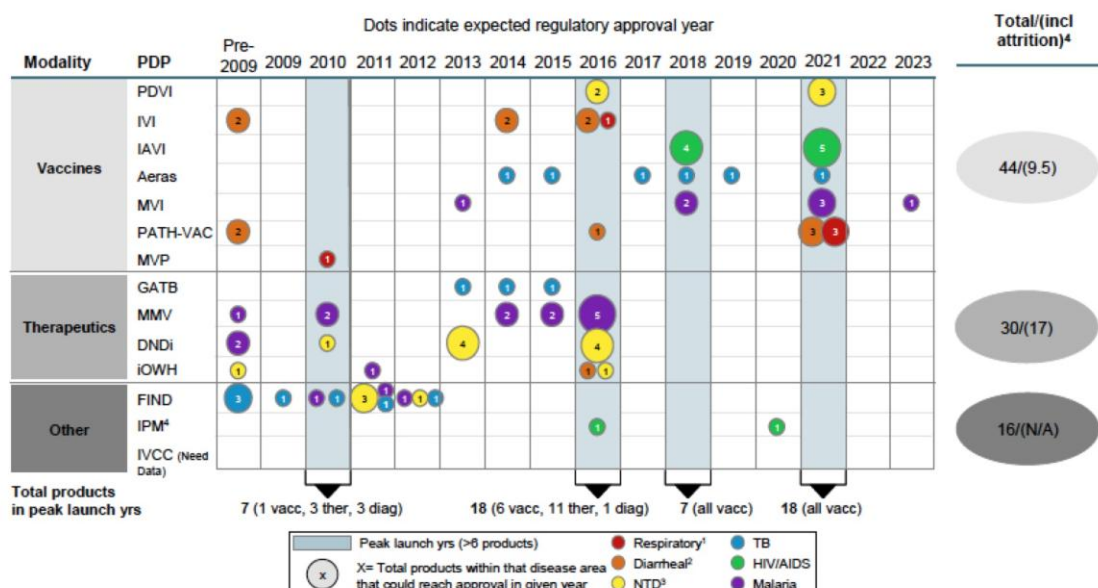
A RAND analysis suggests that a rapid, low-cost, easy-to-use test for bacterial pneumonia could save 405,000 children's lives a year. One for antenatal syphilis could save 138,000 lives and avert more than 148,000 stillbirths a year, and a rapid diagnostic test for TB could save around 400,000 lives a year.

Access to the public infrastructure of a specimen bank, a technology platform, and a clinical trial network could derisk the R&D pipeline, but also be made available to manufacturers willing to accept push or pull financing in exchange for close-to-marginal cost pricing in low- and middle-income countries. Applying the ASSURED criteria, target product profiles would shape the criteria for awarding grants from push financing or milestone prizes from pull financing. The use of some of these diagnostics for biodefense and home health care in industrialized countries suggests a potential dual market business strategy as well.

*6. Public health need that the proposed project aims to address: (max 400 words)

Diagnostic tests for bacterial infections could speed treatment to those in need, but have encountered barriers of therapeutic, financial and structural access. Despite the significant need, companies have failed to deliver low-cost diagnostics suited for resource-limited settings. Compared to drugs and vaccines, there is a dearth of public-private partnerships focused on diagnostics and in the pipeline of novel diagnostics in the outbound years (as seen in the following snapshot of existing PDP portfolios).⁴ Yet a RAND study suggested that where there is no infrastructure, a TB test with 85% sensitivity and 97% specificity would save 263,000 lives, or 15% of the world's TB deaths (adjusted for the opportunity costs or treatment resources required).⁵

C: Snapshot of PDP Portfolios, June 2009^{4,5}



1. Includes pneumonia and meningitis. 2. Includes cholera, typhoid, and rotavirus. 3. Includes HAT, visceral leishmaniasis, chagas, hookworm, and dengue. 4. IPM products listed are a subset of all candidates in development. This is due to IPM's novel approach to Phase III clinical trials, which includes forced product attrition. Sources: To estimate time until launch, survey responses from the 2008 PDP Access meeting were used where available. Next, public sources were referenced including the STOP TB website and PDP websites. Where no launch dates were available, vaccine launch dates were estimated using industry averages published by BIO, the biotechnology industry association (Pre-clin=3yrs, PII=2yrs, PIII=2yrs, Reg=3yrs). Drug launch dates were estimated using the industry averages as reported in a 2007 IFPMA report (Pre-clin=1yr, PII=1yr, PIII=1.5yrs, Reg=1.5yrs). Microbiome launches were estimated using data from the IPM Strategic Plan 2009-15. For all estimates, it was assumed that candidates were starting the current phase 5. Drug attrition was estimated using industry averages of success by phase, published by IFPMA in 2007 (Pre-clin=0.51, PII=0.7, PIII=0.5, Reg=0.9). Vaccine attrition was estimated using industry average success rates by phase, published by Andrew Farlow from the University of Oxford in the TB Vaccine Scoping Study, 2008 (Pre-clin=0.6, PII=0.8, PIII=0.6, Reg=0.75). Microbiome attrition is assumed to be included in IPM's total expected products. IPM uses a novel approach to Phase III clinical trials, which includes forced product attrition. Diagnostic attrition was excluded because diagnostics follow a unique regulatory path.

The cost of diagnostics can add another barrier of financial access. Even breakthrough diagnostics introduced for resource-limited settings still come at considerable expense. For example, the Xpert MTB/RIF impressively tests for both TB and rifampin resistance using a proprietary, cartridge-based system that minimizes hands-on sputum processing and delivers results in two hours.⁶ But each machine costs US\$17,000, and even with volume discounts, comes to just under US\$10 per test.⁷

As a structural access challenge, there still remains the need for a POC test not only for TB, but also for the evaluation of fever in children, the diagnosis of various bacterial neglected tropical diseases such as trachoma and rheumatic heart disease, and improved screening for sexually transmitted diseases. WHO guidelines suggest that diagnostic tools for resource-limited settings should follow the ASSURED criteria: 1) affordable, 2) sensitive, 3) specific, 4) user-friendly, 5) rapid and robust, 6) equipment-free, and 7) delivery to those who need it.⁸ Desirable characteristics for point-of-care diagnostics are: 1) disposability, 2) cost-effectiveness, 3) ease of use, and 4) portability.⁹

For bacterial infections, better diagnostic tests can avert unnecessary antibiotic treatment, minimizing both resistance and adverse drug reactions. Providing savings, diagnostic tests may not only reduce the expense of unnecessary treatments and even obviate the need for presumptive use of broader spectrum, more expensive antibiotics before de-escalation, but also lower the costs of

clinical trial recruitment. The gains in treatments averted increase as the diagnostic developed can extend beyond tertiary referral centers towards the base of the pyramid of care. Disproportionately this burden of disease falls upon low- and middle-income countries, notably for co-infection of HIV and TB, where Africa and Southeast Asia account for 93% of the mortality worldwide.

*7. Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate? (max 300 words)

A project focused on bringing novel diagnostics forward could demonstrate multiple, innovative approaches to financing and coordinating R&D. At several points in the value chain, diagnostic development would benefit from pooling R&D inputs—a specimen bank that serves as a reference against which to test diagnostics; the key components of the diagnostic platform technology; and patients recruited to a clinical trial network for testing. By lowering the marginal cost of production markedly, a microfluidic paper-based analytic device could keep the material costs to a minimum, quite possibly less than US\$0.01 for the cost of both paper and patterning it for diagnostic purposes.¹⁰ Applying delinkage here, this would make the approach of upfront public funding in exchange for an end-product priced close to marginal cost very attractive.

Access to the R&D pools could be coupled with push or pull financing mechanisms. Using push mechanisms, grants might support the development of novel diagnostics, but condition scale-up to ensure close-to-marginal cost pricing. Using pull mechanisms, prizes might offer incentive for firms to develop these diagnostics and to provide technical assistance to scale their manufacture for those in need. The public infrastructure of a specimen bank, a technology platform and a clinical trial network could reduce R&D costs, but be made available only to those manufacturers willing to accept push or pull financing in exchange for close-to-marginal cost pricing. The potential use of some of these diagnostics for both resource-limited settings and also for biodefense and home health care in industrialized countries suggests funding and sales revenue opportunities as part of a dual market business strategy.

*8. Evidence of market failure/research landscape: (Max 200 words)

Compared to drugs or vaccines, the landscape for diagnostic R&D for resource-limited settings shows both fewer product development partnerships, notably FIND and PATH, and many fewer candidate technologies beyond the short-term time horizon.¹¹ This is, in part, a reflection of the much shorter time it takes to bring a diagnostic from bench to bedside. The required public investment is also more modest than bringing a drug or vaccine to market. For antibiotics, there may also be a collective action failure, whereby multiple firms working on the same bacterial target may not have a compelling reason to develop a diagnostic that the others would free-ride off.

9. The scientific and technical feasibility: (max 500 words)

Microfluidic systems hold great promise in delivering a diagnostic suited for resource-limited settings. There are high performing benchtop assays, disposable assay cards that carry the needed reagents with a portable reader capable of assay automation and quantitative optical measurement, and disposable dipstick assays.¹² The last of these has particular appeal in reaching the bottom of the pyramid of care. Microfluidic devices that can be mass produced, be built at low cost out of disposable materials like paper [e.g., fast lithographic activation of sheet (FLASH)], and offer rapid and sensitive diagnosis warrant priority attention. Paper networks also obviate the need for highly precise pumps or pneumatic control systems that add cost and power requirements to diagnostic testing.¹³ Lack of refrigeration, electrical power, and trained healthcare personnel also shape the conditions under which these paper diagnostics must work. There also remain important challenges for using microfluidic devices with biological samples, including passivation and the prevention of fouling, for which targeted public sector intervention might help. Passivation involves modifying surfaces, so as to reduce non-specific binding, and fouling refers to unintended binding to device surfaces and the blocking of microchannels by the biological sample used.¹⁴ Sample volume and pre-treatment requirements must be kept to a minimum in these resource-limited settings.

While not based on microfluidic technology, the fielding of immunochromatographic strip (ICS) tests afford useful insight into the approach that might be taken for other tests targeted to low-resource settings. ICS tests offer POC diagnosis where laboratory processing of samples, the use of external instruments, and electricity or cold storage might not be available. An example would be the lateral flow strip that tests for gonorrhea.¹⁵ While significantly better than syndromic management, the sensitivity and specificity of such tests leave much room for improvement. Microfluidic immunoassay platforms offer several potential advantages over existing tests: 1) improving the characteristics—sensitivity and specificity—of existing diagnostic tests; 2) extending the spectrum of pathogens detectable by POC testing; 3) offering multiplex capability to detect more than one pathogen at the same time; and 4) enabling nucleic acid amplification that may be more sensitive and specific than immunoassay tests.¹⁶

An innovation platform for development of such paper analytical devices could also have useful complementary applications. Notably, inexpensive test cards may provide for rapid field screening of beta-lactam antibiotics (ampicillin, amoxicillin), combinations of first-line TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide), substitute ingredients (acetaminophen and chloroquine) often used in counterfeit pharmaceuticals, and binders and fillers not customarily detected by traditional chromatographic methods (chalk, talc and starch).¹⁷

10. Reasons for proposing: (approx 200 words)

Diagnostics play a critical role in ensuring the effective use of antibiotics. This proposed innovation demonstration project would enable bringing to market novel diagnostic tests for the management of bacterial infections and detection of drug resistance as well as low-quality antibiotics. These tests could be built upon a microfluidic platform and offer non-instrumented, disposable point-of-care tests particularly suited for use in low-resource settings. This technology could improve clinical outcomes by obviating the presumptive use of broad-spectrum and novel antibiotics in the face of clinical uncertainty; lower clinical trial recruitment costs; ensure effective stewardship of novel antibiotics; signal to policymakers the prevalence of drug-resistant organisms in the food chain by making a latent problem visible; and enable more tailored targeting of the mass administration of antibiotics. A RAND analysis supports the need for a broadly available diagnostic and documented the value of improved diagnostics across a range of bacterial infections:¹⁸

- A quick, easy-to-use test for bacterial pneumonia could save at least 405,000 children's lives each year.
- A widely accessible, easy-to-use diagnostic for antenatal syphilis would save at least 138,000 lives and avert more than 148,000 stillbirths annually.
- A rapid, easy-to-use test for TB could save approximately 400,000 lives per year.

11. Who could potentially develop the technology/carry out the research?
(Max 100 words)

This proposal could engage a range of stakeholders, including: 1) South-South research networks like the African Network for Drugs and Diagnostics Innovation and the ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicines Innovation; 2) product development partnerships like PATH and the Foundation for Innovative New Diagnostics (FIND); 3) the Critical Path to TB Drug Regimens, for which TB diagnostic development will become part of its work; 4) research institutions involved in the study of microfluidic, paper analytical devices¹⁹; and 5) diagnostic device groups, including such non-profit groups as "Diagnostics for All."

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

The manufacture of paper-analytical devices could be decentralized, with licensing and technology transfer distributed to local manufacturers. Qualifying manufacturers that meet the target product profiles for diagnostic tests and that successfully measure up to prequalification and specific procurement criteria, set by the WHO procurement service for diagnostics, would be eligible for

procurement contracts in low- and middle-income countries. To access the publicly financed innovation platform pooling R&D inputs, manufacturers would have to commit to the affordable access provision, grant back incremental improvements to the pool, sharing pre-clinical and clinical testing data, and quality controls.

13. What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition? (max 200 words)

WHO could serve a convening role in bringing key stakeholders together. The intergovernmental agency can draw upon its experience in prequalifying diagnostic manufacturers, in facilitating Member States' access to high quality procurement of diagnostics, in ensuring quality of diagnostics, and in providing guidance and training for diagnostic laboratories. The WHO Prequalification of Diagnostics Programme involves 1) review of the application and product dossier; 2) laboratory evaluation of the product; and 3) inspection of the manufacturing site(s).²⁰ Established in 1990, the WHO procurement service for diagnostics has expanded over the years to include diagnostics for HIV/AIDS, malaria, hepatitis B and hepatitis C in addition to basic laboratory consumables and equipment. The WHO has provided guidance to the procurement of accurate, safe and appropriate diagnostics and reliable laboratory services.²¹ The National Serology Reference Laboratory in Australia serves as a WHO Collaborating Center for producing and distributing HIV QC samples to laboratories in the Southeast Asian, Western Pacific and African regions.²² WHO also has provided guidance and targeted training programs on diagnostics and improving the quality of laboratories for WHO member states.²³ Aliquots of specimens from adults with symptoms of pulmonary tuberculosis from the WHO/TDR collection are now consolidated and stored through FIND and made available to commercial and academic researchers developing TB diagnostics for low- and middle-income settings.²⁴

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? (max 200 words)

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

- Development of target product profiles for both diagnostic tests for bacterial pathogens and drug-resistant strains as well as for detection of low-quality antibiotics;
- A scientific roadmap for guiding the development of these diagnostic tools, including key performance indicators for a specimen bank, the pooling of

essential patents for paper-based analytical devices, and their clinical trial testing;

- A legal and policy analysis that would examine the intellectual property landscape for both the technology platform and the identification of specific bacterial pathogens and low-quality antibiotics, the potential licensing models for ensuring delinkage, and optimal way to structure the pooling arrangements involved;
- A strategic plan for linking and/or resourcing one or more networks of centers at different points in the diagnostic value chain (e.g., specimen banks like FIND's, PDPs like FIND and PATH, research networks like ANDI and ASEAN-NDI, and clinical trial networks like those supported by the European and Developing Countries Clinical Trials Partnership); and
- A business plan for sustainably resourcing these activities over time.

The components of this proposed diagnostic platform can unfold in stages, piggybacking in some cases on existing research infrastructure.

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? (max 400 words)

The intellectual property landscape will require identifying essential patents related to the key technology platform and conducting a freedom-to-operate analysis. Various research groups involved in paper analytical devices are not infrequently already dedicated to applying these technologies for resource-limited settings in low- and middle-income countries. For example, Diagnostics for All—a non-profit dedicated to “creating low-cost, easy-to-use, point-of-care diagnostics”—holds an exclusive worldwide license on patterned paper technology from Harvard University for its medical diagnostic and other applications.²⁵

Intellectual property arrangements influence 1) the patenting and licensing of diagnostic technology, including R&D tools related to the product; 2) the material transfer agreement for reference specimens; and 3) access to pre-clinical and clinical testing data. Each of these R&D inputs might benefit from pooling arrangements that facilitate the cross-licensing of this intellectual property.

As in patent pools in the electronics industry, certain essential patents are required for implementing a standard, like MPEG-2 video and systems coding standards in DVD players and recorders, TVs and personal computers. Applied to microfluidic, paper-based diagnostics, the patent portfolio would need to pool the essential patents that would enable innovation and implementation of these diagnostic technologies. These may be field limited by indication (e.g., the testing of bacterial pathogens, resistant strains and low-quality antibiotics) and by geography (extending to both low- and middle-income countries or globally).

Each licensor would grant to the pool a worldwide, nonexclusive license, such that the pool would be able to license or sublicense these patents under the terms of the bundled portfolio license. Existing institutions, like MPEG LA or the Medicines Patent Pool, might provide such a service.

The goals for arranging such a patent portfolio license would be to ensure 1) low barriers to entry for those seeking to innovate new diagnostics for resource-limited settings; 2) minimal or no royalty costs associated with licensing such technology; and 3) commitment to close-to-marginal cost pricing and affordability of the resulting inventions for low- and middle-income countries. Licensors committing to these arrangements might receive various incentives, from publicly funded patent buyouts to preferential access at low or no royalty rates to the patent portfolio license. Making a commitment to close-to-marginal cost pricing, licensees similarly might receive the patent portfolio license under the preferential arrangement. The commitment to close-to-marginal cost pricing would entail not only meeting the unit price set under the target product profile for the diagnostic, but also involve the option of independent audit to verify the product's marginal cost base. Derivative patents or the patenting of inventions improving upon the IP in the patent portfolio license would require grant back to the pool.

To ensure the commercial viability of this R&D work, innovative financing through push or pull mechanisms might be applied in conjunction with the pool. Pull financing that pays for the outputs of R&D could buy out patents for licensing in the patent portfolio license or provide milestone payments for diagnostics meeting the specifications of the target product profile. Push financing that pays for inputs of R&D could support research groups to develop such diagnostics, and these grants could be conditioned to ensure close-to-marginal cost pricing and affordability in resource-limited settings of the resulting diagnostic technologies.

*16. What would be the strategy to ensure access to the product once it is developed? (max 400 words)

The proposed innovation demonstration project takes into consideration all three dimensions of access—therapeutic, financial and structural access—from the outset. Helping to ensure therapeutic access, the reference specimen bank, the patent portfolio license, and access to the clinical trial network significantly derisk the pipeline for diagnostic R&D, and in exchange, the fair returns on this public investment would come in the form of a commitment to close-to-marginal cost pricing and affordable end products.

The push and pull financing also seeks to ensure financial access by derisking the R&D pipeline and removing market exclusivity on these public goods for resource-limited settings. Such innovative financing also importantly offsets the market failure in delivering such technologies for these settings.

To ensure structural access, the target product profiles established for diagnostic R&D will help shape the R&D direction taken and define the milestones for pull financing. These target product profiles will reflect the ASSURED criteria for a diagnostic. For paper-based analytical devices, there is the advantage that the fixed and marginal costs of fabricating and using patterned paper technology is inherently low-cost.

The vision for this family of paper-based analytical devices is well captured in this description from the Diagnostics for All website:²⁶

To fabricate a diagnostic device, DFA patterns channels and assay zones (or wells) of water-repellant materials into a piece of paper roughly the size of a postage stamp. Biological and chemical assay reagents are then deposited in the wells. When blood, urine, saliva, sweat or other biological samples are applied to the device, the paper wicks the sample through the channels to the assay zones, without external pumps or power. Upon contact, the assay zone quickly changes color and results are then easily read by comparing the color change with a reference scale printed on the device. After use, the device can be easily disposed of by burning. As we develop more advanced diagnostics, DFA's patterned paper-based devices can be embedded with electrical circuitry to enable resistive heating, electrochemical assays, or initial processing of assay results. Additionally, multiple sheets of patterned paper can be stacked to generate three-dimensional devices capable of automatically performing a variety of complex fluid operations such as splitting, filtration, mixing, and separations.

Building these expectations upstream in the R&D pipeline promise greater assurances that the diagnostic technologies will perform effectively in resource-limited settings downstream in the delivery system.

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.

Disruptive innovation, by definition, initially focuses on technologies with “lower gross margins, smaller target markets, and simpler products and services that may not appear as attractive as existing solutions when compared against traditional performance metrics.”²⁷ In this innovation demonstration project, the paper-based diagnostic technologies fill unmet needs in non-paying markets, but also have potential application in industrialized country markets.

By their nature, such disruptive technologies may alienate traditional sources of financing. Groups like Diagnostics for All support their mission through “general public donations, project-specific funding, and philanthropic support.” For

example, Diagnostics for All has drawn its prior support from the Bill & Melinda Gates Foundation, governmental sources (DARPA, Grand Challenges Canada, Norwegian Ministry of Foreign Affairs, UK Department for International Development, USAID, and the World Bank), and Goodwin Procter LLP, a law firm.

While systematic estimates of the costs of developing diagnostics are wanting, the following table provides a summary of costs related to the development of selected TB diagnostic tests [Costs of Developing Selected TB Diagnostics (see Table 6.1, p. 145)].²⁸ The opportunity cost of capital is not reflected in these estimates, but public financing importantly can keep these opportunity costs lower than private sector venture capital. The total out-of-pocket costs for R&D ranges up to \$10,600,000 in the United States and the European Union (assuming the participation of such companies and research institutions in public-private partnerships) to \$995,000, an order of magnitude lower in the rest of the world. However, for multi-drug resistant bacterial pathogens, clinical trial recruitment will be more challenging and more costly.

The baseline costs associated with establishing and maintaining a reference specimen bank might best be reflected in the WHO/TDR experience in doing this for the TB Specimen Bank, subsequently transferred to FIND. By comparison to pharmaceuticals, the clinical trial costs for diagnostics are relatively modest.

The financing of these diagnostics allows the piloting of push and pull mechanisms that result in close-to-marginal cost pricing. Using pull mechanisms, prizes could pay for milestone achievements defined by a specified target product profile for a diagnostic. The prize could result in public sector buy-out of the intellectual property, thereby enabling the generic licensing of the diagnostic test to multiple manufacturers. Using push mechanisms that pay for inputs of R&D, such as licensed access to the technology platform for paper diagnostics, such public support might be conditioned to ensure affordable access and application tailored to low- and middle-income country settings. Both push and pull financing approaches could demonstrate delinkage, that is, divorcing the return on investment from the prices of the resulting products.

These diagnostic tests for resistant bacterial pathogens also afford the opportunity for a dual market. Their potential use in home health care and by first responders dealing with pandemics or biowarfare agent release²⁹ suggest a paying market that might further reduce the costs of bringing such diagnostic tests to market or making them available at or below marginal cost in low- and middle-income country markets.

Table 6.1: Costs of Developing Selected TB Diagnostics (US\$)

Item	Type of test				
			Nucleic acid amplification	Screening test	Drug susceptibility testing
Location of company	Rest of world	United States and European Union	United States and European Union	United States and European Union	United States and European Union
Market research costs	10,000	100,000	50,000	500,000	500,000
Technology acquisition and patent fees		275,000	250,000	50,000	200,000
Development of prototype		3,775,000	4,000,000	4,662,000	2,825,000
Consumables used during development		1,575,000		75,000	150,000
Scale-up and validation			600,000	200,000	200,000
Total product development costs	575,000	5,625,000	4,850,000	4,987,000	3,375,000
Total costs of clinical trials(location of study sites)	180,000 (disease-endemic countries)	1,450,000 (United States and European Union)	2,000,000 (United States and European Union)	294,000 (disease-endemic countries)	
Regulatory approval costs (agencies)	100,000 (FDA, European Union)	800,000 (United States)	454,000		
Marketing and launch support costs	80,000	1,500,000	200,000		
Product support costs for one year	50,000	1,125,000	20,000		
Total	995,000	10,600,000	7,574,000	5,781,000	3,875,000

Source: <http://www.who.int/tdr/about/resources/default.htm>.

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

Governance and coordination of this project would grow out of the initial stakeholder discussions organized by WHO. Early in the process, steps would be taken to identify key stakeholders and institutions capable and willing to manage the key components of the innovation platform (reference specimen bank, pooling of IP for patent portfolio license, and clinical trial network). A product development partnership would ideally take on the role of continued coordination of the virtual value chain for diagnostic R&D. Key public sector stakeholders, including research institutions from low- and middle-income countries, would be represented in the governance of this entity to ensure fair returns on the public investment. The design of this innovation demonstration project also does not require starting from scratch. Many of its components might piggyback or be grafted upon existing institutions, if they are willing to take on the additional mandate. MPEG LA and the Medicines Patent Pool have experience with pooling IP; WHO/TDR and FIND, with managing the TB Specimen Bank; and the European & Developing Countries Clinical Trials Partnership, with supporting a clinical trials network. FIND and PATH both have served as PDPs for diagnostic R&D.

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

Canvassing for interest among public and philanthropic funders would be important to undertake. As evident from the funding of product development partnerships, biomedical research funders (Bill & Melinda Gates Foundation, NIH) and other governmental agencies (DFID, Irish Aid, Government of the Netherlands, BMBF—the Federal Ministry of Education and Research in Germany) have supported diagnostics R&D in the past. Donors focused on the “Big Three” infectious diseases (e.g., UNITAID, the Global Fund to Fight AIDS, Tuberculosis and Malaria) are already paying attention to a leading bacterial pathogen—tuberculosis.³⁰ G-FINDER also has identified leading funders for bacterial disease targets, such as bacterial pneumonia and meningitis R&D (see Table 11 below),³¹ rheumatic fever (see Table 17),³² and trachoma (see Table 18).³³ Both research funding agencies in industrialized and developing countries appear on this list.

Table 5. Top 12 TB funders

FUNDER	AMOUNT (US\$)	%
US National Institutes of Health	121,741,199	29.7
Bill & Melinda Gates Foundation	115,864,538	28.2
European Commission	21,455,029	5.2
UK Medical Research Council	12,710,433	3.1
Dutch Ministry of Foreign Affairs	12,187,935	3.0
US Centers for Disease Control	11,617,000	2.8
Institut Pasteur	7,996,742	1.9
German Federal Ministry of Education and Research*	4,391,435	1.1
Irish Aid	4,111,435	1.0
UK Health Protection Agency	3,903,521	1.0
United States Agency for International Development	3,893,436	0.9
Statens Serum Institute	3,672,882	0.9
Subtotal	323,545,584	78.8
Disease Total	410,428,697	100.0

* The German Federal Ministry of Education and Research did not participate in the survey. Their contribution was compiled from grant information provided by funding recipients and may be an underestimate of their true investment

Table 11. Top 12 bacterial pneumonia & meningitis R&D funders

Funder	FY2007 (US\$)	FY2008 (US\$) ^A	FY2007%	FY2008%	FY2007 Rank	FY2008 Rank	Change in reported funding
Aggregate pharmaceutical and biotechnology company respondents ^A	15,747,037	50,494,753	48.4	55.6	1	1	100
Bill & Melinda Gates Foundation	5,598,040	26,282,476	17.2	28.9	2	2	100
US National Institutes of Health (NIH)	4,194,589	4,030,496	12.9	4.4	3	3	
UK Medical Research Council (MRC)	1,776,977	1,985,766	5.5	2.2	4	4	
Butantan Institute ^B	-	1,599,229	-	1.8	-	5	
US Centers for Disease Control and Prevention (CDC)	1,455,973	1,402,671	4.5	1.5	5	6	
Brazilian Ministry of S&T: National Council for Scientific and Technological Development (CNPq) ^C	-	963,391	-	1.1	-	7	
State of Sao Paulo Research Foundation (FAPESP) ^C	-	963,391	-	1.1	-	8	
Research Council of Norway ^B	-	589,942	-	0.6	-	9	
Australian National Health and Medical Research Council (NHMRC)	315,006	504,622	1.0	0.6	10	10	
Bio Manguinhos	0	385,945	-	0.4	-	11	
French National Research Agency, Agence Nationale de la Recherche (ANR) ^B	-	291,451	-	0.3	-	12	
Subtotal top 12 funders ^D	(32,317,719)	89,494,134	(99.4)	98.5	-	-	
Disease Total	32,517,311	90,844,284	100.0	100.0	-	-	

^A Figures are adjusted for inflation and reported in 2007 US dollars^A Includes new survey respondents in 2008^B New survey respondent in FY2008^C Contributions compiled from grant information provided by funding recipients so may be incomplete^D 2007 top 12 has been updated to include aggregate industry data, and therefore differs from published top 12 figures for 2007

Table 17. Rheumatic fever R&D funders

Funder	FY2007 (US\$)	FY2008 (US\$) ^A	FY2007%	FY2008%	FY2007 Rank	FY2008 Rank	Change in reported funding
Aggregate pharmaceutical and biotechnology company respondents ^A	-	963,391	-	44.2	-	1	
US National Institutes of Health (NIH)	1,284,919	629,315	76.9	28.9	1	2	
Australian National Health and Medical Research Council (NHMRC)	385,170	338,310	23.1	15.5	2	3	
Australian Government Department of Innovation, Industry, Science and Research ^B	-	106,805	-	4.9	-	4	
Swedish Research Council ^B	-	58,887	-	2.7	-	5	
Australian National Heart Foundation ^C	-	54,212	-	2.5	-	6	
Undisclosed funder	-	28,691	-	1.3	-	7	
Disease Total	1,670,089	2,179,609	100.0	100.0	-	-	

^A Figures are adjusted for inflation and reported in 2007 US dollars^A Includes new survey respondents in 2008^B New survey respondent in FY2008^C Contributions compiled from grant information provided by funding recipients so may be incomplete

Table 18. Trachoma R&D funders

Funder	FY2007 (US\$)	FY200 8 (US\$) ^A	FY2007%	FY200 8%	FY2007 Rank	FY200 8 Rank	Change in reported funding
US National Institutes of Health (NIH)	0	1,037,612	-	50.0	-	1	8
Statens Serum Institute (SSI)	0	703,674	-	33.9	-	2	
Brazilian Ministry of Health, Department of Science and Technology	0	170,326	-	8.2	-	3	
Aggregate pharmaceutical and biotechnology company respondents ^A	104,000	96,339	6.2	4.6	2	4	
Swedish Research Council ^B	-	38,276	-	1.8	-	5	
Institut Pasteur	0	27,432	-	1.3	-	6	
Disease Total	1,679,711	2,073,659	100.0	100.0	-	-	

^A Figures are adjusted for inflation and reported in 2007 US dollars

^A includes new survey respondents in 2008

^B New survey respondents in FY2008

ENDNOTES

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