COMMENTARY

BVGH'S FEVER DIAGNOSTIC PRIZE: KUDOS AND COMMENTS

The Center for Global Health R&D Policy Assessment's analysis of BIO Ventures for Global Health's milestone-based prize for point-of-care fever diagnostics

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Results for Development Institute

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Overview

BIO Ventures for Global Health (BVGH) recently unveiled its proposal for a milestone-based prize for point-of-care (POC) fever diagnostics ("The Global Health Innovation Quotient Prize") at the Partnering for Global Health Forum in Washington, DC and submitted it to the WHO Consultative Expert Working Group on R&D: Financing and Coordination.

It's exciting to see this proposal on the table, along with others like the X Prize proposal for TB diagnostics and the Knowledge Ecology International prize fund proposals.

We released our own analysis of prizes for global health innovation earlier this year, concluding that prizes are a promising tool that should be tested.

We've taken a look at the full BVGH prize donor proposal and asked: In light of what we learned about prizes from our own work, should donors consider funding this proposal? What questions should they be asking as part of their due diligence?

The BVGH proposal is specific—it makes the case for a new technology to diagnose fever in low-resource settings, presents a target product profile (TPP), and lays out a detailed prize design. The proposal would offer a $150 million prize purse to incentivize the development of a low-cost POC diagnostic that could distinguish among childhood fevers caused by several common diseases in developing countries, including leading killers like malaria and pneumonia, using a single sample (blood, sputum, saliva, mouth swab, or urine)[1]. Nearly nine million children under the age of five die each year, and diseases presenting non-specific febrile symptoms account for more than 30% of the global childhood mortality.

Overall, we applaud the BVGH team for a thoughtful and well-designed proposal addressing an important public health need. We believe their prize idea should be seriously considered by potential funders.

BVGH is soliciting feedback that might help them to improve their proposal. In that spirit, we explore a series of topics below, expressing praise for certain features of the fever prize and highlighting other areas where we feel that key questions still need to be answered and some additional design effort may be required.

[1] The BVGH proposal distinguishes between a "minimum" and an "optimal" TPP. Unless noted, our discussion and analysis generally refers to the "minimum" TPP, which focuses on malaria, bacterial pneumonia, and pan-bacterial infection.

The Key Questions

1. Is a multiplex POC fever diagnostic an important priority?

On this question, the BVGH proposal makes a strong case, arguing persuasively that there is a great need to accurately diagnose fever in low-resource settings and that the existing technology—malaria rapid diagnostic tests (RDTs)—has significant limitations. Three points worth emphasizing include:

- *As malaria burden falls in previously high-burden areas, other causes of fever will become proportionately more important.* Malaria control efforts over the last decade have been successful in many places, bringing down the prevalence of malaria in highly endemic countries. As this trend continues, fewer people with fever will actually have malaria, and it will become more important to pinpoint other causes of fever.
- *Timely and accurate diagnosis of these fevers makes appropriate treatment more likely and prevents misuse of antimalarial drugs.* Negative results from malaria tests have not proven sufficient in many settings to motivate and guide proper treatment: health workers and patients often ignore the results and use antimalarial treatments anyway, including artemisinin-combination treatments (ACTs). Getting healthcare workers and patients to adjust their assumptions about the cause of fevers will be easier if a diagnostic can tell them what illness they *have* as well as what they *don't have*. Such a diagnostic could help to curtail the rise of resistance to both antimalarials and antibiotics.
- *Many patients seek care for fever in the informal private sector: getting treatment right will require a cheap and true POC test.* Since the majority (perhaps 60-80%) of people with fever in Africa seek treatment in the informal retail sector (drug shops), there is an increasing need for accurate diagnosis in the kinds of settings that BVGH has identified.[2] A test that requires little infrastructure and training and provides results quickly would help diagnose fevers in many more children, including those in rural areas who cannot reach clinics easily, than existing technologies. The need for good fever diagnosis in the informal private sector has been made even more urgent by the launch of the Affordable Medicines Facility for Malaria, which is bringing less costly ACTs to these outlets.

2. Is a prize the appropriate incentive mechanism?

In order to answer this question, we need to understand the technological challenges and opportunities facing the development of a fever diagnostic. Our research on prizes for TB diagnostics suggests that prizes, which don't require the sponsor to choose a path or a product developer, are most useful when the way forward is unclear and new ideas and innovators are

[2] Foster S. Treatment of malaria outside the formal health services. Journal of Tropical Medicine and Hygiene. 1995;98(1):29-34. Marsh VM, Mutemi WM, Willetts A, BayahK, Were S, Ross A, et al. Improving malaria home treatment by training drug retailers in rural Kenya. Trop Med Int Health. 2004 Apr;9(4):451-60. Snow RW, Peshu N, Forster D, Mwenesi H, Marsh K. The role of shops in the treatment and prevention of childhood malaria on the coast of Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1992;86:237-9.

needed. In other circumstances, when the necessary work is straightforward and the sponsor can identify a capable developer to carry it out, a conventional grant or contract may be simpler and cheaper. Prizes are also less useful when only a small number of developers stand a chance of solving the problem.

According to BVGH, biomarkers for the 5-6 common diseases causing fever have been identified, so it is unlikely that more discovery work is needed. Rather, what is required to develop the diagnostic is complex engineering and the adaptation of existing platforms to meet the stringent technical specifications. In deciding whether a prize is the right mechanism in this case, the key questions are: will resolving these engineering challenges require new ideas and multiple approaches, and are there a sufficient number of firms out there who might be able to solve the challenges? It seems likely that the answer is yes to both questions, but we found a few cautionary points.

Developing a test that can use a single sample to detect multiple diseases and give a result in 30 minutes for less than $5, without running water or electricity, is a tough but feasible challenge. BVGH found that none of the 80 companies it surveyed are currently in a position to meet the TPP, but several are relatively close to meeting the requirements for the first of the several proposed development milestones (proof of concept). Since there may be several possible technological approaches, and many biotech firms apparently have a shot at winning, a prize would be useful to attract a diversity of solutions.

However, an important technical question that remains to be sufficiently addressed is whether the known biomarkers for the diseases in question are found in the same sample type. For example, the malaria markers used in RDTs are in blood: are there reliable blood markers for bacterial pneumonias as well? If a full set of biomarkers is unknown for any of the sample types, then the technological challenge might be too great for biotechnology firms, which this kind of prize mechanism aims to target. Generally, university labs are behind biomarker discovery so their expertise may also be required.

3. Is the prize proposal well designed?

A key strength of the BVGH proposal is the overall prize structure and its focus on creating incentives for a specific class of product developers – biotechnology companies. Biotechs are more likely to provide the type of innovation needed in earlier R&D stages and to respond to a series of reward payments for achieving defined milestones, rather than to a single big prize for a finished product. The prize includes four milestones (proof of concept, platform build, clinical validation, and regulatory approval) and anticipates a total of 22 award payments to multiple developers, with the goal of bringing two products all the way to the finish line. Consistent in many ways with standard biotech business models, the BVGH prize design allows firms to reduce risk and upfront costs, and possibly to gain "early wins."

Some technical assistance may be necessary to further reduce barriers to participation and success for biotechs. For example, giving participants shared access to sample banks, helping aggregate demand in a fragmented market, and clarifying regulatory pathways in developing countries could be important to allow firms to test their technologies and abate the "market fog" perceived by the industry. While the BVGH proposal recognizes that certain core interventions are required to facilitate product development, it largely places the onus on potential innovators to carry them out. BVGH could consider partnerships with appropriate organizations to provide these in-kind benefits.

Under the proposed structure, contestants entering the prize competition are required to complete milestone 1[3]. If the most difficult challenges may be in getting from milestone 1 to 2, as BVGH has noted, then it might be worth considering a structure in which contestants can enter at the second stage, and, at least under some circumstances, draw on the work of firms that reach milestone 1. Otherwise the pool of innovators at the critical step could be unnecessarily limited to only those who can reach the first milestone.

4. Is the prize the right size?

How big should the fever diagnostic prize be? The simplest answer to this difficult question is that it should be large enough to persuade a sufficient number of product developers to invest in the required R&D, but not larger than the value of the product to the prize sponsors. From a product developer's perspective, the prize has to be big enough to cover costs and provide an attractive return, after technical and competitive risks and the cost of capital are taken into account. A prize can be smaller if a successful developer can also expect revenues from product sales.

The value to society of the target product comes from the health benefits from faster and more accurate diagnosis leading to appropriate treatment and averted healthcare costs. As the BVGH proposal points out, in the long run poor targeting of antimalarials and antibiotics can lead to resistance, with potentially catastrophic cost implications. Irrational drug use wastes resources in the short run too, as expensive ACTs are mis-used to treat fevers that aren't malaria. The economic savings could be large; by 2009 158 million treatment courses of ACTs were procured globally, according to the WHO's World Malaria Report 2010, and this will increase in 2011 with the Affordable Medicines Facility – malaria which is providing an additional subsidy for private sector ACTs in 10 countries.

As described in their proposal, BVGH arrives at the prize amount by estimating R&D costs for each phase and then adjusting for risk. The total reward payment that the proposal would offer a developer who meets all four milestones and meets the minimum TPP[4] has been set at about $40 million. From our own analysis of diagnostic industry costs and returns, this reward is in a

[3] A competitor could enter midstream if earlier milestones have been satisfied.

[4] The total reward payment to a competitor for meeting the optimal TPP increases to about $50M.

reasonable range and should be sufficient to attract the interest of biotechs. However, the BVGH prize may be larger than necessary, given that there is some potential market for the product. In this case, the prize doesn't have to cover R&D costs entirely, as there's another source of return that firms will take into account. A significant prospect of market returns could allow the prize to be smaller, which BVGH doesn't attempt to factor into its prize calculations.

Our own prizes report revealed that commercial opportunities for POC tests in rich countries are limited by reimbursement systems and the incentives that they create for providers. But there could be a donor-subsidized market in developing countries for the fever POC diagnostic. One proxy measure to consider is the market for malaria RDTs, since the new diagnostic seeks to essentially replace these tests. A WHO study estimates that annual procurement of RDTs will grow to 60 million tests by 2015; at about $1 per test, though not a significant market, this could amount to some revenue potential for test manufacturers. It is possible that there is some private sector market for the fever diagnostic in emerging countries like India and China too. A more thorough market analysis would help to validate the proposed prize purse.

Another issue is whether it makes sense to aim for two separate winning products, as this doubles the total cost of the proposed prize mechanism. Paying for two products might be worthwhile if there's good reason to believe that the winning products would be useful in different epidemiological or healthcare settings or for different purposes. But if the reason for having multiple products is primarily to assure security of supply and build in competition, it is probably cheaper to achieve these objectives by arranging for competitive supply of a single product. Winning firms could be offered strong incentives to license their technologies to other suppliers, subject to appropriate restrictions limiting its use to the fever diagnostic and to sales in developing countries. Such an approach could have the additional advantage of making the product more affordable, by bringing in low-cost manufacturers in India or China.

The Bottom Line

We have raised some questions about the BVGH fever diagnostic prize and suggested ways that BVGH might strengthen their proposal. But our general reaction is positive. We would like to see prospective sponsors and funders, including the US government, the Bill and Melinda Gates Foundation, and new donors to global health R&D examine this proposal carefully. We believe it puts forward an innovative and carefully thought-out approach to spurring the development of a technology that could have significant health impact in poor countries.