To the Editor — In 2017, 10 million people became infected with tuberculosis (TB) and over 1.6 million died from the disease (over 4,000 people every day), almost exclusively in low- and middle-income countries (LMICs). These numbers have mobilized political will around the world to address the disease. TB was on the agenda at the 2018 United Nations General Assembly in New York—specifically, how to meet the global United Nations Sustainable Development Goal of ending the TB epidemic by 2030. Progress has also been made in attracting increased and sustained investment in R&D into the area; last year, funding for TB R&D hit $772 million—its highest ever level. This has resulted in a growing pipeline of new vaccines, drugs and diagnostics. But there remains an annual R&D funding shortfall of $1.3 billion, industry investment is low (in 2016, it was the lowest in a decade, although there was a small uptick in 2017), and perhaps the biggest worry is that 80% of the 2016 investment in TB R&D came from just five sources.

In light of this precarious situation, during the summer of 2018 we contacted some key stakeholders from pharmaceutical and diagnostic companies, as well as donor and research organizations, to (i) discern the main factors impeding private sector investment in tools to combat TB and (ii) garner proposed mechanisms to incentivize greater engagement. Telephone interviews were conducted with 13 people from 12 organizations spanning the United States, UK, Netherlands, Japan, Canada and India: 9 from industry, 1 nongovernmental organization, 1 donor organization and 2 research organizations. Opinions were provided on condition of anonymity. Feedback from our interviews is presented below.

**Barriers to investment**

Complexity of disease and treatment was identified as a major barrier to industry investment. Current drug regimens are long and complex even for drug-sensitive TB, and become even more so for the treatment of drug-resistant strains. Simplifying the treatment would require improved therapy of drug-resistant diseases, the ability to simultaneously treat TB and HIV/AIDS, and/or shortened therapy of latent TB infection. In addition to these complexities, full understandings of the infection and disease mechanisms are still lacking, making it difficult to develop effective interventions.

That a disproportionately high burden of disease falls on LMICs complicates both development and regulatory pathways. There is a limited network of clinical trial sites in which studies can be conducted, and if a clinical trial site is not up to expected standards, questions of data validity can arise. Phase 2 studies for TB typically require a minimum of two years; for phase 3 trials, this increases to three years; and the requirement for multi-drug therapy is an added challenge. These practical considerations are compounded in an already confusing and fragmented regulatory landscape, particularly for smaller companies with limited funds, knowledge or capabilities for LMIC success.

Companies also lack incentives for development. LMICs are often heavily dependent on inadequate international funding, so profit margins for drugs and diagnostics do not generally attract companies to invest in development. Although international support from the public sector has contributed to bringing some diagnostic tools and drugs to market, some interviewees thought this support may have had the adverse effect of creating a barrier for potential new commercial entrants if they are not able to secure similar funding and obtain adequate pricing for their products. Others view the role of these funders as critical to the progress made thus far.

Poor preparedness on the part of countries is a roadblock to effective implementation, uptake and continued use of a product. Without educational programs for medical professionals, public disease awareness, infrastructure for distribution of medication, accessible testing facilities with appropriate technologies, drug supply replenishment systems, and other infrastructure and logistics considerations, testing and treatment cannot be effectively administered.

**Proposed solutions**

The overwhelming majority of interviewees mentioned that a sense of community across the TB ecosystem is lacking. The public sector would like to see more industry investment and involvement, whereas the private sector feels unsupported by the public sector. These barriers must be broken down so that the community can work together to problem solve, bridging innovators and implementers to enable a smoother pathway.
through continued communication. An easy comparison can be made with the AIDS community, who effectively mobilized to effect change on a global scale.

Interviewees mentioned the need to recruit more scientists to TB research. A campaign to educate the science community on the burden of TB might inspire a moral obligation for the ‘best and the brightest’ to tackle the challenges TB presents. Monetary incentives might be offered to these individuals (for example, tuition payment or scientific positions at institutions willing to target TB tools). We propose that these solutions might be augmented by reaching out to professional organizations and the private sector to encourage a certain proportion of their activities to be devoted to TB research and development, as a matter of professional responsibility.

Interviewees also pointed to the need for harmonized regulatory pathways to reduce the cost and risks associated with development and introduction of TB tools. Greater emphasis by the World Health Organisation (WHO; Geneva) on establishing clear international norms and uniform standards would address a major impediment to investment. Additionally, many interviewees from the private sector pointed to evolving guidelines as a continuing challenge. Companies require a clear understanding of the goalsposts at the beginning of the development process to devise appropriate trials and programs, and it is challenging to adapt programs to new guidelines that are released after trials have commenced. A stronger disease-control approach should be adopted in place of, or to complement, the current evidence-based approach underlining WHO guidelines so that changing recommendations do not impair development.

Social incentives could encourage international companies operating in countries with a high TB incidence to include TB in their corporate responsibility initiatives. Countries should be encouraged to adopt legislation requiring domestic companies to devote a certain percentage of their profits to addressing infectious diseases, including TB. For example, legislation in India now requires businesses with a certain minimum revenue to give 2% of their net profits to charity.

Advancing purchase commitments were mentioned as another means to provide market incentives. Purchasers could commit to purchasing new tools for LMICs at predetermined prices, in advance of a commitment to purchasing new tools for LMICs. Market incentives might be offered to purchasing new tools for LMICs. Markups at the wholesale level could thereby make it a more attractive market in which to invest. Markups at local laboratories and pharmacies could be addressed with reimbursements and local cost-capping legislation.

Conclusions

It was clear that all interviewees recognized the health crisis that TB engenders and the urgent need to address the impediments that deter greater financial investment if the ambitious goal of ending the TB epidemic by 2030 set by the United Nations is to be achieved. Interview insights demonstrate that the barriers to TB investment are wide-ranging and require action from many stakeholders.

Of the solutions proposed, the most pressing is clearly the need for public- and private-sector stakeholders to work closely and more transparently together—for example, in the form of public–private research partnerships between public institutions and drug, diagnostic and vaccine developers. Although multiple public and private organizations are already involved in TB research and development, better coordination would provide greater efficiency and address some of the concerns expressed by some of the interviewees. In the past, early public investments have attracted confounding from other sectors; the use of some of the funding solutions proposed above would be a catalyst for more funding. The TB community has demonstrated the ability to develop collaborative research platforms that combine contributions from different funders (for example, the joint BRICS TB Research Network (of Brazil, Russia, India, China and South Africa) and the Life Prize). The Bill & Melinda Gates Foundation has recently launched its Medical Research Institute to provide resources to advance drug and vaccine TB candidates from the laboratory to human studies. Such efforts must be amplified and sustained. Partnerships will not only help reach funding targets but will also support buy-in of the final product by all stakeholders. Sharing data and being open to technology transfer could also accelerate both development and deployment of tools. Aside from using the traditional push/pull incentives, TB stakeholders have not tapped into the multi-billion-dollar funding available from impact investors (investors interested in generating a measurable, beneficial social or environmental impact alongside a financial return); if approached, we believe such investors would be interested in TB.

Unless the $1.3 billion annual funding gap is closed, the TB epidemic will continue to persist. The steep rise of drug-resistant strains of TB is only making the quest for new tools more difficult—and the longer stakeholders look the other way, the farther away the target moves.

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