Antimicrobial resistance (AMR) affects a wide range of pathogens and treatment options, and tuberculosis (TB) is no exception. A spectrum of resistance from rifampicin-resistant tuberculosis (RR-TB) to multidrug-resistant tuberculosis (MDR-TB) and even extensively drug-resistant tuberculosis (XDR-TB) threatens the health of millions globally every year, leading to 160,000 deaths in 2022 alone. Worryingly, only about two in five people with drug-resistant TB (DR-TB) are estimated to have accessed accurate diagnosis and proper treatment. Without sufficient testing and treatment, others will unknowingly expose their families and communities to drug resistance. The US is one of the world’s lower-incidence countries for TB, but DR-TB could put this status at risk. After decades of slow decline in the national case counts for DR-TB and TB overall, cases began rising again in 2021 and 2022. In addition, this may not fully represent the true increase in TB; many people with TB in the US are initially misdiagnosed, and it may take years to receive an accurate diagnosis that includes the drug-susceptibility of a person’s disease.

TB diagnostics and drug-susceptibility testing has dramatically improved in recent years, with tests offering both more rapid and more comprehensive results closer to the point of care. Unfortunately, even the most advanced diagnostic technologies are still in the early stages of implementation and more research is required to improve test accuracy for new DR-TB drugs such as bedaquiline and pretomanid, with unclear funding outlooks. Meanwhile, the best available rapid DR-TB tests (i.e., targeted next-generation sequencing) are not yet approved for use in the US, and the high prices of these tests make them unaffordable for state and local TB programs. In an even more troubling trend, new resistance to the standard of care for MDR-TB (bedaquiline-based regimens) is emerging — and limited knowledge of the mutations that cause bedaquiline resistance also limits the utility of existing rapid tests. While drug-susceptibility testing using mycobacterial culture can detect resistance to bedaquiline and other new TB drugs, test results can take up to six weeks. All of these factors contribute to a concerning landscape for DR-TB in the US and globally and are unlikely to be addressed alone by industry partners, who face a low likelihood of typically high profitability to justify research and development (R&D) (and even FDA registration) costs.

All hope is not lost, however. The Advanced Research Projects Agency for Health (ARPA-H) at the Department of Health and Human Services (HHS) funds and conducts research on innovative approaches to health challenges, especially those that are not supported by existing public or private channels. ARPA-H recently announced funding awards for diagnostic solutions to antibiotic resistance that can specifically identify the types of resistance present in bacteria and pinpoint the appropriate antibiotic treatment. This opportunity has been named the Defeating Antibiotic Resistance through Transformative Solutions (DARTS) project, and it is well-poised to foster solutions to the imminent DR-TB challenges the US faces.
in coming years. Though TB was not included in initial plans for DARTS, it is a perfect fit for this and any future funding awards that ARPA-H will focus on AMR. An infusion of funding and coordination support from ARPA-H would make it possible for researchers to study emerging resistance to bedaquiline and other new TB drugs and more rapidly identify genetic mutations associated with drug resistance.

From this information supported by ARPA-H, scientists could improve existing diagnostics and accelerate the development of new diagnostics that can be used in state and local health department laboratories to rapidly determine where sampled bacteria fall on the DR-TB spectrum. Similar efforts have previously been funded through the National Institutes of Health (NIH) and work in these areas is still ongoing. ARPA-H could coordinate with NIH and build on these results, ushering vital medical countermeasures through approval and making them most relevant to domestic settings. This technology could then be used to continue identifying resistance to any new TB drugs coming down the R&D pipeline, safeguarding the health of countless future generations of Americans.

Such a program holds the key to averting a public health crisis in the US, but only if ARPA-H prioritizes DR-TB within their portfolio of work on AMR and researchers seize the opportunity that DARTS and other funding awards provide. Though TB scientists and ARPA-H administrators may not yet see each other as typical partners, their collaboration could pave the way for one of the most important health milestones in this century. To truly change the scope of drug resistance in the US and globally, DR-TB must be addressed by ARPA-H as a priority pathogen.

ENDNOTES