Each year, 10 million people develop active tuberculosis (TB) disease, but 3.6 million of these individuals are “missed” each year by health systems and do not get the TB care they need and deserve. More than 75 percent of missed cases are concentrated in just 13 countries. Among these cases, an estimated 405,323 children and 248,300 people with drug-resistant forms of the disease are missed. Without proper treatment, up to two-thirds of people sick with TB will die. In addition, in a single year, people who are living with TB disease can infect up to 10 to 15 people/others with whom they are in close contact. This means that each missed case can add to the current TB burden, compounding the challenge to end TB.

Many of the missing cases are among vulnerable or underserved populations that are hard to reach or have difficulty accessing public health services, such as children, people living with HIV (PLHIV), migrants, refugees, and mine workers, among others. Diagnosis of TB is more challenging for certain groups, such as children and PLHIV because traditional diagnostics – like sputum smear microscopy – do not perform as well and can fail to diagnose TB even when it is present. Another challenge is the growing private and informal health sectors in many countries. These sectors often do not have access to or utilize quality-assured diagnostics or the anti-TB drugs needed to appropriately diagnose and cure patients, which can lead to under-diagnosis or inappropriate treatment, contributing to drug resistance.

Finding these missing cases and breaking the cycle of transmission is a major priority for the U.S. Centers for Disease Control and Prevention (CDC) and the global community working to end TB. Finding these cases, however, requires a strong health care system, a public health workforce that can reach those who need care, the laboratory capacity to quickly and effectively diagnose the disease, innovative approaches to meet people where they receive care, and expand access to TB diagnostic and treatment services.

CDC's role in finding these missing cases revolves around five distinct but related streams of work:

- Building the evidence base to improve case-finding approaches and diagnostic algorithms;
- Scaling-up access to TB screening and diagnosis among PLHIV;
- Providing guidance and technical support for implementing and evaluating new TB diagnostic tools, assuring quality laboratory services, and developing laboratory strategic plans with ministries of health to ensure the right diagnostic tools are in the right place;
- Strengthening national surveillance systems to document the burden of TB disease and identify gaps in case-finding efforts; and
- Expanding access to household contact tracing as a means to finding cases among child and adult household contacts.

Building the evidence base to improve case-finding and diagnostic algorithms

- In 2011, CDC led a study in Southeast Asia that ultimately changed the World Health Organization (WHO) guidelines to include a simplified diagnostic algorithm for screening and diagnosing TB among PLHIV. This approach found three times as many cases of TB than the standard at the time. Because this improved algorithm strengthened confidence that patients who screen negative do not have TB disease, the guidelines called for providing TB preventive treatment (TPT) to all PLHIV who screened negative to prevent them from developing active TB disease.

- In 2015, WHO indicated that the total number of people started on preventive treatment globally was 910,124, more than 10 times higher than in 2010. WHO attributed much of this progress to the changed algorithm in 2011.

CDC’s work to improve screening and diagnosis for TB among PLHIV

- After the change in these guidelines, CDC evaluated the implementation and performance of these screening and diagnostic algorithms when used routinely for evaluation of PLHIV at every clinic visit. These repeated screenings continued to find new cases and ultimately
documented an overall prevalence of TB among PLHIV, nearly 57 times greater than in the general population, suggesting that repeated screening is useful for diagnosing TB and evaluating eligibility for preventive treatment.

- CDC, through the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), is moving to dramatically scale-up TPT to eligible PLHIV across PEPFAR-supported countries, more than tripling the annual number screened by 2019. In 2018, PEPFAR projects that, across 22 priority countries, 2.83 million PLHIV will receive TPT.

**Scaling-up TB screening among PLHIV**

- CDC has been working closely with ministries of health to incorporate and scale-up systematic TB symptom screening among PLHIV through PEPFAR and national HIV programs. TB screening among PLHIV has improved dramatically since the new guidelines were released, with more than 85 countries reporting systematic TB screening for PLHIV. By mid-2018, nearly 85 percent of PLHIV in PEPFAR-supported care and treatment programs were systematically screened for TB.

- CDC continues to provide technical and program support to PEPFAR-supported programs to improve TB/HIV service integration and facilitate ART uptake among PLHIV diagnosed with TB. In 2017, CDC supported TB screening for 4.7 million PLHIV, including 400,000 children. CDC provided HIV treatment for 140,000 individuals suffering from both TB and HIV (HIV-associated TB).

**Strengthening laboratory capacity**

- CDC continues to play a critical role in the global effort to roll out Xpert MTB/RIF®, a rapid molecular diagnostic test endorsed by WHO in 2010. This test can diagnose TB and rifampicin-resistant TB in a matter of hours (compared to days or weeks for traditional diagnostics) and shows vastly improved performance in diagnosing TB among PLHIV and children.

- Since 2010, more than 33 million tests have been delivered to high-burden countries worldwide. The U.S. Government was the lead bilateral donor for scaling up Xpert MTB/RIF®, with PEPFAR and CDC playing major roles in providing the guidance, training, technical assistance, and monitoring and evaluation support needed to implement this test.

- CDC continues to build the evidence base for improved global guidance on implementation and provide intensive support to in-country partners for GeneXpert proficiency testing and quality assurance programs to ensure patient access to high quality TB diagnosis.

- Since the global rollout of Xpert MTB/RIF®, diagnoses of MDR TB have doubled and the number of PLHIV systematically screened for TB has more than doubled.

- Strengthening surveillance systems in-country through assessments and technical support and informing global guidance and tools remain a critical priority for CDC.

**Measuring the burden**

- The global burden of TB and the proportion of cases that are missed each year were revised upward in 2016 because, as global and national surveillance systems improve, so does the understanding of the burden of TB disease and the gaps and weaknesses in the surveillance system itself. Improving disease burden estimates provides a better understanding of where progress has been made toward global TB targets.

- CDC has been working closely with WHO to establish surveillance standards and benchmarks, assist with surveys of TB prevalence to document burden of disease, provide technical support to strengthen national surveillance systems, and conduct inventory studies to understand how many patients are actually diagnosed and/or started on TB treatment but are unknown to the national TB program.

- National TB prevalence surveys provide an approach to directly measuring the burden of TB disease. Since 2016, CDC has supported 21 countries in assessing their burden of disease. According to WHO, 25 surveys were completed between 2007 and 2017 in high TB burden countries.

**FUTURE EFFORTS**

CDC will continue to lead operational and programmatic research to identify innovative approaches to case-finding, scaling up screening for TB, optimizing the use of diagnostic tools, and improving surveillance systems.
Improving screening approaches and diagnostic algorithms

- CDC is currently leading a multi-year study to develop a diagnostic algorithm to diagnose TB among children and establish a new gold standard for diagnosis.

- CDC is working with multiple partners in southern Africa to identify approaches to screen and diagnose TB among mine workers and their families, who are at increased risk of TB and often have limited access to TB diagnostic and screening services. This project will identify optimal screening modalities, contact tracing among their home communities and families, and approaches to ensure continuity of care as these workers travel between mining camps and their home communities.

- Children who have been exposed to TB, especially children living with HIV, can move rapidly from infection to disease and develop more severe forms of TB more quickly. CDC is implementing a model for comprehensive screening at the household level through a family-centered care model which could identify children at risk of TB more quickly, prevent development of active disease, and ensure rapid diagnosis and initiation of therapy.

- CDC is demonstrating the impact of combined TB and HIV case-finding, treatment and prevention interventions as a model program to accelerate the decline in TB incidence and reduce mortality due to HIV and TB.