to progress once infected have the potential to substantially decrease the prevalence of TB and its associated mortality.

Tuberculosis

The ability to rapidly and accurately identify *Mtb* as well as drug resistance (eg, through NAAT, line probe, molecular beacon, and Xpert MTB/RIF assays) reflects substantial advances. While rapid tests for TB diagnosis still have a sensitivity of 70%–90%, they may fail to detect paucibacillary pulmonary TB. They also remain relatively expensive, making them difficult to implement in high-burden, low-resource settings. Ideally, what is needed is a simple, inexpensive, rapid (ie, hours) test that is highly accurate (>95% sensitivity and specificity). Rapid tests for detection of drug resistance are approaching the desired level of accuracy, at least for rifampin. However, these tests also are relatively expensive and need to be expanded to allow for detection of resistance to other TB medications. Such expansion is currently limited by gaps in knowledge of the molecular basis of resistance to most first- and second-line drugs. In this regard, improved functional tests for resistance may prove useful.

Other significant gaps remain in the diagnosis of pediatric and extrapulmonary TB. First, the yield of AFB smear and culture in children is low compared to that in adults, which leads to excessive morbidity and mortality due to delayed and missed diagnoses, especially in resource-limited settings. Conversely, the inability to exclude TB results in overtreatment when the diagnosis cannot be excluded. In areas of the world where TB is diagnosed entirely based on smear microscopy, children will be almost completely neglected and untreated for TB. In areas with greater resources, low yields of microbiologic specimens in children deter many clinicians from even attempting culture collection. This may result in prolonged treatment with extra TB drugs (in jurisdictions that use 4 drugs for 6 months in patients lacking susceptibility data). Alternatively, drug resistance will not be identified and the child could suffer dire consequences receiving inadequate care. Second, similar challenges exist for the accurate diagnosis of those with extrapulmonary TB. Finally, diagnostic approaches to the identification of those likely to fail TB treatment are needed. These limitations in the diagnosis of paucibacillary TB highlight the need to develop testing strategies based on either host or bacterial markers of infection that can be measured from readily available clinical sources such as plasma or urine.

Latent Tuberculosis Infection

Individuals with immunological evidence of exposure to *Mtb* antigens, but without evidence of clinical disease are termed "latently" infected. However, it is clear that there is considerable heterogeneity within this classification. As was described previously, those with recent infection (<2 years) are at increased risk for progression to clinical disease, and functionally might be considered acutely infected. Conversely, those more remotely infected are at substantially lower risk, but remote infection remains difficult to define operationally. Those with negative TSTs or IGRAs are unlikely to progress to TB. However, the PPV of either test is relatively modest, as current estimates would suggest that among household contacts, 20–40 people require treatment to prevent one case. While the number needed to treat based on IGRAs is not known with certainty, early evidence suggests that it is not likely to be dramatically different [24, 55]. Nonetheless, a careful evaluation of which diagnostic is more closely associated with the development of TB remains a research priority. Given the relatively poor PPVs of current diagnostics for the prediction of progression to TB disease, a diagnostic that can accurately identify those at risk is needed. It should be noted that both QFT and T-SPOT are largely measures of CD4 T-cell immunity, but additional markers of inflammation, cellular, or humoral immunity may prove useful. Clearly, the identification of biomarkers associated with the development of tuberculosis following infection will require carefully performed prospective investigation. In this regard, the prospective evaluation of populations at risk for disease progression, and the use of sophisticated imaging such as positron emission tomography–computed tomography (PET-CT) are likely to further delineate markers associated with either disease progression or subclinical infection.

Operationally, the intent of targeted testing is to identify those who would benefit from treatment. While much is now known about the accuracy of both the TST and IGRAs, much less is known about their performance with regard to treatment completion. Additional research on the use of IGRAs with regard to provider and patient perceptions is needed to establish optimal diagnostic and treatment strategies. Finally, the literature addressing the performance of IGRAs in children <5 years old is still limited and studies to inform the appropriate use of these tests to accurately diagnose LTBI in this age group are needed. Studies of young household contacts in low-incidence countries would be especially informative.

GUIDELINE STATEMENT

These guidelines are not intended to impose a standard of care. They provide the basis for rational decisions in the diagnostic evaluation of patients with possible latent tuberculosis or tuberculosis. Clinicians, patients, third-party payers, stakeholders, or the courts should never view the recommendations contained in these guidelines as dictates. Guidelines cannot take into account all of the often compelling unique individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion. Qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.