Clinical and logistic systems to support the timely diagnosis of tuberculosis are currently not preventing large numbers of tuberculosis deaths in South Africa. Context-appropriate systems for the diagnosis of tuberculosis are entirely dependent on effective and responsive management of human resources and an uninterrupted supply of clinical materials. Attention to these components of the tuberculosis program is urgently needed before new diagnostic technologies can be expected to impact on tuberculosis mortality in resource constrained settings.

Effective diagnosis of tuberculosis, with point-of-care human immunodeficiency virus (HIV) testing, is the most urgent public health issue in South Africa. Tuberculosis is currently the leading cause of death in South Africa, increasing from 6.5% of reported deaths in 1997 to 12.6% (74,863 deaths in 2008) [1, 2]. HIV infection is the most potent known risk factor for active tuberculosis; nationally, an estimated 460,600 tuberculosis cases were diagnosed in 2007, with 70% being HIV co-infected in high HIV prevalence areas such as KwaZulu-Natal [3, 4]. The large number of HIV-infected adults living in South Africa (an estimated 5.2 million people) accounts for the majority of tuberculosis deaths, including undiagnosed multidrug-resistant tuberculosis [5–7]. However, most cases of tuberculosis are still caused by pansusceptible organisms that are curable with current treatment regimens [7, 8]. Rifampicin-based antitubercular therapy is available free at primary care clinics in accordance with World Health Organization (WHO) guidelines, with many districts additionally offering supervised outpatient or inpatient therapy [9–11]. The inescapable conclusion is that tuberculosis is being diagnosed too late for effective treatment, both to save lives and prevent the onward transmission of infection.

Tuberculosis is a disease of poverty [12, 13]. South Africa has the largest economy in Africa but is one of the most inequitable societies in the world, illustrated by the disparity between private and public sector health-care funding. In 2006/7, US$8.05 billion in contributions to the private medical insurance industry funded health care for 15% of the population; the public health service received a similar amount (US$7.24 billion) to meet the needs of the remaining 85% of South Africans [14, 15]. The burden of tuberculosis falls on the majority who are dependent on the underfunded public health sector [16]. Notwithstanding these constraints, South Africa has been able to achieve substantial public health successes, notably free provision of condoms, widely available HIV counseling and testing, prevention of mother to child transmission of HIV, the antiretroviral rollout and, more recently, the medical male circumcision campaign [17].

Sputum smear microscopy for acid-fast bacilli (AFB), a cornerstone of the DOTS strategy, appears to be a cheap and simple diagnostic strategy, and therefore feasible for resource-constrained health-care settings.
and sputum has the highest culture yield in active disease. Cough shown in Table 1. Sputum is the most important specimen for completing before the patient has a test result. These steps are uncommon [29, 30]. Once a patient has been recognized as a tuberculosis suspect, however, many discrete steps have to be well documented, and delays of up to 6 months are not uncommon [29, 30]. Once a patient has been recognized as a tuberculosis suspect, however, many discrete steps have to be completed before the patient has a test result. These steps are shown in Table 1. Sputum is the most important specimen for diagnosing tuberculosis because culture-positive (pulmonary) tuberculosis is responsible for onward transmission of infection and sputum has the highest culture yield in active disease. Cough

**LOGISTIC COMPONENTS**

Health-care systems are extraordinarily complex [26, 27]. The most effective tuberculosis control systems have been integrated into primary care services that allow patients easy access to diagnostic and treatment services [28]. The phenomenon of patient and provider delay in diagnosing tuberculosis has been well documented, and delays of up to 6 months are not uncommon [29, 30]. Once a patient has been recognized as a tuberculosis suspect, however, many discrete steps have to be completed before the patient has a test result. These steps are shown in Table 1. Sputum is the most important specimen for diagnosing tuberculosis because culture-positive (pulmonary) tuberculosis is responsible for onward transmission of infection and sputum has the highest culture yield in active disease. Cough

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Entry of patient's name and contact details into the tuberculosis suspect register.</td>
</tr>
<tr>
<td>2.</td>
<td>Collection of clinically relevant specimens, including at least 2 sputum specimens coughed on the same day ('spot-spot') [31]</td>
</tr>
<tr>
<td>3.</td>
<td>Labeling the specimen container (preferably before it is used by the patient) and tightening lid to prevent leakage</td>
</tr>
<tr>
<td>4.</td>
<td>Completion of the laboratory form</td>
</tr>
<tr>
<td>5.</td>
<td>Uniting specimen and form either in a plastic bag or with an elastic band</td>
</tr>
<tr>
<td>6.</td>
<td>Storage of specimens at a single point for collection and transport to the district laboratory</td>
</tr>
<tr>
<td>7.</td>
<td>Transport of the bio-hazardous specimens to the laboratory in a safe and timely manner*</td>
</tr>
<tr>
<td>8.</td>
<td>Return of smear and culture results to the clinic</td>
</tr>
<tr>
<td>9.</td>
<td>Results filed, given to the patient and acted upon</td>
</tr>
</tbody>
</table>

* Delayed transport to the laboratory may increase specimen contamination rates.

Effective implementation of diagnostic systems is entirely dependent on trained and motivated staff. In the context of tuberculosis diagnostics, poverty is experienced as both the lack of modern technology and substantial obstacles to implementing and sustaining logistics that enable patients to effectively access technology. There is a substantial mismatch between the need for the service and the ability to meet that need. Skilled and continuous leadership is needed from managers to find a “middle way,” to optimize work output and avoid burnout, navigating between the Scylla of presumption and the Charybdis of despair [34]. In South Africa, health-care management is in disarray due to many factors, including undertraining, political interference, poor institutional support, corruption, and budget constraints. Promisingly, however, the Department of Health has recently come under responsive and effective political leadership [35, 36]. Health-care workers in the public sector tend to move into the private health-care sector (which employs 58% of nurses and 70% of doctors), nongovernmental organizations, and academia, or immigrate to the developed world. Presently, insufficient
health-care workers are being trained as replacements [37, 38]. Experienced managers who decide to remain in the public service are often pulled into crises managing other areas of the public service at the expense of the tuberculosis program.

Excessive workload fragments health-care teams into antagonistic groups that disrupt systems. Morale needs to be maintained in the face of high volume and repetitive tasks. Frontline health-care workers experience the anguish of telling ill patients that their culture and susceptibility test result has been lost or was never processed, or are unable to bring patients with MDRTB into timely care (in KwaZulu-Natal only 32% of patients with culture-confirmed MDR-TB were started on treatment in 2007 [K Wallengren, personal communication, 2011]). Health-care workers are often under intense personal stressors such as debt, family expectations, HIV-positive status, and/or higher rates of tuberculosis (including drug-resistant infection) [39], patients’ rights and demands with attendant political fallout, and peer pressure that favors a culture of non-performance. Employees need to take annual leave, but their absence while on vacation can precipitate collapse of an overstretched and undercapacitated system. Managing absenteeism and poor performance in South Africa is difficult as current labor laws require complex and time-consuming disciplinary procedures. In South Africa, a large national survey to determine risk factors associated with default in TB treatment, noted that unfavorable perception of health-care workers’ attitude by patients carried a 12-fold higher risk of default [40].

In the context of military strategy during the Cold War, the British historian Michael Howard commented that “manpower is the ultimate manifestation of national commitment” [41]. This is as relevant in the very different war against tuberculosis: the tuberculosis program cannot flourish without human resource management being a key strategic component [42].

**DESIGNING, IMPLEMENTING, AND REFINING TUBERCULOSIS DIAGNOSTIC SYSTEMS**

Systems, like politics, are local. Managers need to be aware of the issues faced by on-the-ground health-care workers and ensure their continued “buy-in” to systems changes [43–45]. It is possible to workshop a new or modified system or workflow with key personnel; suggestions made by other staff members can then be incorporated, and finally the system can be pilot at 1 or 2 well-functioning sites or areas.

Ideas are easy; sustained implementation in highly stressed resource-constrained health programs is remarkably difficult. Importantly, the impact of a new system on current workload should be kept to a minimum and ideally should make the lives of health-care workers easier rather than more difficult. Before or during the pilot process, it is essential to match anticipated workload to capacity. Work output expected from employees should be benchmarked, and, if demand exceeds capacity, a transparent and rational prioritization plan should be made. Failure to do this will erode trust and respect and severely damage the system’s credibility. Key outcomes from the system need to be determined and a simple standardized data collection tool developed. Each health-care worker in the system should be aware of her/his role in making the system work and the positive impact the system will have on patients’ health. Regular meetings need to be held to present outcomes (eg, number of specimens collected, number of positive results, and number of patients started on treatment), discuss problems, and develop refinements. Written policies or standard operating procedures should be easily accessible both as prominently visible hard copies and in electronic format. Finally and crucially, the manager or coordinator who has overall responsibility for the system’s success must be readily available to troubleshoot problems as they arise and communicate solutions.

**MANAGEMENT OF ITEMS NEEDED TO OBTAIN SPECIMENS**

Supply chain management for antitubercular antibiotics from production to distribution in clinics has been evaluated and studied [46]. Much less attention has been paid to maintaining uninterrupted supplies of items needed to secure suitable specimens for tuberculosis testing. A list of disposable clinical items that need to be routinely available in district clinics and hospitals is shown in Table 2. Maintaining these supplies in the clinics and wards again requires multiple steps: stock levels have to be monitored daily and timely orders placed with the central store which, in turn, has to order supplies through management’s financial control systems that may not appreciate the importance of maintaining stocks of seemingly mundane materials in the face of numerous competing priorities. Items have to be sourced on tender or ordered from an approved provider, paid for, delivered, and accounted for in the central store, and then dispersed to clinics and wards. Finally, stores of clinical material have to be protected from theft. A management bottleneck at any step can prevent crucial supplies from being available in the clinic.

**MANAGEMENT ISSUES IN DIAGNOSING CHILDHOOD TUBERCULOSIS**

Historically, the global fight against tuberculosis has focused on diagnosis of infectious adults. Now, as rates of pediatric tuberculosis rise in South Africa, a drastic shift in thinking and practice is needed. Such an evolution will require system changes. The tuberculosis burden in South Africa rightfully leads to a high index of suspicion for the disease in any coughing child or in any ill infant with compatible systemic manifestations. However, diagnostic services are limited and must be used wisely. Research from South Africa has shown that well-defined
In the face of overwhelming disease burden, prevention of childhood tuberculosis through contact tracing and isoniazid prophylaxis is often side-lined. In South Africa, it is encouraging that current tuberculosis guidelines recommend prophylaxis in children under the age of five—the age group at greatest risk for tuberculosis including life-threatening infection—and in HIV-infected children [49]. Basic evaluation for HIV risk factors and household TB exposure should be integrated into the routine childhood examination in South Africa. Having tools and guidelines is one thing; capacity on the ground to carry them out is entirely different. Tracers are hired, but practically spend most of their time following up new diagnoses of MDR TB. The responsibility for evaluating the vast majority of childhood contacts will fall upon nurses working in peripheral clinics, who are burdened with many other responsibilities. Data on the implementation of contact tracing are lacking and official registers to document contact follow up must be developed and maintained. A serious attempt to implement contact tracing should involve nurses hired for this task alone, an unlikely prospect in low-resource systems, or task-shifted to appropriately trained lay personnel.

**SPECIAL SITUATIONS IN CERTAIN PATIENT GROUPS**

HIV coinfection makes the diagnosis of tuberculosis substantially more difficult, and adult physicians can learn from their pediatrician colleagues. Many patients with HIV-associated tuberculosis present with extrapulmonary or sputum smear-negative pulmonary disease [50]. All these cases need investigation by medical practitioners, including interpretation of chest radiograph or ultrasound scan, and invasive investigations such as fine needle aspiration or needle core biopsy of lymph nodes, pleural aspiration, ascitic paracentesis, or lumbar puncture. Medical practitioners need special training to become adept at performing procedures and interpreting imaging and laboratory results. The training cycle needs to be repeated frequently as junior physicians move away to further their careers, consuming the time of experienced practitioners who have multiple responsibilities outside the tuberculosis program. Retention of skills in the public service is essential.

Many patients with pulmonary or disseminated tuberculosis have a nonproductive cough or are too weak to cough effectively. Sputum induction using ultrasonic nebulization with hypertonic saline is an effective technique to obtain respiratory secretions from adults with a nonproductive cough and from

symptoms and objective weight measurement can be quite helpful in diagnosing pediatric TB [47]. These and other findings could inform the development of evidence-based tools for
children [51–53]. However, expensive equipment and trained personnel are required, and suitable infection control measures should be employed. Gastric lavage can be used to retrieve swallowed respiratory secretions in patients too young or too weak to cough effectively; buffer solution to neutralize gastric acid needs to be added to these specimens. While the standard for children is gastric aspiration on three consecutive mornings [51, 54], access to the service is limited for children managed as outpatients (e.g., gastric lavage is offered one morning each week at Edendale Hospital). Due to bed shortages, admitting a tuberculosis suspect who is otherwise clinically stable to hospital is rarely an option. Health-care workers need ongoing supervision when performing sputum induction or gastric lavage in order to optimize diagnostic yield.

The logistic implications for these additional investigations are substantial. Patients have to travel beyond their primary care clinic to a district or regional hospital to access health-care workers with the necessary clinical skills and equipment and may need to make many repeat visits, which is not economically feasible for many patients’ families. After proper specimens have been obtained, patients and their caregivers must be given a follow-up appointment. Failure to do so may result in a waste of resources, the family’s time, and the risk of missing tuberculosis in a child or HIV-infected adult. Timing the appointment is hit-and-miss as it may take weeks before specimens arrive at the regional laboratory and months before the result is returned to the clinic.

LABORATORY CONSIDERATIONS

Quality assurance (QA), the foundation of any laboratory management program, aims to ensure that the results produced by the laboratory are truly representative and reliable [55]. The QA process ensures greater consistency and trustworthiness of results, but it is an expensive process and requires meticulous and often time-consuming record-keeping, which inadvertently adds to the workloads of the laboratory staff [56].

Supply chain management is more often than not the proverbial weak link in the laboratory system. Between 15% and 45% of a laboratory’s budget is spent on supplies; therefore, careful stewardship of precious equipment and materials in a resource-limited setting is crucial [57]. Often this is not the case, and delays in both ordering and delivery of supplies results in laboratories lacking critical testing material. This negatively affects turnaround time of results and compounds the problem of the backlog of work. Conversely, overordering supplies leads to a waste of resources when media and reagents exceed their expiry dates.

Maintenance of equipment is an expensive exercise [58]. Tuberculosis laboratories need to become familiar with highly sophisticated technology following the advent of liquid culture systems and molecular technology. Technical assistance and support is a crucial component of the maintenance plan of any equipment installed in the laboratory, but the long distances needed to travel to the more peripheral laboratories can hinder this process [59]. Staff also needed to be trained and deemed competent to operate the equipment and site-specific standard operating procedures need to be written.

Human resource management is a logistical challenge. Flagging morale and lack of motivation occurs frequently in laboratories, understandably given the huge burden of work, long shifts, and perpetual understaffing. There is often a rapid turnover of staff who may succumb to the allure of employment in the private health-care system or relocate to cities [56]. Training of staff and continued education of qualified staff usually falls to the more senior staff in the laboratory who themselves may not have much experience [58, 60].

THE WAY FORWARD

Our current systems are not adequately structured to win the war against tuberculosis. Effective implementation of tuberculosis diagnostics is in the national interest as economically active adults and children are severely affected by the disease. Clearly focused vision and leadership to promote the rapid diagnosis and effective treatment of tuberculosis is essential as a national priority, supported by cost efficacy and operational research data [60]. Transparency of the national tuberculosis program’s budget would ensure accountability. The need for staff members with the financial training needed to run the tuberculosis budget in institutions and districts cannot be overlooked. Every South African Rand needs to be accounted for and effectively used, and front line managers should be given an increased say in how the tuberculosis budget is spent. Andrew Krepinevich, commenting on the effect of the American budget deficit on military strategy, quoted physicist Ernest Rutherford’s observation “We’ve got no money, so we’ve got to think.” [61]. This could apply just as well to the South African tuberculosis program, as well as in any other resource constrained setting.

Despite the human-resource crisis in the health-care system, and the many barriers faced by clinical providers struggling with multiple competing priorities, there are health-care workers motivated by more than self-interest, who would be willing to work as a part of a well-functioning tuberculosis service. National government needs to rebuild the tuberculosis program’s prestige, beginning with sufficient funding and improved retention efforts. Media campaigns using sophisticated and audience-appropriate advertising with celebrity endorsement will ensure the public is aware of their right to rapid laboratory testing and clinical evaluation to assist in the diagnosis of tuberculosis. Health-care workers involved in all levels of the program should pass an accreditation examination every 3–5 years to ensure a baseline level of competency; continuing medical education will be paramount as new tools become available and new algorithms are implemented. Specific aspects of the program...
such as recognition of tuberculosis suspects and sputum collection can be task-shifted to appropriately trained and supervised lay personnel, leaving fully trained professional staff to focus on diagnosis and treatment of tuberculosis cases (including MDRTB), and management of systems and human resources. Personnel involved in the program should be easily recognizable by specific badges or special uniforms. Outstanding performance should be acknowledged. Frontline health-care workers who are routinely exposed to tuberculosis need to receive a special salary allowance to compensate for their specialized knowledge and the infection risks involved, and they need to be supported by sound infection control procedures, regular testing for HIV infection, and isoniazid prophylaxis [62]. Line management structures need to be transparent, accountable, and empowered to support effective local solutions.

Shrewd use of robust information technology, such as that used widely in the private sector, including financial institutions and retailers, could be helpful in managing large numbers of specimens. Scanning in bar coded specimens at several points through the system, including at the point of collection, would ensure that a computerized log is maintained that would monitor for discarded specimens and delayed processing; ideally, the system would generate automated reports for the clinic manager and laboratory manager. In addition to use of mobile technologies for monitoring specimens, the same could be done to track patients, sending alerts from the district hospital where the diagnosis is made, to the patients’ local clinic and DOT support organization. The cost of installing dedicated information technology for tuberculosis in South Africa can be justified by the large number of specimens and tuberculosis cases that need to be processed each year (in 2010 the South African National Health Laboratory Service processed more than 3 million smears and 900,000 cultures; Gerrit Coetzee, personal communication, 2011).

If highly effectively new technologies for diagnosing tuberculosis are made available in the public sector in South Africa, rational mechanisms need to be in place to prioritize onward referral of patients most likely to benefit from tests more expensive than sputum microscopy. Prioritization (rationing) will place additional logistic burdens both on patients and the laboratory. For example HIV-infected tuberculosis suspects with negative sputum smears and children are likely to benefit from additional nucleic acid amplification testing or liquid media culture—this means that these patients must either return to submit more specimens or the laboratory must be triggered to further process the original specimens.

Finally, tuberculosis diagnostics in South Africa cannot function in isolation but must be seen as an integral component of the tuberculosis program, aiming to achieve the WHO-determined targets of detecting of more than 70% of tuberculosis cases and achieving at least 85% treatment success. Innovative partnerships are needed to realize the remarkable potential of new diagnostics technologies and to consistently ensure that every patient receives a reliable result. The formidable challenges to implementation can be overcome with appropriate and innovative attention to the logistics of diagnosis in clinics and laboratories.

Notes

Acknowledgment. We appreciate Ted Cohen’s comments on the manuscript.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References