

# Infection Control for Drug-Resistant Tuberculosis: Early Diagnosis and Treatment Is the Key

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Multidrug-resistant (MDR) tuberculosis, “Ebola with wings,” is a significant threat to tuberculosis control efforts. Previous prevailing views that resistance was mainly acquired through poor treatment led to decades of focus on drug-sensitive rather than drug-resistant (DR) tuberculosis, driven by the World Health Organization’s directly observed therapy, short course strategy. The paradigm has shifted toward recognition that most DR tuberculosis is transmitted and that there is a need for increased efforts to control DR tuberculosis. Yet most people with DR tuberculosis are untested and untreated, driving transmission in the community and in health systems in high-burden settings. The risk of nosocomial transmission is high for patients and staff alike. Lowering transmission risk for MDR tuberculosis requires a combination approach centered on rapid identification of active tuberculosis disease and tuberculosis drug resistance, followed by rapid initiation of appropriate treatment and adherence support, complemented by universal tuberculosis infection control measures in healthcare facilities. It also requires a second paradigm shift, from the classic infection control hierarchy to a novel, decentralized approach across the continuum from early diagnosis and treatment to community awareness and support. A massive scale-up of rapid diagnosis and treatment is necessary to control the MDR tuberculosis epidemic. This will not be possible without intense efforts toward the implementation of decentralized, ambulatory models of care. Increasing political will and resources need to be accompanied by a paradigm shift. Instead of focusing on diagnosed cases, recognition that transmission is driven largely by undiagnosed, untreated cases, both in the community and in healthcare settings, is necessary. This article discusses this comprehensive approach, strategies available, and associated challenges.

**Keywords.** multidrug-resistant tuberculosis; infection control; diagnosis; treatment; community.

In 2001, Lee Reichman described multidrug-resistant (MDR) tuberculosis as “Ebola with wings,” and the specter of an untreatable, airborne infectious disease to which everyone is vulnerable arose [1]. Fourteen years later, MDR tuberculosis has become a substantial threat to tuberculosis control efforts in all settings where tuberculosis remains a significant burden [2]. In many settings, the emergence of even more highly resistant tuberculosis strains—namely, extensively drug-resistant (XDR) tuberculosis—has replaced MDR tuberculosis as the predominant fear.

At the time Reichman published his book, the prevailing view was that tuberculosis drug resistance arose through poor treatment of individuals with tuberculosis and that the resulting drug-resistant strains were not as “transmissible” as the drug-susceptible originator strains [3, 4]. This assumption, now discounted [5], led to a paradigm favoring “prevention” through the World Health Organization’s (WHO) directly observed

treatment, short-course (DOTS) strategy of addressing drug-sensitive tuberculosis over MDR tuberculosis, resulting in a lack of will and resource allocation to both diagnose and treat MDR tuberculosis, particularly in low-resource settings, where the cost and complexity of MDR tuberculosis treatment was considered a barrier to treatment provision [4, 6]. This paradigm has shifted, and efforts have now been made to expand MDR tuberculosis treatment provision, predominantly in the last 5 years, yet access to both diagnosis and treatment for MDR tuberculosis remains extremely poor globally. Less than 20% of the estimated 450 000 cases that emerge globally each year have access to appropriate, second-line antituberculosis treatment regimens [2]. The vast majority of the MDR tuberculosis burden is undiagnosed and untreated, and is driving transmission in high-burden settings [7–9].

Healthcare workers (HCWs) in low- to middle-income countries (LMICs) are at particular risk of contracting tuberculosis. The risk of tuberculosis attributable to nosocomial, occupational exposure ranged from 25/100 000 per year to 5361/100 000 per year in a 2006 systematic review [10]. Although data on drug-resistant tuberculosis among HCWs are more limited, several reports have described a substantial burden among HCWs with predominantly poor outcomes [11–13]. Nosocomial transmission of tuberculosis and MDR tuberculosis is not just a risk

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**Clinical Infectious Diseases**® 2016;62(S3):S238–43

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to HCWs; transmission between clients of health services is also a significant risk, particularly in settings of high human immunodeficiency virus (HIV) prevalence [14–18]. Appropriate and sustainable measures to reduce the risk of nosocomial MDR tuberculosis transmission are clearly required.

Since the introduction of the DOTS strategy, tuberculosis control efforts at a population level have centered on case detection and treatment provision to reduce the infectiousness of individuals and thereby halt onward transmission [19]. In contrast, specific tuberculosis infection control (TBIC) efforts in healthcare facilities have traditionally focused on known, diagnosed tuberculosis cases, often with a focus on tuberculosis clinics and tuberculosis inpatient wards. Yet, investigation of tuberculosis and MDR tuberculosis among HCWs has consistently shown that staff in other areas are at just as high, if not higher, risk than those working solely in tuberculosis areas [10, 11, 20]. Although long, arduous, and associated with overall poor outcomes, second-line treatment for MDR tuberculosis has now been demonstrated to rapidly reduce individual infectiousness [21], in a similar fashion to first-line treatment for drug-susceptible tuberculosis.

Lowering transmission risk for MDR tuberculosis requires a combination approach centered on rapid identification of active tuberculosis disease and tuberculosis drug resistance, followed by rapid initiation of appropriate treatment and adherence support, complemented by universal TBIC measures in healthcare facilities. The FAST (Find cases Actively, Separate safely, and Treat effectively) strategy has been proposed [22]. For MDR tuberculosis, this approach requires a paradigm shift from the classic infection control hierarchy of managerial, administrative, environmental, and personal protective controls in healthcare facilities toward a novel, decentralized approach across the continuum from early diagnosis and treatment to community awareness and support, based on the reality that the current epidemic is driven by undiagnosed and untreated individuals in the community and in the health system. This article aims to discuss this comprehensive approach, strategies available, and associated challenges.

### EARLY MDR TUBERCULOSIS DETECTION

The need for early detection of MDR tuberculosis is increasingly recognized [23]. However, in many settings, there are significant barriers to increased early detection and treatment of MDR tuberculosis. Until recently, detection of resistance relied on culture followed by drug susceptibility testing (DST), access to which is often restricted to central reference laboratories, with results only available after weeks or months. As a result, in 2013, <10% of patients with newly bacteriologically confirmed tuberculosis globally received any DST [2].

In 2010, the WHO recommended the use of the Xpert MTB/RIF test, a rapid polymerase chain reaction assay to detect tuberculosis and rifampicin resistance simultaneously [24, 25].

Although less sensitive than culture and phenotypic DST, the Xpert test has the potential to make universal access to DST a reality. However, cost remains a barrier in many settings despite negotiated cost reductions for LMICs [26]. To date, South Africa is likely to be the only high-burden country to implement universal access to DST via Xpert [27]. Even with universal access, effective use of rapid DST requires testing individuals with presumptive tuberculosis at first presentation. Patients often have several encounters with the health system before tuberculosis testing is offered, resulting in significant transmission risk [28]. Changing this requires both changing HCW practice to “think” tuberculosis, in addition to community-based awareness around tuberculosis symptoms and early presentation.

### RAPID MDR TUBERCULOSIS TREATMENT INITIATION AND THE NEED FOR DECENTRALIZED, AMBULATORY MODELS OF CARE

Once diagnosed, access to second-line treatment is severely limited in many settings. High cost, complexity of treatment, poor outcomes, and lack of setting-specific models of care are listed as barriers to widespread treatment provision [29, 30]. Early recommendations for a centralized model of care only where affordable [4] resulted in the treatment of small cohorts of patients in highly specialized DR tuberculosis hospitals, often with considerable delays [31].

Although the number of patients receiving treatment is increasing, albeit slowly (>90 000 patients were reported to have been initiated on treatment in 2013 [2]), the gap between the number of patients diagnosed and those receiving treatment is also increasing. Between 2012 and 2013, the number of patients with diagnosed MDR tuberculosis not initiated on treatment increased from 16 000 to 39 000, excluding the unknown number of patients detected in previous years and not treated [2, 32]. With increased access to the Xpert test, the numbers diagnosed will rapidly increase. Reliance on centralized treatment models will increase the need for hospital beds—and thus the treatment gap—exponentially. For example, in South Africa, only 10 663 of the 26 023 patients diagnosed with rifampicin-resistant tuberculosis were reported to have been started on treatment in 2013. Similarly, >40% of diagnosed patients in India were not initiated on treatment in 2013 [2]. Centralized models of care, which remain the norm in many high-burden settings, are reliant on medical specialists and long periods of hospitalization. Such models of care may become major bottlenecks for rapid scale-up of treatment, resulting in ongoing transmission in communities and healthcare facilities.

In low-burden settings with significant resources, hospitalization may provide an opportunity for specialist, individualized care and true isolation of patients in single, negative-pressure rooms [33]. In contrast, in most settings with a high MDR tuberculosis burden, hospitalization is associated with significant delays to receive treatment, and patients are most often admitted

to multiple-bed wards, with a significant risk of nosocomial cross-infection from a small number of patients for whom treatment is ineffective [16]. Decentralized, ambulatory models of care for MDR and XDR tuberculosis treatment, with potential for nurse case management [34], are more patient-centered, improve continuity of care, can lead to improved outcomes, and are associated with much-improved case detection [35–39]. A recent systematic review found outcomes of community-based MDR and XDR tuberculosis treatment to be similar to overall treatment outcomes from 3 systematic reviews on MDR tuberculosis therapy [35]. In addition, a smaller burden of patients requiring hospitalization allows more effective use of hospital beds, potentially allowing for smaller wards or single-bed rooms, and prioritization of clinician time for patients who need it most. The provision of more effective treatment regimens, utilizing new and repurposed drugs, from the outset should also reduce the proportion of patients for whom treatment fails and the consequent transmission risk associated with these individuals [40].

Decentralized models of care are substantially cheaper, allowing scarce health resources to go further [41]. Furthermore, a mathematical modeling study based on the transmission of XDR tuberculosis in South Africa suggests that a large proportion of newly transmitted cases could be averted through a combination of community-based care, simple mask wearing, and more appropriate use of inpatient facilities [42]. Based on the need to scale up treatment and improve access, ambulatory, decentralized models of care are now supported [43], and WHO recommendations rightly emphasize the high risk of transmission among patients and personnel in healthcare facilities with poor infection control measures.

### **FEAR, MISCONCEPTIONS, AND INVISIBLE CASES**

In contrast to WHO recommendations, several settings have adopted models of care with extensive use of hospitalization to ensure specialized care and, in some cases, based on the premise of isolation of patients to prevent transmission [2, 44–46]. Fear and stigma among communities, policy makers, and HCWs may lead to irrational and discriminatory policies, practices, and behaviors. It is not uncommon for HCWs to be afraid of and even refuse to care for patients with diagnosed MDR tuberculosis on treatment, but not of the undiagnosed (and therefore untreated) patients sitting in the waiting room or patients who do not respond to first-line treatment several months after treatment initiation (“invisible” cases). Removing patients from the community who have been diagnosed and initiated on appropriate treatment fails to acknowledge that transmission is driven by the much larger proportion of undiagnosed and untreated patients. Such policies and practices create a false sense of security among HCWs, and in health systems generally, that all DR tuberculosis patients are now isolated in the hospital and no longer constitute a risk to the community or themselves.

Changing this perception requires a much greater focus on training and education at all levels of the health system and in the general community. Essential to this will be emphasizing the contribution of direct transmission by invisible cases in the current epidemic, and reversing years of poor attitudes toward patients with drug-resistant disease based on incorrect assumptions that MDR tuberculosis is the result of poor behavior by patients themselves. Examples of successful strategies exist and also result in much-improved support for individual patients [47].

### **TUBERCULOSIS INFECTION CONTROL STRATEGIES**

Strategies for infection control for MDR tuberculosis are exactly the same as for drug-susceptible tuberculosis. In the absence of effective detection and treatment for MDR tuberculosis, healthcare facilities are often sources of infection for the community [31, 48, 49]. Although TBIC policies have been in existence for some time, implementation of these has been extremely variable across high-burden settings. A lack of evidence to support which interventions result in the greatest benefit has led to a lack of clear implementation strategies and motivation among policy makers and HCWs. In addition, many infection control policies focus on already identified patients, restricting infection control measures to areas where these known tuberculosis patients are to be found and neglecting other congregate areas with significant transmission risk from persons with undiagnosed tuberculosis.

The emergence of MDR and XDR tuberculosis can potentially drive increased efforts in TBIC, thus reducing the risk of all tuberculosis transmission. Given the challenges that remain for expanding early case detection and rapid treatment initiation, specific TBIC, coupled with step-by-step implementation plans, are needed. These need to be context-specific, easy to implement, and sustainable within already stressed health systems. While cost and lack of resources are commonly cited as barriers to TBIC, these costs need to be seen in the light of the high cost of treating a single MDR tuberculosis patient, recently estimated at a mean of approximately US\$8000 in South Africa [50].

### **STRUCTURAL TBIC MEASURES**

While there is often a disproportionate focus on personal protective equipment (PPE) for TBIC, this is likely a reaction to the failure to provide a safer environment in healthcare facilities. Table 1 demonstrates that overcrowding, lack of space, and the absence of viable environmental TBIC measures are common barriers. Several studies also suggest that even when implemented, such structural measures are focused primarily on designated tuberculosis clinics and wards. Diagnosed tuberculosis patients, including those with MDR tuberculosis, should be receiving appropriate treatment, thereby lowering transmission risk. While structural TBIC measures are needed in these areas, they are also required throughout healthcare facilities, particularly in settings of high tuberculosis and high MDR tuberculosis. The provision of adequate resources is clearly a challenge,

**Table 1. Barriers to Adherence to Tuberculosis Infection Control Measures Among Healthcare Workers (2010–2015)**

Interpersonal	Health Facility	Health System
<ul style="list-style-type: none"> <li>Lack of training and knowledge [51–64]</li> <li>Disconnect between TBIC knowledge, attitudes, and practices [51, 53, 57, 58, 62, 64, 65]</li> <li>Failure to utilize supplied PPE measures [54, 66]</li> <li>Belief that using PPE increased patient stigma [65]</li> <li>Perceived lack of patient compliance [55, 56, 60, 64, 65]</li> <li>Desire for higher salaries to compensate additional risk [52, 65]</li> <li>Distrust of TBIC strategies [52]</li> <li>Unclear guidance on TBIC implementation [55]</li> <li>Lack of habit forming due to irregular supply of PPE [55]</li> <li>Belief that administration does not care about HCW safety [56, 65]</li> <li>Lack of motivation, complacency, and lack of solidarity among HCWs [57, 61]</li> <li>Cross-cultural communication challenges [60]</li> </ul>	<ul style="list-style-type: none"> <li>Lack of, or limited, TBIC plan [51, 53, 54, 56, 57, 59, 60, 63, 64, 66, 67]</li> <li>No designated IC staff [53, 56, 59, 62, 63, 66]</li> <li>No or limited structural ventilation or UVGI strategies [51, 53, 54, 60, 62–64, 66]</li> <li>No or poor separation of coughing, sputum smear-positive or MDR tuberculosis patients [51–54, 59, 63, 64, 66]</li> <li>Insufficient supply of, or access to, PPE [11, 52, 53, 56, 58–63, 65, 67]</li> <li>Lack of resources for TBIC [52]</li> <li>Overcrowding and lack of physical space [52, 55, 63]</li> <li>Disproportionate focus on PPE [52]</li> <li>Staff shortages [60]</li> <li>Focus only on designated tuberculosis areas [11]</li> </ul>	<ul style="list-style-type: none"> <li>Failure to provide a regular supply of PPE materials [51, 55]</li> <li>Lack of a national TBIC plan [54, 59]</li> <li>TBIC policies available but no resources or motivation for implementation [52, 66]</li> <li>Inadequate infrastructure for TBIC implementation [55]</li> <li>Tuberculosis stigma among healthcare workforce [11, 52, 56, 57, 60, 64]</li> <li>No or limited availability of DST [59]</li> </ul>

Abbreviations: DST, drug susceptibility testing; HCW, healthcare worker; IC, infection control; MDR, multidrug-resistant; PPE, personal protective equipment; TBIC, tuberculosis infection control; UVGI, ultraviolet germicidal irradiation.

but the lack of low-cost, low-maintenance interventions for resource-constrained settings is also of concern. These should include appropriate modifications to improve ventilation for existing physical structures [68] and design options for new buildings. Developing an evidence base for such interventions is much needed.

### BEHAVIORAL STRATEGIES TO IMPROVE TBIC IMPLEMENTATION

Healthcare workers remain at greater risk of tuberculosis infection and active tuberculosis disease [10]. Despite mounting evidence of the impact of TBIC interventions, HCWs struggle with implementation, despite reporting heightened fear of infection with drug-resistant tuberculosis strains.

In complex clinical settings, individual-, facility-, and systems-level barriers to TBIC measures (eg, the use of PPE

as well as environmental and administrative interventions) reduce HCW adherence (Table 1), thereby increasing their risk of repeated exposure, infection, and active tuberculosis disease. The lack of attention and resources for TBIC are consistent barriers across multiple studies in different settings. The repeated reports of deficient TBIC across clinical settings, countries, and years, demonstrates that a comprehensive, multicomponent TBIC program is required to address these issues. The study and application of human factor analysis in healthcare to improve patient and HCW safety is urgently needed.

### MONITORING AND EVALUATION

Whereas the DOTS strategy has had comprehensive monitoring and reporting embedded within the program since its inception, reporting for MDR tuberculosis has been more ad hoc. It is only since 2013 that the WHO has produced reports on the numbers of cases diagnosed, treatment initiation, and treatment outcomes. Given that case detection and treatment initiation are key to reducing transmission, monitoring progress in this area is fundamental [29]. Unfortunately, many national programs only report on patients receiving treatment, and not the large proportion who are diagnosed but do not receive treatment [2].

Given that tuberculosis and, specifically, MDR tuberculosis among HCWs are important indicators of efforts to reduce community transmission through early detection and treatment initiation, along with efforts to reduce nosocomial transmission through TBIC, monitoring disease among HCWs should be a priority. Clearly addressing issues of confidentiality, stigma, and income protection for HCWs would be important to moving this priority forward.

Monitoring and evaluation of TBIC measures requires collaboration and information sharing among different stakeholders (eg, programs related to tuberculosis, HIV, hospital management, occupational health, quality control and assurance, and infection control). Existing opportunities should be continuously explored to synergize efforts and improve efficiency.

### CONCLUSIONS

Reducing transmission of DR tuberculosis will require concerted efforts to improve case detection and initiate appropriate treatment rapidly. This requires a response from the whole health system, and should encompass universal implementation of specific TBIC measures in healthcare facilities. These 2 spheres of activity are intricately linked, and should be seen as part of a single response. A massive scale-up of rapid diagnosis and treatment is necessary to control the MDR tuberculosis epidemic. This will not be possible without intense efforts toward the implementation of decentralized, ambulatory models of care. Increasing political will and resources need to be accompanied by a paradigm shift. Instead of focusing on diagnosed cases, recognition that transmission is driven largely by

undiagnosed, untreated cases, both in the community and in healthcare settings, is necessary.

## Notes

**Supplement sponsorship.** This article appears as part of the supplement “Healthcare Workers and Tuberculosis Prevention,” sponsored by Aeras.

**Potential conflicts of interest.** H. C. is employed by the Wellcome Trust and the University of Cape Town, and has received grants or has grants pending from the Bill & Melinda Gates Foundation and the UK Medical Research Council. All other authors report no potential 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.

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