Linking Surveillance with Action against Drug-Resistant Tuberculosis

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The speed at which most countries with high burdens of multidrug-resistant tuberculosis (MDRTB) have scaled up their capacity to diagnose and treat individuals with these forms of TB has failed to keep pace with the problem. Limited availability of drug susceptibility testing, high costs and inefficiencies in the supply of second-line drugs, and inadequate capacity for the management of patients with MDRTB have contributed to the wide gap between the estimated need for and the delivery of MDRTB treatment. The most recent global estimates indicate that only about 1 in 20 individuals with incident MDRTB will be properly diagnosed; fewer still receive quality-assured treatment. As policy makers confront the threat of growing levels of drug-resistant TB, there is a clear role for improved surveillance methods that can facilitate more effective public health responses. In countries that cannot yet test all incident cases for drug resistance, analysis of programmatic data and use of periodic, efficient surveys can provide information to help prioritize the use of limited resources to geographic areas or population subgroups of greatest concern. We describe methods for the analysis of routinely collected data and alternative surveys that can help tighten the link between surveillance activities and interventions.

Keywords: tuberculosis; multidrug resistant; surveillance; survey; mapping

Before 1994, systematically collected data on the global burden of drug-resistant tuberculosis (DRTB) were not available. At that time, in response to concern about the potential for drug resistance to erode the effectiveness of the newly launched DOTS (directly observed treatment short-course) strategy, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases launched an ambitious project to document the global burden of DRTB (1). Since 1994, 64 countries with capacity for comprehensive and continuous drug susceptibility testing (DST) have contributed surveillance data, and 63 countries where continuous susceptibility testing is not feasible have communicated the results of at least one population-representative survey (2). Based on information collected through these sources, the WHO estimated that there were approximately 650,000 prevalent cases of multidrug-resistant TB (MDRTB) among the estimated 12 million prevalent TB cases in 2010 (3).

Despite global consensus on the importance of addressing drug resistance, the implementation of interventions directed at controlling the spread or amplification of DRTB has been very slow. In 2010, less than 2% of treatment-naive and 6% of treatment-experienced patients received a DST (3). Consequences of this failure to scale up our response include poor treatment outcomes for individuals with MDR disease (4), acquisition of additional resistance while receiving ineffective therapy (e.g., appearance of extremely DRTB) (5), and increased opportunity for transmission of drug-resistant disease in communities.

The slow pace of the response to DRTB has previously been attributed to several causes, ranging from inefficient models of care to lack of resources and political urgency (6). Here we suggest an additional contributing cause of this sluggish reaction: we believe that country-level policymakers do not have adequate tools to inform them of the distribution of DRTB within their jurisdictions. Currently implemented survey approaches typically produce countrywide estimates of the proportion of incident TB that is drug resistant (7). These population-representative surveys have an important role in providing national data that are useful for the global community and, if surveys can be repeated periodically, for understanding temporal trends in drug resistance at a country level. However, because both the burden and drivers of DRTB can differ markedly within the borders of a single country, we believe that efforts to obtain information about subnational geographic variability of DRTB will also help support the design of rational local responses (8).

For countries that have sufficient resources to test all microbiologically confirmed TB cases for drug susceptibility, identifying local variability in resistance does not require specialized methods but does require the willingness to report and analyze disaggregated data. However, for most countries with a large TB burden, this level of screening is not feasible given current resource allocations (2). In these settings, national TB program managers may still be able to use program data, such as the local concentration of cases requiring retreatment after standard first-line therapy, to identify areas where MDRTB may be problematic. However, informal use of such routinely collected data may not generate reliable insight about the local risk of drug resistance, as there can be other mechanisms unrelated to resistance that can create local concentration of individuals requiring retreatment (e.g., high rates of reinfection). Accordingly, in countries where only a subset of individuals is tested for resistance, alternative methods are needed to (*1*) systematically analyze programmatic data to identify geographic areas of greatest concern, and (*2*) conduct periodic surveys to determine local variability.

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This Pulmonary Perspective is divided into two sections to address each of these objectives. First, we describe how spatial analysis of routinely collected data (i.e., the observed data on the distribution of drug resistance among those tested under normal program conditions) can be applied to identify areas where risk of resistance is greatest among incident cases. Second, we present an alternate survey approach that aims to classify subnational areas according to specified thresholds. We present illustrative examples of each of these two approaches from recent work.

IDENTIFYING "HOTSPOTS" OF DRUG RESISTANCE USING PROGRAMMATIC DATA

National TB programs collect standardized data for patients identified at diagnostic facilities. Among other elements, these data typically include some information about the location of individuals with TB (either in the form of home or clinic address), the type of patient (e.g., treatment-naive or treatment-experienced), and information about drug susceptibility (when testing was obtained). In principle, these data could be used to identify geographic clusters of drug-resistant disease using one of several conventional statistical methods to identify spatial patterns of disease within populations (9–11). These cluster identification methods include both "density-based methods" that aim to identify locations with relatively high concentrations of individuals with drug-resistant disease (e.g., Kulldorff scan statistic [12], kernel density estimation [13], and generalized additive models [14]) and "distance-based methods" that aim to identify areas where individuals with drug-resistant disease are located more closely to each other than expected (*M*-statistic of Bonetti and Pagano [15], the distance-based mapping statistic proposed by Jeffery [10], Local Moran's I [16], and the Getis-Ord statistic [17]). When all TB cases are observed and all cases have been tested for drug susceptibility, applying these cluster detection methods is straightforward. However, when some resistant cases remain hidden because DST is not universally available, cluster detection methods cannot be used directly to identify hotspots of resistance.

This concern is illustrated in a previous analysis of data from Lima, Peru, where the drug-resistance status for all notified TB cases was not ascertained (18). Peru presents an important case study because, despite the presence of what is regarded as a well-functioning national TB program that has reduced the estimated TB incidence by 3.3% per year since the mid-1990s, the incidence of MDRTB was rising by 4.3% per year over the same period (2). Between January 1, 2005 and December 31, 2007, there were 11,577 TB cases notified from community health centers within our study area in Lima. Access to DST was limited to those at highest risk of resistance (e.g., known contacts of MDR cases) or to those at highest risk of poor outcome if resistance was not diagnosed early (e.g., HIV-coinfected TB cases). Accordingly, only about 10% of notified cases in this dataset received a DST. Among those tested, approximately 21% of treatment-naive cases tested and 40% of treatment-experienced patients had MDRTB; in total, 368 MDRTB cases were detected. Crude applications of cluster detection techniques to these data would identify areas where there are relatively high numbers of *tested and confirmed* cases of MDRTB. However, because access to DST was restricted, and those tested were not a random subset of all TB cases, the observed pattern may reflect the distribution of testing, not necessarily the distribution of resistance.

To attempt to identify true hotspots of resistance from a dataset in which the majority of cases did not have DST, we recently proposed using adjusted cluster detection methods that incorporate additional information summarizing the estimated underlying burden of undetected resistance and the usage patterns of DST (19). Informed by a population-representative drug resistance survey that had been done during the same time frame of our study (20) and which we assumed was representative of our study population, a total of 5.23% of treatment-naive patients and 24.22% of treatment-experienced patients would have had MDRTB. Based on this survey, we inferred that the programmatic testing targeted to high-risk individuals actually captured less than 30% of MDRTB in our study area.

To attempt to adjust for underdetection of MDRTB, we systematically relabeled a subset of patients with TB who did not receive DST as MDRTB cases (19). In separate analyses of the Peru data, we used two different assumptions to inform this relabeling process: (*1*) unidentified cases of MDRTB were randomly distributed among untested individuals, and (*2*) unidentified cases of MDRTB were more likely to occur in areas with sparse testing (i.e., untested individuals from areas where relatively high proportions of cases were tested were deemed lower risk). Based on repeated augmentation of the data under these different assumptions, we obtained a qualitatively different picture of the local risk of drug resistance than we did when we simply analyzed the dataset that included only notified MDRTB cases. Predictably, the first relabeling assumption resulted in low power to detect clusters of resistance, because the process of random reassignment masked any clustering that was actually present.

Furthermore, our reanalysis of these data from Lima suggests that attempts to use measures of the local risk of retreatment as a proxy for the local risk of drug resistance may be misleading. We estimated that the area with the highest proportion of cases requiring retreatment did have a relatively high overall *burden* of multidrug resistant disease, but had a lower *risk* of multidrug resistance among these retreatment cases than other areas of Lima (19). This could be consistent with a local risk of reinfection with strains that were not MDR.

Although we believe that accounting for patterns of DST use can help provide an improved understanding of the distribution of MDRTB, these methods rely on the availability of additional information about the distribution of and access to DST. Improved estimates of both the burden of MDR that is not diagnosed and the reasons for differences in usage of DST can greatly improve our ability to reliably correct for underdetection when identifying hotspots using this type of augmented cluster detection method.

USING CLASSIFICATION-BASED SURVEY APPROACHES TO IDENTIFY GEOGRAPHIC HETEROGENEITY IN DRTB

Current WHO guidelines recommend that all previously treated patients presenting with recurrent disease receive a DST at the time of diagnosis. For countries that do not provide a DST for all patients diagnosed with TB, the WHO and International Union Against Tuberculosis and Lung Diseases advise periodic surveys of representative samples of incident TB cases. Each of the recommended study designs offered in the guidelines shares the primary goal of generating a point estimate of the prevalence of MDR among incident TB cases (7). We have previously argued that this countrywide estimate may mask important heterogeneity and does not permit identification of geographic areas in which TB cases are at relatively high risk of resistance (8, 21).

An alternative approach for survey design integrates lot quality assurance sampling (LQAS) (22) into the WHO surveillance guidelines. In contrast to the standard survey methods that produce a point estimate for an entire country, the objective of LQAS surveys is to classify subregions into predefined categories (e.g., low/high or low/moderate/high). Implementation of LQAS classification is relatively straightforward. In the simplest static two-way LQAS classification, samples from each area are collected and tested and compared with a predetermined decision rule allowing for classification of areas into either the "low" or "high" MDR category.

The value of the additional information gained through the classifications was illustrated by a recent reanalysis of a DRTB surveillance study conducted in Vietnam in 2001 (23). The original study (24), conducted in accordance with standard guidelines, produced an encouragingly low estimate of the fraction of treatment-naive patients with MDRTB at the time of diagnosis of 1.8% (95% confidence interval, 1.0–3.3%). In contrast, when we reanalyzed the data as if it had been collected in an LQAS study, we found one of the four areas with sufficient sample size for classification by LQAS had a "high" MDRTB prevalence among new cases. On further discussion of this finding with local investigators, this site was noted to be worrisome because of its proximity to the Cambodian border and groups previously identified to be at higher risk for MDRTB and transnational migration (25).

To design a two-way LQAS system for detection of MDRTB heterogeneity, several parameters must be chosen, namely: (*1*) p_u, the threshold for a "high" classification; (*2*) α, the allowable misclassification error at p_u (the risk that an area truly at the high threshold will be misclassified as "low"); (*3*) p_l, the threshold for a "low" classification; and (*4*) β, the allowable misclassification error at p_l (the risk that an area truly at the low threshold will be misclassified as "high") (23, 26). For the Vietnam example above, the sample size and decision rules were set with a high MDRTB threshold of 20% with less than 5% probability of misclassification ($p_u = 20\%$, $\alpha \leqslant 5\%$) and low MDRTB threshold of 5% with less than 10% probability of misclassification ($p_l = 5\%$, $\beta \leqslant 10\%$). Determining the thresholds and acceptable levels of misclassification can be challenging and should depend both on the local epidemiology and the types of interventions that will be used based on the results of the study (e.g., universal DST or implementation of intensified infection control measures). Accordingly, the design of LQAS studies ideally requires the involvement of local policy makers; we consider this need for involvement of decision-makers to be a strength of this approach, because this should improve the link between surveillance activities and subsequent public health responses.

CONCLUSIONS

All individuals with incident TB should have access to DST, because universal testing will facilitate timely, appropriate treatment for those who are unlikely to be cured with standard first-line regimens (27). The introduction of new diagnostic tools offers hope for rapid susceptibility testing at peripheral sites (28). However, until these diagnostic tests are available everywhere, policymakers will need to grapple with the challenging problem of deciding how best to scale up responses to MDRTB given limited information and resources. We believe that spatial analysis of programmatic data and surveys intended to identify local heterogeneity are tools that can be used to support these decisions. The availability of inexpensive hardware for measuring and recording spatial data and freely available software for analyzing spatial data should further increase the appeal of these approaches.

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