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Introduction and evaluation of multidrug-resistant tuberculosis supplemental surveillance in the United States☆

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ABSTRACT

The current tuberculosis (TB) case reporting system for the United States, the Report of Verified Case of TB (RVCT), has minimal capture of multidrug-resistant (MDR) TB treatment and adverse events. Data were abstracted in five states using the form for 13 MDR TB patients during 2012–2015. The Centers for Disease Control and Prevention Guidelines for Evaluating Public Health Surveillance Systems were used to evaluate attributes of the form. Unstructured interviews with pilot sites and stakeholders provided qualitative feedback. The form was acceptable, simple, stable, representative, and provided high-quality data but was not flexible or timely. For the 13 patients on whom data were collected, the median duration of treatment with an injectable medication was 216 days (IQR 203–252). Six (46%) patients reported a side effect requiring a medication change and eight (62%) had a side effect present at treatment completion. A standardized MDR TB supplemental surveillance form was well received by stakeholders whose feedback was critical to making modifications. The finalized form will be implemented nationally in 2020 and will provide MDR TB treatment and morbidity data in the United States to help ensure patients with MDR TB receive the most effective treatment regimens with the least toxic drugs.

1. Introduction

Tuberculosis (TB) is caused by bacteria that is spread through the air from person to person [1]. In 1953, the United States (U.S.) introduced national TB surveillance with aggregate data reported by local jurisdictions [2]. In 1985, a standardized reporting form, the Report of Verified Case of TB (RVCT) was introduced for individual TB case reporting. The RVCT underwent revisions in 1993 and 2009 to add and modify variables [2,3]. In 2016, the Centers for Disease Control and Prevention (CDC) convened a national workgroup to review the RVCT and propose revisions to be implemented by 2020.

Multidrug-resistant (MDR) TB is TB that is resistant to isoniazid and rifampin. The U.S. reports 90–100 cases of MDR TB a year. Compared to drug-susceptible TB treatment, MDR TB treatment requires a longer duration of therapy with more toxic medications and frequent monitoring [4,5]. One limitation of the current RVCT is minimal capture of treatment data with only the initial medication regimen being recorded, which even for patients with MDR TB is frequently the standard first-line medication prior to drug susceptibility results being available. Except as a reason for treatment discontinuation, adverse drug reactions are not recorded on the RVCT, which for MDR TB treatment can cause significant long-term morbidity [4,5]. Due to limited MDR TB surveillance data outside of research projects, we do not have a clear understanding of national treatment practices and the long-term effect of these treatments on patients in the United States. Currently no U.S. national guidelines for the treatment of MDR TB exist. Practical guidelines are based on data from international sites, special research studies and expert opinion [5]. In December 2015, the United States Government published *The National Action Plan for Combating MDR TB* (NAP) [6]. The NAP calls for upgrading national TB surveillance to ensure complete and accurate detection of drug-resistant TB including treatment for drug-resistant TB [6].

Our objectives were to create and pilot an RVCT MDR TB supplemental surveillance form and to evaluate the proposed MDR TB

☆ **Ethics considerations:** The project was reviewed by CDC (Atlanta, GA) and the California Health and Human Services Agency and determined not to require approval by an institutional review board as this was considered program evaluation. The electronic survey was completed by federal employees only and exempt from the U.S. Paperwork Reduction Act.

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surveillance form and variables. The goals of the new variables were to provide clinical insight into the treatment, management, and morbidity of MDR TB treatment in the United States.

2. Methods

This is a mixed methods project with both quantitative and qualitative components.

2.1. MDR TB surveillance variable pilot

2.1.1. Data collection and analysis

A MDR TB surveillance form was created that consisted of two parts to be collected at one year into treatment and at the end of treatment. Data were collected through a retrospective review of a convenience sample of U.S. MDR TB patients reported during 2012 through 2016. Local TB control programs, with assistance from CDC medical officers, abstracted data from charts in the location were CDC medical officers were stationed. These sites represent high and low MDR TB morbidity and are located in rural and urban settings. Any patient diagnosed with MDR TB during 2012 through 2016 located at the site where a CDC medical officer was stationed was abstracted. Data were de-identified and descriptive analyses were conducted.

2.1.2. Definitions

MDR TB was defined as having isoniazid and rifampin resistance by growth/phenotypic- or molecular-based drug susceptibility testing. Expert consultation was defined as having received consultation by a physician, organization, or health institution with MDR TB treatment and management expertise [7]. MDR TB treatment start date was defined as the date the patient had at least two second-line medications in their treatment regimen. Second-line medications were anti-tuberculosis medications other than isoniazid, rifampin, pyrazinamide, or ethambutol. Medications initiated within 4 weeks of the MDR TB treatment start date and used for a minimum of 2 weeks were considered part of the initial MDR TB drug regimen. Drugs used for at least 2 weeks at any point after the treatment start date were included in "drugs ever used." Liver toxicity was defined as liver function tests exceeding three times the upper limit of normal (ULN) with associated symptoms, or five times ULN without associated symptoms. Renal dysfunction was defined as a change from a patient's baseline kidney stage to another stage using the National Kidney Foundation definitions [8]. Cardiac abnormality was defined as an electrocardiogram with a heart rate-corrected QT interval (QTc) of >500 ms.

2.2. MDR TB surveillance evaluation

The CDC Guidelines for Evaluating Public Health Surveillance Systems were used to assess the MDR TB surveillance supplemental form [9]. We evaluated the following five variables: simplicity, flexibility, data quality, acceptability, and timeliness [9]. Participants provided open-ended feedback to specific variables on the form and via a semi-structured phone interviews. CDC field staff, stakeholders including individuals and TB programs caring for the majority of U.S. MDR TB patients and national TB organizations provided unstructured qualitative feedback. Additionally, all TB programs in the United States were given the opportunity to provide feedback.

3. Results

3.1. MDR TB surveillance variable pilot

Five CDC field staff representing four states abstracted data for 13 MDR TB patients. Of the 13, seven (54%) were female, the median age was 51 years (interquartile range (IQR) 28–57), two (15%) had been previously treated for TB, and all received expert consultation. The median duration of injectable medication was 216 days (IQR 203–252) and one patient (8%) had surgery (Table 1). The median numbers of drugs in the initial regimen and drugs ever used were six (IQR 5–6 and 6–7, respectively, Table 1). The most commonly used drugs were ethambutol ($n = 10$, 77%), linezolid ($n = 10$, 77%), amikacin ($n = 9$, 69%), and pyrazinamide ($n = 8$, 62%). Nine patients received moxifloxacin initially (69%) and 10 (77%) at any point in treatment. Eight patients received cycloserine in the initial regimen (61.5%) and nine at any point in treatment (69%). No patients received isoniazid, rifapentine, bedaquiline, or clofazimine and two patients received rifampin (Table 2).

Six patients (46%) had a side effect resulting in a change of medication (Table 2). Of these, two had liver toxicity (33%) and one reported suicide attempt or ideation (17%, Table 3). Eight patients (61%) experienced residual side effects at the end of treatment (Table 2): peripheral neuropathy ($n = 3$, 23%), renal dysfunction ($n = 3$, 23%), hearing loss ($n = 2$, 15%), tinnitus ($n = 2$, 15%), and vision change/

Table 1
Demographic and clinical characteristics of convenience sample of MDR TB patients in the United States, 2012–2016 ($N = 13$).

Patient characteristics	*n*, median (%, IQR)
Sex, male	6 (46%)
Age, years	51 (28–57)
Previous TB treatment with second-line drugs	2 (15%)
Expert consultation obtained	13 (100%)
Duration of treatment with second-line injectable, days[a]	216 (203–252)
Number of drugs in initial MDR TB treatment regimen	6 (5–6)
Number of drugs ever used for treatment MDR TB	6 (6–7)
Number patients experiencing side effect leading to a change in medication	6 (46%)
Number patients experiencing side effect at the end of treatment	8 (61.5%)
Number patients received surgery to treat MDR TB	1 (8%)
Number hospitalized related to TB	8 (61.5%)

Note: IQR = interquartile range, MDR = multidrug resistant that is resistant to at least isoniazid or rifampin.
[a] Calculated using the second-line injectable stop date and MDR TB treatment start date.

Table 2
Anti-TB medications used for the treatment of MDR TB patients in the United States, 2012–2016. ($N = 13$).

Drug	Initial regimen[a]	Ever used[b]
First-line medications		
Isoniazid	0 (0%)	0 (0%)
Rifampin	2 (15%)	2 (15%)
Rifabutin	1 (8%)	2 (15%)
Rifapentine	0 (0%)	0 (0%)
Pyrazinamide	8 (61.5%)	8 (61.5%)
Ethambutol	10 (77%)	10 (77%)
Streptomycin	0 (0%)	1 (8%)
Second-line injectables		
Amikacin	9 (69%)	9 (69%)
Capreomycin	4 (31%)	4 (31%)
Fluoroquinolones		
Levofloxacin	5 (38%)	5 (38%)
Moxifloxacin	9 (69%)	10 (77%)
Bedaquiline	0 (0%)	0 (0%)
Clofazimine	0 (0%)	0 (0%)
Cycloserine	8 (61.5%)	9 (69%)
Ethionamide	6 (46%)	6 (46%)
Linezolid	10 (77%)	10 (77%)
Para-Amino Salicylic Acid	5 (38%)	5 (38%)

MDR = multidrug resistant, i.e., resistant to at least isoniazid and rifampin.
[a] Initial regimen indicates any drug initiated within four weeks of the MDR TB treatment start date, and used for a minimum of two weeks.
[b] Drugs ever used indicates any drug used at any point after MDR TB treatment start date, and used for a minimum of 2 weeks.

Table 3
Number of MDR TB patients who experienced a side effect that led to a change in an anti-TB medication, 2012–2016. (N = 13).

Side effect	Number (%)
Liver toxicity[a]	2 (15%)
Suicide attempt or ideation	1 (8%)
Cardiac abnormalities[b]	0 (0%)
Other	3 (23%)
Tinnitus	2 (67%)
Vestibular dysfunction	1 (33%)
Hearing loss	1 (33%)
Hypothyroidism	1 (33%)
Peripheral neuropathy	1 (33%)
GI disturbance	1 (33%)
Depression	1 (33%)
Foul taste/burning smell	1 (33%)

MDR = multidrug resistant, i.e., resistant to at least isoniazid and rifampin.

[a] Liver toxicity was defined as liver transaminases exceeding three times the upper limit of normal with associated symptoms, or five times the upper limit of normal if the patient is asymptomatic.

[b] Cardiac abnormalities included clinically significant ventricular arrhythmia or a QTc of >500 ms and confirmed by repeat ECG.

Table 4
Number of MDR TB patients who had a persistent side effect at the end of MDR TB treatment, 2012–2016. (N = 13).

Side effect	Number (%)
Peripheral neuropathy	3 (23%)
Renal dysfunction[a]	3 (23%)
Hearing loss	2 (15%)
Vision change/loss	1 (8%)
Tinnitus	0 (0%)
Vestibular dysfunction	0 (0%)
Liver toxicity[b]	0 (0%)
Other	2 (15%)
Tremor	1 (50%)
Depression	1 (50%)

MDR = multidrug resistant, i.e., resistant to at least isoniazid and rifampin.

[a] Renal dysfunction was defined as a change in baseline renal function such that a patient has transitioned from baseline kidney stage to another, higher stage.

[b] Liver toxicity was defined as liver transaminases exceeding three times the upper limit of normal with associated symptoms, or five times the upper limit of normal if the patient is asymptomatic.

loss (n = 1, 8%, Table 4).

3.2. MDR TB surveillance evaluation

Six CDC field staff members and seven stakeholders or stakeholder groups contributed feedback by email or telephone.

3.2.1. Acceptability

Because the completion of the RVCT is a funding requirement and a long-established surveillance tool with mandatory participation in the U.S., there is high acceptability. Because MDR TB surveillance will be a part of the RVCT reporting process, participants and TB program staff reported high acceptability of the new form and introduction of national MDR TB surveillance.

3.2.2. Data quality

Participants agreed the proposed variables provide a snapshot of a patient's MDR TB treatment course given the complexities of MDR TB treatment. Participants and stakeholders acknowledged that completely capturing the intricacies of a patient's course would be beyond the scope of surveillance, and the proposed variables represented the essential elements without being too burdensome to the user. Data quality was dependent on the quality of recording in patients' charts; however, there was consensus that data quality would improve with the introduction of standardized MDR TB supplemental surveillance.

3.2.3. Flexibility

Participants agreed the form was appropriately inflexible, a good companion to the RVCT and took approximately 15–30 min to complete. Stakeholders voiced concern regarding the logistics, information technology expertise and required financial resources to incorporate MDR TB surveillance into current local electronic systems. Further, there were concerns about required expertise and personnel time to input data.

3.2.4. Simplicity

Participants agreed the form was simple, easy to use, and appreciated the limited data variables. There are several methods for submitting the RVCT, making reporting MDR TB surveillance equally simple. The pilot variables had detailed definitions, instructions and an example case.

3.2.5. Timeliness

There would be a delay between MDR TB diagnosis and reporting of the new MDR TB variables as final data would be collected after a patient completes treatment 18–24 months after diagnosis. Participants acknowledged MDR TB data would not represent real-time results or the ability to intervene in treatment, but thought it was appropriate for state and national surveillance purposes. Local programs involved with direct patient care or patient oversight collect data more frequently to inform treatment, management and contact investigations.

4. Discussion

The current RVCT collects minimal data on U.S. MDR TB patients. More comprehensive MDR TB data have been collected from research projects [4,10–16]. This pilot supplemental MDR TB surveillance form has been reviewed for incorporation into the 2020 RVCT and will provide the first national standardized MDR TB clinical surveillance data for the United States [17]. New laboratory data on drug resistance has also completed piloting and will be included in the 2020 RVCT. While treatment of MDR TB is complicated with patients changing regimens a median of seven times [4], participants felt the pilot variables appropriately captured the key surveillance elements. The form was considered to be acceptable, simple, and collected good quality data. Because reporting will be approximately 2 years after diagnosis, real-time data will not be available for MDR TB patients. However, current RVCT treatment outcome reports are also delayed by several months.

Participant and stakeholder comments were used to make modifications to the surveillance variables. Variables were removed, further defined, and consolidated to be collected once at the end of treatment. To capture the MDR TB treatment regimen more effectively, duration categories were introduced instead of yes/no options. Children treated for MDR TB are underreported because of challenges with obtaining quality specimens for laboratory data testing, which is necessary for the current surveillance system [12]. The new form will allow a patient with nonculture-confirmed TB who is being treated using an MDR TB regimen to be reported if the individual is a known contact to an MDR TB or there is a clinical suspicion of MDR TB [12]. The modified form is available in the supplement.

The surveillance pilot provided a glimpse of MDR TB in the United States. The median numbers of medications in a patient's initial regimen and of medications ever taken were the same (n = 6). Because of the

time overlap between medications used in the initial regimen and ever used, the pilot likely did not yield granular details to describe medication regimens throughout treatment. By grouping medications into 6-month periods, the modified form should provide a more detailed picture of the drugs involved in a patient's regimen. When implemented, the new data in conjunction with RVCT data will provide considerable insight. For example, using the MDR TB treatment start date and the RVCT treatment end date will allow calculation of the total duration of MDR TB therapy. As we move into the advent of shorter therapies, the MDR TB variables could allow for future analysis of MDR TB clinical outcomes by duration of therapy [18,19]. Further, these new variables can provide an understanding into national trends in MDR TB treatment and guide future national treatment guidelines.

Medications for MDR TB are often very toxic. Our pilot 62% ($n = 8$) patients experienced a residual side effect at the end of treatment. The most common were peripheral neuropathy, renal dysfunction, hearing loss, tinnitus, and liver toxicity. Though we were unable to associate a specific medication with a particular side effect, the residual side effects observed are known side effects for the most commonly used MDR TB drugs (Tables 3 and 4). Aside from special research projects [4], these variables will be the first attempt to systematically collect anti-TB medication side effect data through a surveillance system in the United States. Clinical trials of new anti-TB regimens with less toxic medications and without an injectable medication are ongoing and might change how MDR TB is treated in the future [18,19]. MDR TB surveillance may allow us to track new medications over time and their effect on tolerability and successful treatment outcomes, potentially decreasing cost and disability attributed to TB disease.

4.1. Limitations

The RVCT is under review for 2020 revisions, and this MDR TB supplemental surveillance form needed to be completed by early 2018. Due to constrained time, this project was completed by a convenience sample of programs where CDC TB medical officers are stationed. The sampling and limited time did not allow for complete capture of a representative sample of MDR TB cases in the United States. However, we attempted to collect data from diverse patient populations including areas that report many of the U.S. MDR TB cases. Further, we obtained stakeholder feedback from jurisdictions reporting the largest burden of MDR TB cases and from all U.S. TB programs.

4.2. Conclusions

Our study represented the first attempt to nationally standardize and quantify clinical features of MDR TB treatment and management in the United States. The final form has been preliminary accepted for inclusion in the national surveillance system that will be implemented in 2020 and will affect all U.S. states and territories. Some questions remain about implementation of the surveillance form. Who will input the data? Will all programs need to update their electronic surveillance software? Will data be complete? Should we include resistance to only rifampin and isoniazid in the future? Because there are only 90–100 MDR TB cases in the United States, the reporting burden may not be overwhelming and may not affect every state. The variables proposed for MDR TB surveillance in combination with RVCT data can provide substantial insight into MDR TB disease management, treatment, and morbidity. Data collected regarding uptake and utilization of medications can help drive pricing, insurance access, drug policy and possible future medication development.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflicts of interest

There are no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2019.01.005.

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