Insights into drug-resistant tuberculosis treatment: results of The Union DR-TB Working Group Survey, 2017

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The past 4 years have seen the introduction of new regimens and new drugs to treat multidrug-resistant tuberculosis (MDR-TB). To identify implementation trends over time, the DR-TB Working Group of the International Union Against Tuberculosis and Lung Disease (The Union), in collaboration with RESIST-TB, launched an online survey to Union members around the world. Survey results showed substantial diversity in treatment roll-out: 36% of respondents stated that their country is using the 9-month regimen for MDR-TB treatment; 41% are using bedaquiline and delamanid, but not the 9-month regimen; 28% are using both; and 22% of respondents indicated that their country does not currently offer either of these treatment options. Survey respondents also identified specific challenges to the introduction of shorter MDR-TB regimens and new drugs, including access to rapid diagnosis of fluoroquinolone resistance and case management. The results of this survey are intended to help identify research and implementation gaps while highlighting the importance of global implementation of scalable regimens for the treatment of MDR-TB.

Anti-tuberculosis drug resistance is a major obstacle to the treatment and management of tuberculosis (TB).¹ Multidrug-resistant TB (MDR-TB; defined as TB resistant to at least isoniazid and rifampicin) is complex and multifactorial, fueled, according to the World Health Organization (WHO), by 'improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places'.¹ As the global prevalence of MDR-TB increases, TB case management becomes increasingly difficult. The implementation of a shorter regimen and use of new drugs that might increase cure rates could have major benefits.

Several new treatment strategies for MDR-TB have recently been introduced. In 2014, the WHO recommended the addition of two new drugs, bedaquiline (BDQ) or delamanid (DLM), to regimens for the treatment of extensively drug-resistant TB (XDR-TB; defined as MDR-TB with additional resistance to any fluoroquinolone [FQ] and at least one of the three second-line injectables) and pre-XDR-TB (defined as MDR-TB plus resistance to an FQ or a second-line injectable).^{2,3} In 2016, the WHO recommended a shorter, highly effective 9-month treatment regimen for patients with FQ-susceptible strains of MDR-TB.¹ The shorter regimen is less expensive than the global standard 18–24-month regimen, and it also addresses

other obstacles to successful treatment such as adherence, and specifically loss to follow-up due to high costs, serious adverse events and prolonged treatment.

In 2016, the International Union Against Tuberculosis and Lung Disease (The Union) created a DR-TB Working Group with four objectives: 1) to review annual progress in diagnosis, treatment and prevention of MDR-TB; 2) to collaborate with other groups to enhance the visibility of MDR-TB treatment options; 3) to share best practices in scaling up MDR-TB prevention, diagnosis and treatment; and 4) to identify practice and research gaps in MDR-TB prevention, diagnosis and treatment. To assess MDR-TB treatment options available in working group countries in 2017, an internet-based survey was designed and implemented.

MATERIALS AND METHODS

Study instrument and study participants

In collaboration with RESIST-TB, a six-question survey was created and circulated using the online survey software and questionnaire, SurveyMonkey (see Appendix for survey questions and answer options). All 1700 members registered in the TB Section of The Union were invited to participate. To increase the response rate, two reminder e-mails were sent out.

As the survey was categorized as exempt from human subjects research, informed consent was not required.

Implementation

The Union TB Section members received the invitation to participate in the survey via e-mail on 1 January 2017, and were given up to 2 months to respond. For the purposes of analysis, the countries were grouped according to their respective WHO Regions: African Region, Eastern Mediterranean Region, European Region, Region of the Americas, South-East Asia Region and Western Pacific Region (<http://www.who.int/about/regions/en/>).

RESULTS

A total of 150 Union TB Section members responded to all or part of the survey. The respondents represented 45 countries across six continents, and included health professionals in a variety of roles. Responses were received from 52 respondents from the African Region, 6 from the Eastern Mediterranean Region, 30 from the European Region, 22 from the Re-

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TABLE 1 Treatment options reported by survey respondents

WHO Region	Treatment option		
	Piloted shorter regimens %	Plan to introduce shorter regimens %	Currently using BDQ/DLM %
African	43	100	65
Eastern Mediterranean	0	67	33
European	50	58	90
Region of the Americas	6	50	65
South-East Asia	30	95	70
Western Pacific	43	75	80

WHO = World Health Organization; BDQ = bedaquiline; DLM = delamanid.

gion of the Americas, 25 from the South-East Asian Region, and 15 from the Western Pacific Region.

The proportions of respondents in each region reporting the use of the 9-month regimen or the new drugs (BDQ and DLM) are shown in Table 1. Specific challenges in the introduction of the shorter MDR-TB regimens and new drugs are shown in Table 2.

Co-prevalence of 9-month regimen and new drugs

The combined use of shorter MDR-TB regimens and the use of BDQ and DLM worldwide is shown in the Figure, which gives the MDR-TB treatment options on a global scale. Of all WHO Regions represented in this survey, 36% responded that their country was using the 9-month regimen, 41% used only BDQ and DLM for MDR-TB treatment, and 28% of respondents stated that their country used both BDQ- and DLM-based treatment regimens in addition to the shorter, 9-month regimens. Finally, 22% of respondents indicated that their country did not currently offer either of these treatment options.

An analysis of co-prevalence by WHO Region revealed that in the Region of the Americas and the Eastern Mediterranean Region, no (0%) respondents indicated that their country was using both the 9-month regimen and the new drugs; 27% of respondents from the South-East Asia Region, 29% of respondents from the Western Pacific Region, and 29% from the African Region indicated that their respective country had coverage of both the 9-month regimen plus BDQ- and DLM-based treatment. The European Region reported the greatest coverage, with 50% of respondents indicating that their country had both treatment options.

DISCUSSION

Although data for the survey were not collected evenly across all six WHO Regions, we believe that the information gathered is useful for drawing general conclusions about available treatment regimens for MDR-TB in 2017. The most striking finding of this survey is the variability of MDR-TB treatment between regions. Globally, only 28% of respondents stated that their country had the option to treat MDR-TB with both the shorter 9-month regimen and a BDQ- or DLM-based regimen. Moreover, 22% of respondents stated that their country had neither of these treatment options, a particularly worrying finding, as drug resistance remains a growing global threat. A second important finding is that despite the global roll-out of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), 35% of the respondents stated that susceptibility testing for rifampicin resistance remains a challenge in their country (Table 2). This may suggest that not all countries are using Xpert in the most efficient manner.

TABLE 2 Specific aspects or challenges in the introduction of shorter MDR-TB regimens that need to be addressed

Responses*	Responses n (%)
Rapid diagnosis of FQ resistance	93 (62)
Case management	72 (48)
Enrollment on treatment	62 (41)
Susceptibility testing for rifampicin resistance	52 (35)
Identification of presumptive DR-TB cases	51 (34)
Recording and reporting system	42 (28)

* Other challenges mentioned less frequently: 1) drug supply challenges, including access to and availability of CFZ; 2) DST availability and cut-offs for BDQ, DLM, LZD and CFZ; 3) need for LPA scale-up; 4) uncertainty regarding FQ screening requirements; 5) need for more research on the treatment and management of XDR-TB, specifically new drugs; 6) procurement and price control of DR-TB drugs, in particular BDQ and DLM; and 7) better education and attention to pediatric regimens and dosing. MDR-TB = multidrug-resistant tuberculosis; FQ = fluoroquinolone; DR-TB = drug-resistant TB; CFZ = clofazimine; DST = drug susceptibility testing; BDQ = bedaquiline; DLM = delamanid; LZD = linezolid; LPA = line-probe assay; XDR-TB = extensively drug-resistant TB.

Overall, 36% of respondents stated that their country offers the 9-month regimen: 28% offer BDQ- or DLM-based treatment options plus the 9-month regimen, while 8% offer only the 9-month regimen. It is interesting to note that among this 8%, five different WHO Regions were represented. This suggests that the shorter 9-month MDR-TB regimen is being introduced in more countries than in previous years. A total of 41% of respondents from six different WHO Regions stated that their country currently uses only BDQ- or DLM-based treatment options. According to Médecins Sans Frontières (MSF), a major barrier to the introduction and use of the two new drugs in 2015 was that 'BDQ [is] registered in just seven of the world's 27 high MDR-TB burden countries, and DLM [is] registered in just four countries, none of which has a high MDR-TB burden (Japan, Germany, the United Kingdom and South Korea)'.⁴ MSF reported in December 2015 that just 2% of people who need BDQ and DLM receive the drugs.⁴ The 41% of survey responses to this question may therefore suggest that the rate at which people eligible for these treatments are receiving them is increasing.

Of all the world regions, the European Region reported the greatest coverage of MDR-TB treatment, including both the shorter regimen options as well as the availability of BDQ- or DLM-based treatment options. Russia comprises the largest proportion of MDR-TB incidence in this region and had the highest MDR-TB incidence rate in 2016.¹ However, survey respondents from other countries with high MDR-TB incidence, such as India and Indonesia, did not state that their country currently used ei-

FIGURE Combined use of shorter multidrug-resistant tuberculosis regimens and use of BDQ and DLM worldwide. BDQ = bedaquiline; DLM = delamanid.

ther the shorter regimens or BDQ- and DLM-based regimens. These findings suggest that many regions with high MDR-TB burdens, such as the South-East Asia Region, may not have had adequate treatment options in early 2017. In these regions, the impact of MDR-TB on mortality and morbidity is significant, but therapy may be limited by a lack of treatment options.

A number of countries announced plans to initiate either the shorter 9-month regimen, the new drugs, or both, during 2017. The Union DR-TB Working Group planned to perform a repeat survey in 2018 to determine if progress in the roll-out of these treatments can be detected. If progress has not occurred, advocacy will need to be directed towards those countries where the most effective MDR-TB regimens are not being implemented.

Limitations and recommendations

These results have limitations that should be taken into consideration. Foremost, distribution among survey respondents was uneven, with some regions of the world having significantly larger numbers of responders than others. For this reason, responses from the Eastern Mediterranean Region and the Western Pacific Region have probably not yielded reliable estimates. Future efforts will be focused on increasing response rates among underreported regions. Second, the professions of the respondents were likely to have been diverse, and it is possible that not all were involved in or had information about national TB program plans and roll-out. However, we were unable to characterize respondents with regard to this involvement. Furthermore, the survey included answer options of 'not sure'; we excluded these responses in our denominator during analysis. Finally, grouping countries by WHO Region obscures variability within regions with regard to burden of disease and drug implementation and management.

CONCLUSION

Substantial progress has been made in implementation of the 9-month regimen and the use of BDQ and DLM for MDR-TB treatment. This progress varies by geographic region. We hope that re-administration of the survey will give insight into implementation trends over time and identify areas where continued efforts need to be focused.

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APPENDIX

Survey

- Q1: Have shorter MDR-TB regimens been piloted in your country?
A: Yes, No, Not sure
- Q2: Does your country plan to introduce shorter MDR-TB regimens under programmatic conditions?
A: Yes, No, Not sure
- Q3: Is your country currently using bedaquiline- or delamanid-based treatment for XDR-TB and pre-XDR-TB?
A: Yes, No, Not sure
- Q4: Is there any specific aspect or challenge in the introduction of shorter MDR-TB regimens that you would like the Working Group to address?
A: Select all that apply:
1) Identification of presumptive DR-TB cases
2) Susceptibility testing for rifampicin resistance
3) Rapid diagnosis of fluoroquinolone resistance (decentralization of Xpert, maintenance of the machines, regular supply of cartridges, quality control, etc.)
4) Enrollment on treatment (delays, etc.)
5) Case management (ambulatory vs. hospitalization, directly observed therapy, etc.)
6) Recording and reporting system
7) Other (open-ended response)
- Q5: Are you interested in sharing your country's experience in the introduction of shorter MDR-TB regimens?
A: Yes, No, Not applicable
- Q6: What is your country of residence?
A: Open-ended response

MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB; DR-TB = drug-resistant TB.

Les quatre dernières années ont vu l'introduction de nouveaux protocoles et de nouveaux médicaments dans le traitement de la tuberculose multirésistante (TB-MDR). Dans le but d'identifier les tendances de la mise en œuvre dans le temps, le groupe de travail sur la TB résistante de l'Union Internationale contre la tuberculose et les maladies respiratoires (L'Union), en collaboration avec RESIST-TB, a lancé une enquête en ligne auprès des membres de l'Union autour du monde. Les résultats de l'enquête ont montré une grande diversité dans le lancement du traitement : 36% des répondants ont affirmé que leur pays utilisait le protocole de 9 mois pour le traitement de la TB-MDR ; 41% utilisent la bédaquiline et le délamanide, mais pas le

protocole de 9 mois ; 28% utilisent les deux ; et 22% des répondants ont indiqué que leur pays n'offrait actuellement aucune de ces options de traitement. Les répondants ont également identifié les défis spécifiques à l'introduction de protocoles plus courts et de nouveaux médicaments de TB-MDR, notamment l'accès à un diagnostic rapide de la résistance aux fluoroquinolones et la prise en charge des cas. Les résultats de cette enquête sont destinés à contribuer à identifier les lacunes en matière de recherche et de mise en œuvre, tout en mettant en lumière l'importance de la mise en œuvre mondiale de protocoles évolutifs pour le traitement de la TB-MDR.

En los últimos 4 años ha tenido lugar la introducción de nuevos esquemas terapéuticos y nuevos fármacos para el tratamiento de la tuberculosis multirresistente (TB-MDR). Con el propósito de evaluar las tendencias de su aplicación en el transcurso del tiempo, el grupo de trabajo sobre TB farmacorresistente de la Unión Internacional Contra la Tuberculosis y Enfermedades Respiratorias (La Unión), en colaboración con la iniciativa RESIST-TB, emprendió una encuesta en línea dirigida a los miembros de La Unión en todo el mundo. Los resultados pusieron de manifiesto una gran diversidad del despliegue del tratamiento. El 36% de quienes respondieron afirmaba que en su país se utiliza el esquema de 9 meses para el tratamiento de la TB-MDR; el 41% utiliza bedaquilina y delamanid,

pero no el esquema de 9 meses; el 28% utilizan ambos; y el 22% de quienes respondieron indicaba que en su país no se ofrece en la actualidad ninguna de estas opciones terapéuticas. Las respuestas a la encuesta revelan también dificultades específicas con la introducción de los esquemas más cortos de tratamiento de la TB-MDR y con los nuevos medicamentos, entre ellas el acceso al diagnóstico rápido de la resistencia a las fluoroquinolonas y el manejo de los casos. Los resultados de esta encuesta tienen por finalidad contribuir a reconocer las lagunas en la investigación y en la ejecución y al mismo tiempo destacar la importancia de la introducción mundial de esquemas ampliables de tratamiento de la TB-MDR.