INT J TUBERC LUNG DIS 26(6):524–528

http://dx.doi.org/10.5588/ijtld.21.0420

Global availability of susceptibility testing for second-line anti-tuberculosis agents

A. Lazarchik,[1] A. U. Nyaruhirira,[2] C-Y. Chiang,[3,4] F. Wares,[5] C. R. Horsburgh, Jr.[1,6]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [2]Management Sciences for Health, Pretoria, South Africa; [3]Division of Pulmonary Medicine, Department of Internal Medicine, Wanfang Hospital, Taipei Medical University, and [4]Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [5]KNCV Tuberculosis Foundation, The Hague, The Netherlands; [6]Departments of Biostatistics and Global Health Boston University School of Public Health and Department of Medicine, Boston University School of Medicine, Boston, MA, USA

SUMMARY

BACKGROUND: The continued development of new anti-TB agents brings with it a demand for accompanying treatment regimens to prevent the development of resistance. Effectively meeting this demand requires an understanding of the pathogen's susceptibility to various treatment options, which in turn makes access to antibiotic susceptibility testing (AST) a paramount consideration in the global treatment of TB.

METHODS: A 12-question, quantitative and qualitative survey was developed to gauge global capacity and access to AST. The survey was disseminated to members of the Global Laboratory Initiative, Global Drug-resistant TB Initiative, and the TB section of the International Union Against Tuberculosis and Lung Disease to solicit responses from pertinent stakeholders.

RESULTS: A total of 323 complete responses representing 84 countries and all WHO Regions were collected. AST capacity for fluoroquinolones and second-line injectables was high in all WHO Regions. AST capacity for the new and repurposed drugs is highest in the European Region, Region of the Americas and the Western Pacific Region, but quite limited in the African and Eastern Mediterranean Regions. The AST turnaround time for second-line drugs was delayed compared to that for first-line drugs as samples needed to be sent farther for analysis. Common barriers to AST for second-line drugs were lack of specimen transportation infrastructure, high costs, and lack of specialised laboratory workers and specialised laboratory facilities.

CONCLUSION: Without expanding global access to AST, the growing availability of new treatment options will likely be threatened by accompanying increase in resistance. There is an earnest and pressing need to improve capacity and access to AST alongside treatment options.

KEY WORDS: tuberculosis; drug resistance; susceptibility testing; DR-TB; TB; MDR-TB

With an estimated 465,000 global incident cases in 2019, rifampicin-resistant/multidrug-resistant TB (RR-/MDR-TB) remains a pressing global threat.[1] Recent years have seen a rapid expansion in the use of new and repurposed drugs to treat disease caused by these organisms. While new drugs offer promising treatment options, without auxiliary protection from other drugs, the risk of acquired resistance is high.[2] Unfortunately, such resistance has already begun to emerge.[3–5] The construction of drug regimens which will curtail the development of resistance relies on knowing the susceptibility of a patient's organism to potential treatment agents. This, in turn, makes global access to antibiotic susceptibility testing (AST) essential. The critical importance of adequate access to AST was emphasised in a recent review.[6] The WHO currently recommends that the following second-line antimicrobials be considered for inclusion in a regimen for RR-/MDR-TB: levofloxacin/moxifloxacin, bedaquiline (BDQ), linezolid (LZD), clofazimine (CFZ), cycloserine/terizidone, delamanid (DLM), ethionamide/prothionamide and *p*-aminosalicylic acid.[7] Therefore, we surveyed clinicians and national TB programme (NTP) personnel to assess global access to AST for the recommended new, repurposed and other second-line drugs.

METHODS

In 2019, RESIST-TB, in conjunction with the Global Laboratory Initiative (GLI) and the Global Drug-resistant TB Initiative (GDI), created a 12-question survey to assess barriers to AST for new and repurposed TB drugs. Questions were also included to assess global

Correspondence to: Adam Lazarchik, Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA. email: adamlazarchik@gmail.com

Article submitted 30 July 2021. Final version accepted 14 December 2021.

Table 1 Proportion of responses to the question: "The country currently has capacity for AST for which drugs (check all that apply)" ($n = 323$)

Drug	%
FQs (ofloxacin, levofloxacin or moxifloxacin)	94
BDQ	37
LZD	50
FQs + BDQ	37
FQs + LZD	50
FQs + BDQ + LZD	33
Clofazimine	41
Delamanid	21
Kanamycin* or amikacin	92
None of these	4

* No longer recommended.
FQ = fluoroquinolone; BDQ = bedaquiline; LZD = linezolid.

access to and utilisation of TB AST. The survey questionnaire was distributed to the members of three global networks: GLI, GDI and the TB section of the International Union Against Tuberculosis and Lung Disease (The Union). The survey was opened for responses in January 2020 and closed at the end of May 2020 (see Supplementary Data for the 2020 survey questions and response options). The survey was determined to be exempt by the Institutional Review Board of Boston University, Boston, MA, USA.

Responses without data on the respondent's country of representation were excluded. Answers to each question were analysed overall, stratified by WHO Region, and by type of organisation affiliation.

Ethics statement

The survey was categorised as exempt from human subject research.

RESULTS

At the close of the survey, 328 responses had been collected, representing 84 different countries. Five responses lacked country identification and were excluded. The African Region (33%), Eastern Mediterranean Region (5%), European Region (15%), Region of the Americas (18%), South East Asian Region (20%) and Western Pacific Region (9%) were all represented in the data. Respondents predominantly belonged to NTPs (49%), non-government organisations (28%) and public health care facilities (other than NTP) (23%). Respondents from academia, reference laboratories, the WHO and other affiliations each comprised less than 7% of the total.

Table 1 portrays the proportion of respondents who reported that their respective country had capacity for AST of various TB drugs and combinations. The vast majority of respondents reported having in-country AST capacity, with most respondents reporting AST capacity for fluoroquinolones (FQs) and second-line injectables (SLIs). Less than half of the respondents reported AST capacity for BDQ, LZD, DLM or CFZ (Table 1). We do not show access to AST for pretomanid, as it is unclear to what extent delamanid susceptibility may predict pretomanid susceptibility and no critical concentration has been established for pretomanid.[8] Of 116 respondents, 66 (57%) had access to AST for either BDQ or LZD.

For diagnosing new cases of TB, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and smear microscopy were reported to be used in most countries. For determining resistance to first-line drugs, GeneXpert use (for rifampicin resistance) was widespread, with liquid culture, first-line line-probe assay (LPA) testing and solid culture reported by the majority of respondents. Little variation in method of determining resistance was observed across the WHO Regions.

AST capacity to FQs and SLIs was reported to be

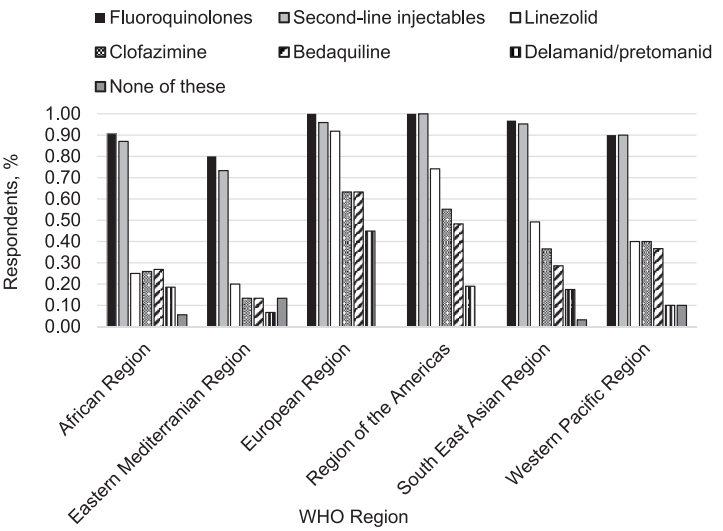

Figure 1 Proportion of responses to the question: "The country currently has capacity for AST for which all drugs (check all that apply)" stratified by WHO region ($n = 323$).

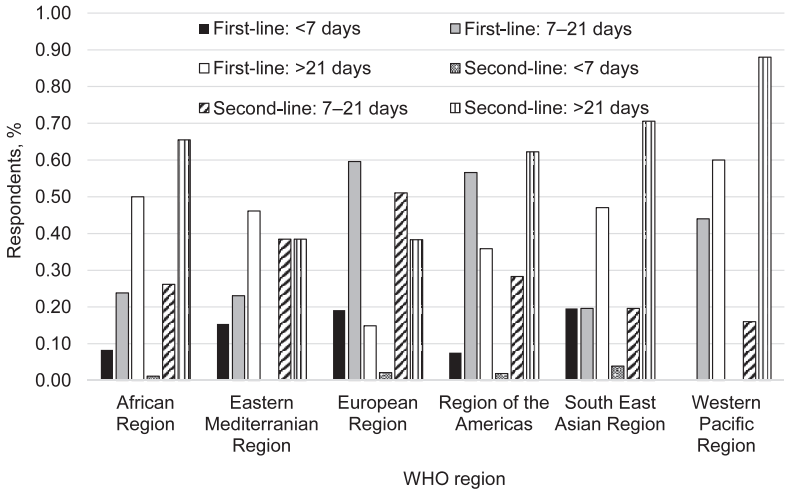

Figure 2 Proportion of responses to the question: "If you have access to phenotypic AST [in/for] your country, what is the average turnaround time (in days) from sample collection to results? (Please check the time period for first- and second-line AST)" stratified by WHO region ($n = 323$). Proportion of respondents answering "I'm not sure" omitted. AST = antibiotic susceptibility testing.

high in all WHO Regions (Figure 1). The European Region, Region of the Americas and the Western Pacific Region were reported to have AST capacity for the greatest number of drugs—repurposed drugs in particular (Figure 1). Significant gaps in AST access to new and repurposed drugs were observed in the African and Eastern Mediterranean Regions, with the latter Region having the lowest availability (Figure 1).

The AST turnaround time for first- and second-line drugs stratified by WHO Region can be seen in Figure 2. Aside from the Eastern Mediterranean Region, samples are sent further for second-line drugs than first-line drugs across all Regions (Figure 2). The Western Pacific Region was observed to have the most severe delays, with 60% and 88% of respondents reporting turnaround times greater than 21 days for first- and second-line AST results, respectively (Figure 2). The distance first- and second-line AST samples were sent stratified by WHO Region can be observed in Figure 3. Apart from the Western Pacific Region, second-line AST results were sent further than first-line AST results across all Regions (Figure 3). Distance posed the greatest challenge for the African Region, with respectively 49% and 40% of respondents sending samples farther than 50 km for first- and second-line drugs (Figure 3).

In countries where AST for second-line drugs is not available, data on the underlying reason(s) were collected and stratified by WHO Region. Lack of infrastructure to transport specimens was only

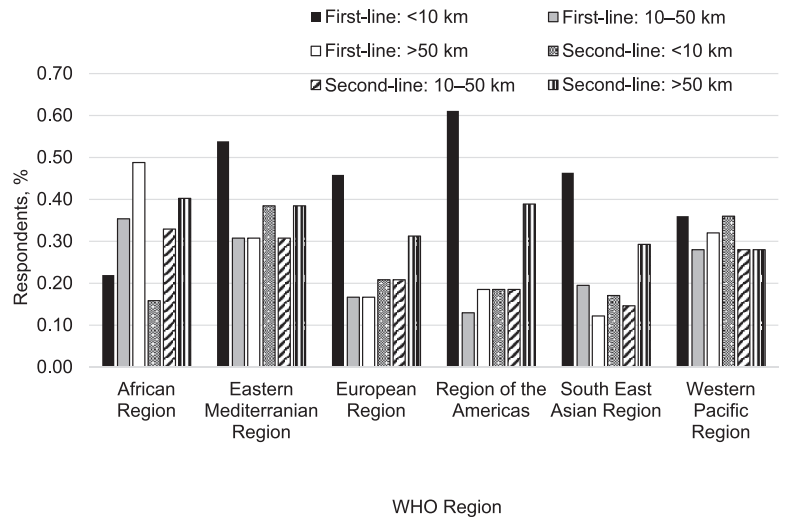

Figure 3 Proportion of responses to the question: "If you have access to phenotypic AST [in/for] your country, how far do you send your samples for culture? (Please check the distance that corresponds for first- and second-line AST)" stratified by WHO region ($n = 323$). Proportion of respondents answering "I'm not sure" omitted. AST = antibiotic susceptibility testing.

Table 2 Responses (in percentages) to the question: "For what reasons is susceptibility testing for second-line drugs not available in your country?" stratified by WHO region ($n = 323$)*

	African Region %	Eastern Mediterranean Region %	European Region %	Region of the Americas %	South East Asian Region %	Western Pacific Region %
Lack of specialised laboratory facilities	30	33	77	89	100	8
Lack of specialised laboratory workers	11	0	54	78	60	8
Cost too high	26	33	46	56	40	0
Lack of infrastructure to transport specimens	7	0	8	0	0	0

* Some respondents selected more than one reason. The proportion of respondents answering "this question does not apply to me because AST testing for second-line drugs are available" was omitted.

reported by respondents as an obstacle for the African and European Regions, with proportions of 7% and 8%, respectively (Table 2). With the exception of the Western Pacific Region, the proportion of respondents reporting high costs as a barrier was the most homogenous by Region, with proportions ranging from 26% to 56%. A lack of specialised laboratory workers was reported in high proportions in the European Region, Region of the Americas and South-East Asian Region. Overall, 100% of respondents from the South East Asian Region and 89% of respondents from the Region of the Americas noted a lack of specialised laboratory facilities as an obstacle. In the remaining Regions, this obstacle was reported by 8% to 77% of respondents.

DISCUSSION

Our previous survey documented that BDQ and DLM were becoming widely available across all six WHO Regions.[9] Our current survey reveals disparities in the capacity and availability of AST for second-line agents. Across all regions, AST capacity for FQ and SLI was available for the vast majority of respondents. A dramatic drop-off in AST availability was observed for all other second-line drugs investigated. These findings are particularly troublesome in light of WHO's recommendation to expand oral RR-/MDR-TB treatment options with regimens including not only BDQ anf DLM, but also LZD and CFZ.[7] Moreover, 43% of respondents reported the lack of availability of AST for either LZD or BDQ, which suggests that they did not have the information necessary for identifying extensively drug-resistant TB (XDR-TB) according to the new WHO definition of XDR-TB (RR-TB that is resistant to any FQ and at least one other Group A drug, e.g., BDQ or LZD).[10] Our results confirm the findings of a recent survey of AST capacity for the new agents carried out in Europe and extend these to the other WHO regions.[11]

Pervasive barriers to AST were observed in the majority of the WHO Regions. The most common barrier was a lack of specialised laboratory facilities to process AST samples. The lack of appropriate facilities was compounded by a shortage of specialised laboratory workers—a combination which leads many communities to outsource their samples. The *Step Up for TB Report 2020*, which examined 37 high-burden countries, found similar obstacles.[12]

Moreover, even among Regions with reported AST capacity, the travel distance and turnaround time for AST samples poses additional challenges. Delays in AST results were substantially greater for second-line drugs than for line-line drugs. Addressing these obstacles will require the development of additional local laboratories and personnel.[12] In addition, delays in setting critical concentrations and challenges in developing molecular resistance testing may further delay expansion of capacity for AST.[13,14]

In 2019, the Southeast Asia and Western Pacific Regions accounted for over half of the estimated global burden of MDR-TB (37% and 22%, respectively), while the African (17%), European (15%), Eastern Mediterranean (8%) and Americas (2%) made up the remainder.[1] Thus, the limitations in access to AST in the Southeast Asia and Western Pacific Regions are particularly troubling.

It should be noted that, because the data were categorised only by respondent status and region rather than by country (because most countries had too few respondents), potential bias may have been introduced in the analyses. Moreover, we did not probe into details such as the critical concentrations being tested, which might make even the capacity identified less useful. Nonetheless, as the incidence of RR-TB continues to increase, this will create substantial demand for new and repurposed drugs. The sizeable gaps in AST for these drugs are an issue that urgently needs to be addressed. Resistance to the new agents can occur even without antibiotic pressure, and such pressure is certain to increase.[15,16] Without a rapid, collaborative effort to expand global access to AST, we are almost certain to face extensive additional TB drug resistance in the coming years.

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report, 2020. Geneva, Switzerland: WHO, 2020.

2 Cegielski JP, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. Clin Infect Dis 2016; 62(4): 418–430.
3 Polsfuss S, et al. Emergence of low-level delamanid and bedaquiline resistance during extremely drug-resistant tuberculosis treatment. Clin Infect Dis 2019; 69(7): 1229–1231.
4 Bloemberg GV, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis [Letter]. N Engl J Med 2015; 373: 1986–1988.
5 Hoffmann H, et al. Delamanid and bedaquiline resistance in *Mycobacterium tuberculosis* ancestral Beijing genotype causing extensively drug-resistant tuberculosis in a Tibetan refugee. Am J Respir Crit Care Med 2016; 193(3): 337–340.
6 Kendall EA, et al. What will it really take to eliminate drug-resistant tuberculosis? Int J Tuberc Lung Dis 2019; 23(5): 535–546.
7 World Health Organization. WHO consolidated guidelines on tuberculosis, Module 4: Treatment: drug-resistant tuberculosis treatment. Geneva, Switzerland: WHO, 2020.
8 Lee BM, et al. Predicting nitroimidazole antibiotic resistance mutations in *Mycobacterium tuberculosis* with protein engineering. PLoS Pathog 2020; 16: e1008287.
9 Heng M, et al. Progress in the roll-out of multidrug-resistant tuberculosis (MDR-TB) treatments. Int J Tuberc Lung Dis 2020; 24(5): 535–536.
10 World Health Organization. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27–29 October 2020. Geneva, Switzerland: WHO, 2021.
11 Farooq HZ, et al. Limited capability for testing *Mycobacterium tuberculosis* for susceptibility to new drugs. Emerg Infect Dis 2021; 27: 985–987.
12 Médecins Sans Frontières, Stop TB Partnership. Step up for TB report 2020. Geneva, Switzerland: MSF International, 2020.
13 Köser CU, Maurer FP, Kranzer K. 'Those who cannot remember the past are condemned to repeat it': drug susceptibility testing for bedaquiline and delamanid. Int J Infect Dis 2019; 80S: S32–S35.
14 Mohamed S, et al. Targeted next-generation sequencing: a Swiss army knife for mycobacterial diagnostics? Eur Respir J 2021; 57: 2004077.
15 Battaglia S, et al. Characterization of genomic variants associated with resistance to bedaquiline and delamanid in naive *Mycobacterium tuberculosis* clinical strains. J Clin Microbiol 2020; 58: e01304-20.
16 Beckert P, et al. MDR M. tuberculosis outbreak clone in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era. Genome Med 2020; 12: 104.

RÉSUMÉ

CONTEXTE : Le développement continu de nouveaux agents antituberculeux s'accompagne d'une demande en schémas thérapeutiques allant de pair avec ces nouveaux agents, afin de prévenir le développement de résistances. Afin de satisfaire efficacement cette demande, il convient de connaître la sensibilité du pathogène aux diverses options thérapeutiques. L'accès aux tests de sensibilité aux antibiotiques (AST) est donc primordial dans le cadre du traitement global de la TB.

MÉTHODES : Une enquête qualitative et quantitative, en 12 questions, a été réalisée pour mesurer la capacité globale et l'accès aux AST. L'enquête a été distribuée aux membres du Global Laboratory Initiative, du Global Drug-resistant TB Initiative, ainsi qu'à la section TB de l'Union internationale contre la tuberculose et les maladies respiratoires, afin d'obtenir des réponses de la part des parties prenantes pertinentes.

RÉSULTATS : Au total, 323 questionnaires complets ont été recueillis, représentant 84 pays et toutes les Régions OMS. La capacité des AST pour les fluoroquinolones et les agents injectables de deuxième intention était élevée dans toutes les Régions OMS. La capacité des AST pour les nouveaux médicaments et les médicaments repositionnés était élevée dans la Région européenne, la Région des Amériques et la Région du Pacifique occidental, mais assez limitée dans la Région africaine et la Région de la Méditerranée orientale. Le temps de traitement de l'AST pour les agents de deuxième intention était plus long que pour les agents de première intention, car les échantillons devaient être envoyés plus loin à des fins d'analyse. Les obstacles fréquents à la réalisation de l'AST pour les agents de deuxième intention étaient le manque d'infrastructures dédiées au transport des échantillons, des coûts élevés et le manque de techniciens de laboratoire spécialisés et de laboratoires spécialisés.

CONCLUSION : Sans élargissement de l'accès global aux AST, la disponibilité croissante de nouvelles options thérapeutiques sera probablement menacée par l'augmentation associée des résistances. Il est urgent d'améliorer la capacité et l'accès aux AST, parallèlement aux options thérapeutiques.