ISSN 1806-3713

JBP
Jornal Brasileiro de **Pneumologia**
www.jbp.org.br

Volume 44, Number 2
March | April
2018

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ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.44, number 2, p. 71-172 March/April 2018

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Expediente

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Office: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218. Website: www.sbpt.org.br.
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ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jpneumo@jornaldepneumologia.com.br
Circulation: 4.000 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

SUPPORT:
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ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.44, number 2, p. 71-172 March/April 2018

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ISSN 1806-3713

Jornal Brasileiro de Pneumologia

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J Bras Pneumol. 2018;44(2):71-72
http://dx.doi.org/10.1590/S1806-37562018000020001

EDITORIAL

Tuberculosis series

Denise Rossato Silva[1,a], Fernanda Carvalho de Queiroz Mello[2,b], Afrânio Kritski[3,c], Margareth Dalcolmo[4,d], Alimuddin Zumla[5,e], Giovanni Battista Migliori[6,f]

Tuberculosis is the leading cause of death from a single infectious agent, ranking above HIV/AIDS. An estimated 10.4 million people fell ill with tuberculosis in 2016, 6.3 million new cases of tuberculosis having been reported. In that same year, there were an estimated 1.3 million tuberculosis deaths among non-HIV-infected individuals and an estimated 374,000 tuberculosis deaths among HIV-infected individuals. The World Health Organization (WHO) End TB Strategy established targets for the 2016-2035 period, including a 90% reduction in tuberculosis-related deaths and an 80% reduction in tuberculosis incidence (new cases per year) by 2030. Globally, the tuberculosis incidence and mortality rates are falling; however, the disease continues to be an important public health issue.[1] Therefore, for the celebration of the World TB Day on March 24th, this issue of the JBP features six articles focusing on tuberculosis, including three editorials and three review articles. This tuberculosis series has the objective of highlighting advances in our understanding of many topics related to tuberculosis.

In 2017, the Brazilian National Ministry of Health issued a document outlining a plan for the elimination of tuberculosis—the *Plano Nacional pelo Fim da Tuberculose como Problema de Saúde Pública* (Brazilian National Plan to End Tuberculosis as a Public Health Problem)—which was designed with a view toward achieving the goal of reducing, by 2035, the incidence of tuberculosis to < 10 cases/100,000 population and tuberculosis-related mortality to < 1 death/100,000 population.[2] Appropriately, the first editorial in this series is an overview of efforts to eliminate tuberculosis in Latin America. Strategies and approaches have been developed to implement all the three pillars of the WHO End TB Strategy, and the initial results are encouraging.[3-5]

It is well known that the third pillar of the WHO End TB Strategy focuses on intensified research and innovation.[1] The *Rede Brasileira de Pesquisas em Tuberculose* (REDE-TB, Brazilian Tuberculosis Research Network) is a private, nonprofit nongovernmental organization concerned not only with assisting in the development of new drugs, new vaccines, new diagnostic tests, and new strategies to control tuberculosis but also with the validation of these technological innovations, prior to their commercialization in the country or incorporation into the Brazilian National Tuberculosis Program. The second editorial provides a general review of the role of the REDE-TB in implementing the WHO End TB Strategy.[6]

The third editorial in this tuberculosis series reports on recently published literature reviews related to the diagnosis and treatment of tuberculosis.[7] In a review article, the tuberculosis series will also address some of the risk factors associated with tuberculosis, including diabetes, smoking, alcohol use, and illicit drug use. Those conditions are associated with tuberculosis infection and the progression to active tuberculosis, as well as contributing to poor tuberculosis treatment results. In addition, tuberculosis can lead to complications in disease course and management of some diseases, like diabetes. It is therefore important to identify these comorbidities in tuberculosis patients in order to ensure better management of both conditions.[8-13]

Another review article will cover tuberculosis in children. Pediatric tuberculosis requires special attention, especially because it represents recent transmission of *Mycobacterium tuberculosis* and the failure of disease control in the community. Investigation of children suspected of having tuberculosis is difficult, and there is a lack of appropriate diagnostic tools. The treatment of tuberculosis in children is also challenging.[14]

The final article in this tuberculosis series is a review on new and repurposed drugs to treat multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Drug-resistant tuberculosis is a growing global health threat. In 2016, there were 600,000 new cases of infection with rifampin-resistant strains, of which 490,000 were cases of multidrug-resistant tuberculosis.[1] The review summarizes what has been achieved to date, as far as new and repurposed drugs are concerned, with a special focus on delamanid, bedaquiline, pretomanid, clofazimine, carbapenems, and linezolid.[15-22]

Therefore, we believe that this tuberculosis series, dedicated to the celebration of the World TB Day, offers a valuable overview of the various aspects of tuberculosis control. We hope that this series will give rise to new ideas for research.

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ACKNOWLEDGMENTS

This paper is part of the European Respiratory Society/Latin-American Thoracic Association and European Respiratory Society/Brazilian Thoracic Association collaborative projects.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Feb 16]. Global tuberculosis report 2017. [Adobe Acrobat document, 147p.]. Available from: http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf
2. Brasil. Ministério da Saúde [homepage on the Internet]. Brasília: o Ministério; [cited 2017 Feb 16]. Brasil livre da tuberculose. Plano nacional pelo fim da tuberculose como problema de saúde pública. 1st ed; 2017 [Adobe Acrobat document, 40p.]. 2017. Available from: http://portalarquivos.saude.gov.br/images/pdf/2017/fevereiro/24/Plano-Nacional-Tuberculose.pdf
3. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015;45(4):928-52. https://doi.org/10.1183/09031936.00214014
4. Rendon A, Fuentes Z, Torres-Duque CA, Granado MD, Victoria J, Duarte R, et al. Roadmap for tuberculosis elimination in Latin American and Caribbean countries: a strategic alliance. Eur Respir J. 2016;48(5):1282-1287. https://doi.org/10.1183/13993003.01549-2016
5. Duarte R, Silva DR, Rendon A, Alves TG, Rahabi MF, Centis R, et al. Eliminating tuberculosis in Latin America: making it the point. J Bras Pneumol. 2018;44(2):73-76.
6. Kritski A, Dalcomo MP, Mello FCQ, Carvalho ACC, Rossato D, Oliveira MM, et al. The role of the Brazilian Tuberculosis Research Network in national and international efforts to eliminate tuberculosis. J Bras Pneumol. 2018;44(2):77-81.
7. Mello FCQ, Silva DR, Dalcolmo MP. Tuberculosis: where are we? J Bras Pneumol. 2018;44(2):82.
8. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J. 2017;50(1). pii: 1700216. https://doi.org/10.1183/13993003.00216-2017
9. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is Associated with Severe Adverse Events in Multidrug-Resistant Tuberculosis. Arch Bronconeumol. 2017;53(5):245-250. https://doi.org/10.1016/j.arbr.2016.10.003
10. Muñoz-Torrico M, Caminero Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data. Rev Port Pneumol (2006). 2017;23(1):27-30.
11. Altet N, Latorre I, Jiménez-Fuentes MÁ, Maldonado J, Molina I, González-Díaz Y, et al. Assessment of the influence of direct tobacco smoke on infection and active TB management. PLoS One. 2017;12(8):e0182998. https://doi.org/10.1371/journal.pone.0182998
12. Slama K, Chiang CY, Enarson DA, Hassmiller K, Fanning A, Gupta P, Ray C. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. Int J Tuberc Lung Dis. 2007;11(10):1049-61.
13. Silva DR, Muñoz-Torrico M, Duarte R, Galvão T, Bonini EH, Arbex FF, et al. Risk factors for tuberculosis: diabetes, smoking, alcohol, and the use of other drugs. J Bras Pneumol. 2018;44(2):145-152.
14. Carvalho ACC, Cardoso CAA, Martire T, Migliori GB, Sant'Anna CC. Epidemiological aspects, clinical aspects, and prevention of pediatric tuberculosis from the perspective of the End TB strategy. J Bras Pneumol. 2018;44(2):134-144 .
15. Tiberi S, Sotgiu G, D'Ambrosio L, Centis R, Abdo Arbex M, Alarcon Arrascue E, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(6):1758-66. https://doi.org/10.1183/13993003.00214-2016
16. Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(4):1235-43. https://doi.org/10.1183/13993003.02146-2015
17. Tiberi S, D'Ambrosio L, De Lorenzo S, Viggiani P, Centis R, Sotgiu G, et al. Ertapenem in the treatment of multidrug-resistant tuberculosis: first clinical experience. Eur Respir J. 2016;47(1):333-6. https://doi.org/10.1183/13993003.01278-2015
18. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J. 2017;49(5). pii: 1700387. https://doi.org/10.1183/13993003.00387-2017
19. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017;49(3). pii: 1602445. https://doi.org/10.1183/13993003.02445-2016
20. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Respir J. 2016;48(3):938-43. https://doi.org/10.1183/13993003.00705-2016
21. Tiberi S, Sotgiu G, D'Ambrosio L, Centis R, Arbex MA, Alarcon Arrascue E, et al. Effectiveness and Safety of Imipenem-Clavulanate Added to an Optimized Background Regimen (OBR) Versus OBR Control Regimens in the Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis. Clin Infect Dis. 2016;62(9):1188-90. https://doi.org/10.1093/cid/ciw088
22. Silva DR, Dalcomo M, Tiberi S, Arbex MA, Munoz-Torrico MM, Duarte R, et al. New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis. J Bras Pneumol. 2018;44(2):153-160.

J Bras Pneumol. 2018;44(2):73-76
http://dx.doi.org/10.1590/S1806-37562017000000449

EDITORIAL

Eliminating tuberculosis in Latin America: making it the point

Raquel Duarte[1,2,3,a], Denise Rossato Silva[4,b], Adrian Rendon[5,c], Tatiana Galvão Alves[6,d], Marcelo Fouad Rabahi[7,e], Rosella Centis[8,f], Afrânio Kritski[9,g], Giovanni Battista Migliori[8,h]

In 2015, the World Health Organization (WHO) launched the End TB strategy, which has three pillars—integrated, patient-centered care and prevention; bold policies and supportive systems; and intensified research and innovation—and has the inbuilt concept of the elimination of tuberculosis.[1-4] The elimination of tuberculosis has been defined as < 1 case per million population, pre-elimination having been defined as < 10 cases per million. Since then, the three pillars have been officially adopted by a number of countries[5]: in 2015, by Brazil, Ethiopia, the Russian Federation, South Africa, and Vietnam; and in 2016, by India, Indonesia, Swaziland, and Thailand.

Following a joint WHO/European Respiratory Society (ERS) consultation with countries with a low incidence of tuberculosis (< 10 cases per 100,000 population), held in Rome in 2014, the WHO launched its *Framework Towards Tuberculosis Elimination In Low-Incidence Countries*.[1] The document identified eight major areas to be tackled in order to eliminate tuberculosis in such countries.[1]

In epidemiological terms, tuberculosis control strategies focus on the early identification and effective treatment of cases of infectious tuberculosis (to break the chain of transmission and reduce the incidence); tuberculosis elimination is an additional strategy which has at its core the identification of latently infected individuals and their treatment (to sterilize the "reservoir" of infected persons and ensure future generations of infection-free individuals),[1,6,7] investing today to prevent tuberculosis cases tomorrow.[1,6,7] There is evidence that, when applied consistently, the tuberculosis elimination strategy has been effective. For example, it has been reported to have reduced the incidence of tuberculosis by up to 17% per year in Inuit populations.[8]

An initial question to be answered is whether there have been any reports of experiences with the tuberculosis elimination strategy in high-burden countries. Recent studies conducted in the countries of Cyprus and Oman have shown that the appropriate implementation of the basic elements of the End TB strategy can drive the epidemiology of tuberculosis toward the pre-elimination threshold.[9,10] A second question is to what extent the tuberculosis elimination strategy can be applied in Latin America and the Caribbean, where there are a number of low-incidence countries—including the Bahamas, Chile, Costa Rica, Cuba, the Dominican Republic, Jamaica, and Puerto Rico, as well as Trinidad and Tobago—and others that are approaching that threshold—including Brazil, Uruguay, and Colombia—those in the latter category also having been invited to the WHO/ERS technical consultation in Rome in 2014.

In parallel with the publication of the WHO framework,[1] the Pan American Health Organization (PAHO) created two important documents. In 2015, the organization issued a document including all three pillars of the End TB strategy, the *PAHO Strategic Plan*,[11] which followed its *Action Plan for the Prevention and Control of Tuberculosis*. Launched in 2013, the PAHO action plan focused on tuberculosis control only, using epidemiological indicators (i.e., increased numbers of patients with bacteriologically confirmed tuberculosis that was treated successfully), promoting cross-cutting approaches in health, and covering comorbidities (e.g., HIV infection and mental health disorders).[12] Those documents were followed by the *Roadmap for Tuberculosis Elimination in Latin America and the Caribbean*, created jointly by the ERS and the *Asociación Latinoamericana del Tórax* (ALAT, Latin-American Thoracic Society), to guide national tuberculosis programs toward implementation of the PAHO strategies. It is clear that there is considerable heterogeneity in Latin America in terms of epidemiological actions and programs, the strategic goals mentioned above therefore being met at different paces.[3,4] One example is provided by the epidemiology of tuberculosis in Mexico (Figure 1), where the reported incidence of the disease is below the low-incidence threshold in one third of the states, < 20 per 100,000 population in another third, and higher than that in the remaining third.

In 2017, the Brazilian National Ministry of Health issued a document aimed at the elimination of tuberculosis, the *National Plan to End Tuberculosis as a Public Health Problem*. The plan was designed with the goal of reducing tuberculosis incidence (to < 10 cases/100,000 population)

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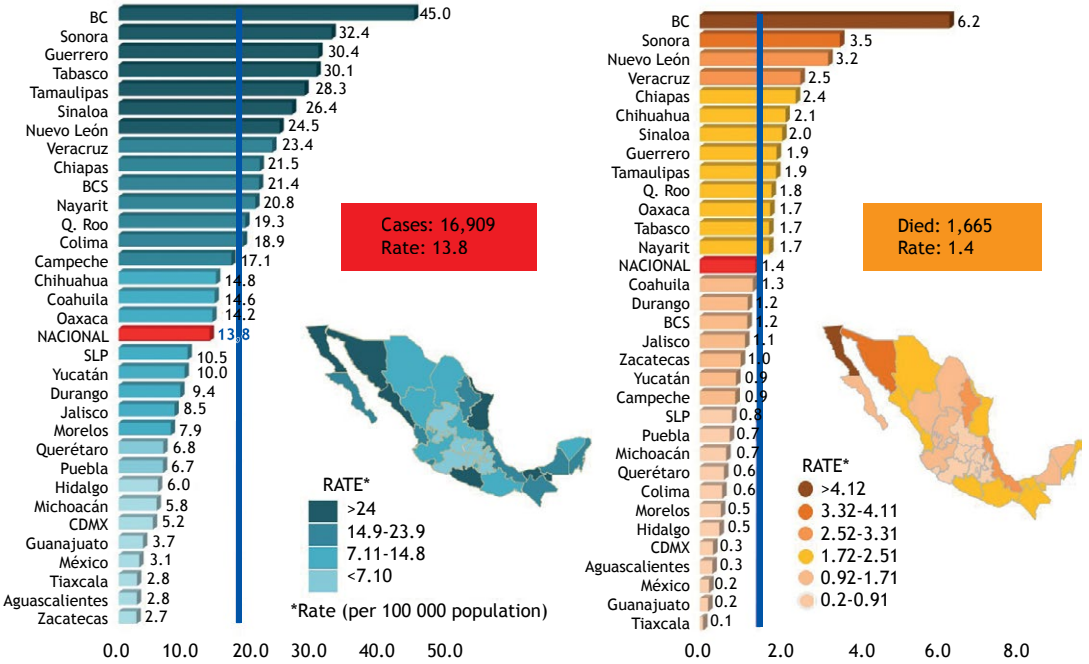

Figure 1. Incidence of reported cases of pulmonary tuberculosis and associated mortality in Mexico (per 100,000 population in 2016 and 2015, respectively), by state. Obtained from the Mexican Ministry of Health.

and mortality (to < 1 death/100,000 population) by 2035, defining the approaches to implementing each of the three pillars of the WHO End TB strategy.[13]

In Latin America, visible progress has been made toward meeting the goals set for tuberculosis incidence, prevalence, and mortality.[3,4] Among the remarkable successes achieved are increased detection rates, improved laboratory quality assurance, better systematic management of cases of multidrug-resistant tuberculosis (MDR-TB), and the promotion of community involvement, as well as coordination of technical and financial partners.[3,4]

Although there has been a decrease in the reported number of new cases in Brazil, that decrease has been modest (only 1.5% per year) and more needs to be done to improve treatment outcomes, reduce losses to follow-up, and prevent the emergence of MDR-TB.[14] Clearly, there is a need for political commitment (with adequate funding and legal framework), true patient-centered care, and attention to comorbidities, as well as the control of risk factors such as diabetes, HIV infection, illicit drug use, smoking, and mental disorders.[15] Special attention should also be given to vulnerable groups (e.g., migrants from rural areas to large cities, south-south migrants (i.e., migrants between developing countries), people living in slums, underserved indigenous populations, homeless individuals, and prisoners).[16]

The eight core areas identified in the ERS/ALAT *Roadmap for Tuberculosis Elimination in Latin America and the Caribbean* provide a clear guide to reaching the tuberculosis elimination targets in the region:

1. identifying and supporting vulnerable populations
2. addressing migration and transborder issues
3. strengthening operational research, channeling it through agreed-upon national research plans prioritized by national tuberculosis research networks and adequately funded to tackle the intensified research/innovation pillar of the End TB strategy
4. fostering political commitment for tuberculosis care and prevention in order to implement elements of the bold policies/supportive systems pillar of the End TB strategy
5. adapting the strategy at the national and regional level while promoting global collaboration
6. enhancing active detection and treatment of latent tuberculosis infection, as well as active tuberculosis, according to the principles of tuberculosis elimination[5,17]
7. ensuring early, high-quality treatment of cases of drug-resistant tuberculosis and MDR-TB while ensuring universal drug-susceptibility testing with conventional and/or new molecular methods and availability of the necessary second-line drugs (in order to tackle, with core area 1, the actions included in the integrated, patient-centered care/prevention pillar of the End TB strategy
8. improving continuous surveillance, monitoring, and evaluating activities to assess the progress toward the planned targets and the elimination of tuberculosis

Indicators for the monitoring and evaluation of each of those components were also proposed (Table 1).[3,4]

The contribution of tuberculosis research networks, as proposed by the WHO in 2015, is key to working in accordance with regional priorities.[18] The joint ERS/ALAT/Brazilian Thoracic Society tuberculosis project and the Brazilian Tuberculosis Research Network are

Table 1. Indicators of the impact and implementation of the World Health Organization End TB strategy for Latin-American and Caribbean countries.

Impact indicators	Milestones		Targets	
	2020	2025	2030[a]	2035[b]
Reduction in number of TB deaths compared with 2015	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015	20%	50%	80%	90%
Families facing catastrophic costs due to TB	0%	0%	0%	0%
Implementation indicators	**Recommended target level**			
TB treatment coverage	≥ 90%			
TB treatment success rate	≥ 90%			
Households that experience catastrophic costs due to TB	0%			
Newly reported TB cases diagnosed using WHO recommended rapid tests	≥ 90%			
Latent TB infection treatment coverage	≥ 90%			
Contact investigation coverage	≥ 90%			
Drug susceptibility coverage for TB patients	100%			
Treatment coverage, new TB drugs	≥ 90%			
Documentation of HIV status among TB patients	≥ 90%			
Case fatality ratio	≤ 5%			
Availability of the planned budget for TB	100%			
Implementation of planned monitoring and evaluation activities	100%			

TB: tuberculosis; and WHO: World Health Organization. [a]Sustainable development goals. [b]World Health Organization End TB strategy targets.

making significant contributions by generating the evidence necessary for successful implementation of the tuberculosis elimination strategy.[19] Some of the preliminary results are quite encouraging,[20-35] showing how important it is to implement all three pillars of the WHO End TB strategy in Latin America.

REFERENCES

1. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015;45(4):928-52. https://doi.org/10.1183/09031936.00214014
2. D'Ambrosio L, Dara M, Tadolini M, Centis R, Sotgiu G, van der Werf MJ, et al. Tuberculosis elimination: theory and practice in Europe. Eur Respir J. 2014;43(5):1410-20. https://doi.org/10.1183/09031936.00198813
3. Rendon A, Fuentes Z, Torres-Duque CA, Granado MD, Victoria J, Duarte R, et al. Roadmap for tuberculosis elimination in Latin American and Caribbean countries: a strategic alliance. Eur Respir J. 2016;48(5):1282-1287. https://doi.org/10.1183/13993003.01549-2016
4. Torres-Duque CA, Fuentes Alcalá ZM, Rendón A, Migliori GB. Roadmap for Tuberculosis Elimination in Latin America and the Caribbean. Arch Bronconeumol. 2018;54(1):7-9. https://doi.org/10.1016/j.arbres.2017.07.004
5. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Nov 27]. Global tuberculosis report 2017; [about 2 screens]. Available from: http://www.who.int/tb/publications/global_report/en/
6. de Vries G, van Hest R, Bakker M, Erkens C, van den Hof S, Meijer W, et al. Policy and practice of programmatic management of latent tuberculosis infection in The Netherlands. J Clin Tuberc Other Mycobact Dis. 2017;7:40-48. https://doi.org/10.1016/j.jctube.2017.02.002
7. Veen J, Migliori GB, Raviglione MC, Rieder HL, Dara M, Falzon D, et al. Harmonization of TB control in the WHO European Region: the history of the Wolfheze Workshops. Eur Respir J. 2011;37(4):950-9. https://doi.org/10.1183/09031936.00019410
8. Grzybowski S, Styblo K, Dorken E. Tuberculosis in Eskimos. Tubercle. 1976;57(4 Suppl):S1-58. https://doi.org/10.1016/0041-3879(76)90059-3
9. Voniatis C, Migliori GB, Voniatis M, Georgiou A, D'Ambrosio L, Centis R, et al. Tuberculosis elimination: dream or reality? The case of Cyprus. Eur Respir J. 2014;44(2):543-6. https://doi.org/10.1183/09031936.00044314
10. Al Yaquobi F, Al-Abri S, Al-Abri B, Al-Abaidani I, Al-Jardani A, D'Ambrosio L, et al. TB elimination, dream or reality? The case of Oman. Eur Respir J. 2018;51(1). pii: 1702027. https://doi.org/10.1183/13993003.02027-2017
11. Pan American Health Organization [homepage on the Internet]. Washington (DC): the Organization; [cited 2017 Nov 27]. Plan of Action for the Prevention and Control of Tuberculosis. [Adobe Acrobat document, 24p.]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=31254&Itemid=270&lang=en
12. Pan American Health Organization [homepage on the Internet]. Washington (DC): the Organization; [cited 2014 Nov 20]. Strategic Plan of the Pan American Health Organization 2014-2019. [Adobe Acrobat document, 147p.]. Available from: http://www.paho.org/hq/index.php?gid=14004&option=com_docman&task=doc_view
13. Brasil. Ministério da Saúde [homepage on the Internet]. Brasília: Ministério; c2017 [cited 2017 Nov 27]. Brasil livre da tuberculose – Plano nacional pelo fim da tuberculose como problema de saúde pública. 1st edition. [Adobe Acrobat document, 40p.]. Available from: http://portalarquivos.saude.gov.br/images/pdf/2017/fevereiro/24/Plano-Nacional-Tuberculose.pdf
14. Rabahi MF, Silva Júnior JLRD, Conde MB. Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country. J Bras Pneumol. 2017;43(6):437-444. https://doi.org/10.1590/s1806-37562017000000004
15. Migliori GB, Lienhardt C, Weyer K, van der Werf MJ, Blasi F, Raviglione MC. Ensuring rational introduction and responsible use of new TB tools. Outcome of an ERS multisector consultation. Eur Respir J. 2014;44(6):1412-7. https://doi.org/10.1183/09031936.00132114
16. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Med. 2016;14:48. https://doi.org/10.1186/s12916-016-0595-5
17. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46(6):1563-76. https://doi.org/10.1183/13993003.01245-2015
18. World Health Organization [homepage on the Internet]. Geneva:

World Health Organization; c2015 [cited 2017 Nov 24]. A global action framework for TB research in support of the third pillar of WHO's end TB strategy; [about 2 screens]. Available from: http://www.who.int/tb/publications/global-framework-research/en/

19. Kritski A, Barreira D, Junqueira-Kipnis AP, Moraes MO, Campos MM, Degrave WM, et al. Brazilian Response to Global End TB Strategy: The National Tuberculosis Research Agenda. Rev Soc Bras Med Trop. 2016;49(1):135-45. https://doi.org/10.1590/0037-8682-0330-2015
20. Arbex MA, Siqueira HR, D'Ambrosio L, Migliori GB. The challenge of managing extensively drug-resistant tuberculosis at a referral hospital in the state of São Paulo, Brazil: a report of three cases. J Bras Pneumol. 2015;41(6):554-9. https://doi.org/10.1590/s1806-37562015000000299
21. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017;49(3). pii: 1602445. https://doi.org/10.1183/13993003.02445-2016
22. Silva DR, Sotgiu G, D'Ambrosio L, Pereira GR, Barbosa MS, Dias NJD, et al. Diagnostic performances of the Xpert MTB/RIF in Brazil. Resp Med. 2018;134:12-15. https://doi.org/10.1016/j.rmed.2017.11.012
23. Amicosante M, D'Ambrosio L, Munoz MA, Mello FCQ, Tebruegge M, Chegou NN, et al. Current use and acceptability of novel diagnostic tests for active tuberculosis: a worldwide survey. J Bras Pneumol. 2017 Sep-Oct;43(5):380-392. https://doi.org/10.1590/s1806-37562017000000219
24. Rendon A, Centis R, D'Ambrosio L, Migliori GB. WHO strategies for the management of drug-resistant tuberculosis. Arch Bronconeumol. 2017;53(3):95-97. https://doi.org/10.1016/j.arbres.2016.07.015
25. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is Associated with Severe Adverse Events in Multidrug-Resistant Tuberculosis. Arch Bronconeumol. 2017;53(5):245-250. https://doi.org/10.1016/j.arbr.2016.10.003
26. Muñoz-Torrico M, Caminero Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data. Rev Port Pneumol (2006). 2017;23(1):27-30.
27. Bastos ML, Cosme LM, Fregona G, Prado TN, Bertolde AI, Zandonade E, et al. Treatment outcomes of MDR-tuberculosis patients in Brazil: a retrospective cohort analysis. BMC Infect Dis. 2017;17(1):718. https://doi.org/10.1186/s12879-017-2810-1
28. Ramalho DMP, Miranda PFC, Andrade MK, Brígido T, Dalcolmo MP, Mesquita E, et al. Outcomes from patients with presumed drug resistant tuberculosis in five reference centers in Brazil. BMC Infect Dis. 2017;17(1):571. https://doi.org/10.1186/s12879-017-2669-1
29. Calderón RI, Velásquez GE, Becerra MC, Zhang Z, Contreras CC, Yataco RM, et al. Prevalence of pyrazinamide resistance and Wayne assay performance analysis in a tuberculosis cohort in Lima, Peru. Int J Tuberc Lung Dis. 2017;21(8):894-901. https://doi.org/10.5588/ijtld.16.0850
30. Evora LHRA, Seixas JM, Kritski AL. Neural network models for supporting drug and multidrug resistant tuberculosis screening diagnosis. Neurocomputing. 2017;265:116-126. https://doi.org/10.1016/j.neucom.2016.08.151
31. Sweetland AC, Kritski A, Oquendo MA, Sublette ME, Norcini Pala A, Silva LRB, et al. Addressing the tuberculosis-depression syndemic to end the tuberculosis epidemic. Int J Tuberc Lung Dis. 2017;21(8):852-861. https://doi.org/10.5588/ijtld.16.0584
32. David SG, Lovero KL, Pombo March MFB, Abreu TG, Ruffino Netto A, Kritski AL, et al. A comparison of tuberculosis diagnostic systems in a retrospective cohort of HIV-infected children in Rio de Janeiro, Brazil, Int J Infect Dis. 2017;59:150-155. https://doi.org/10.1016/j.ijid.2017.01.038
33. de Almeida IN, de Assis Figueredo LJ, Soares VM, Vater MC, Alves S, da Silva Carvalho W, et al. Evaluation of the Mean Cost and Activity Based Cost in the Diagnosis of Pulmonary Tuberculosis in the Laboratory Routine of a High-Complexity Hospital in Brazil. Front Microbiol. 2017;8:249. https://doi.org/10.3389/fmicb.2017.00249
34. Wysocki AD, Villa TC, Arakawa T, Brunello ME, Vendramini SH, Monroe AA, et al. Latent Tuberculosis Infection Diagnostic and Treatment Cascade among Contacts in Primary Health Care in a City of Sao Paulo State, Brazil: Cross-Sectional Study. PLoS One. 2016;11(6):e0155348. https://doi.org/10.1371/journal.pone.0155348
35. Langley, I, Squire SB, Dacombe R, Madan J, Lapa e Silva, JR, Galiez, R, et al. Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control. Clin Infect Dis. 2015;61 Suppl 3:S126-34. https://doi.org/10.1093/cid/civ580

J Bras Pneumol. 2018;44(2):77-81
http://dx.doi.org/10.1590/S1806-37562017000000435

EDITORIAL

The role of the Brazilian Tuberculosis Research Network in national and international efforts to eliminate tuberculosis

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GLOBAL STRATEGY TO ELIMINATE TUBERCULOSIS

In 2015, tuberculosis ranked as the leading cause of death from an infectious disease, surpassing HIV/AIDS.[1] In 2016, an estimated 10.4 million people developed tuberculosis and 1.7 million died from the disease, 5,000 people dying from it every day, including approximately 1,000 individuals with tuberculosis/HIV coinfection.[1] In the past decade, the global tuberculosis community has engaged in activities to successfully attain the Millennium Development Goal target and other international targets for halting and reversing increases in tuberculosis incidence and mortality.[1] However, despite the achievements made to date, the global incidence of tuberculosis is declining at a rate of only 1.5% per year, far from the 10% expected.[1]

In 2014, the World Health Organization (WHO) launched its End TB strategy,[2] with the stated goal of ending the global tuberculosis epidemic by lowering its incidence to fewer than 10 new patients per 100,000 population per year. The End TB strategy, aligned with the Sustainable Development Goals (SDGs), focuses on reducing the number of tuberculosis deaths by 90% and lowering the incidence of the disease by 80%, as well as ensuring that no families of tuberculosis patients are affected by catastrophic costs incurred from diagnosis and treatment, with the objective of meeting all of those goals by 2030. To that end, the End TB strategy has three pillars that leverage the strategy and are critical to ending the global tuberculosis epidemic: integrated patient-centered care and prevention; bold policies and supportive systems, with an emphasis on social protection of vulnerable populations; and intensified research and innovation. The third pillar (intensified research and innovation) promotes the need for research along a continuum that links upstream fundamental research to discovery, to new tool development, and ultimately to operational/implementation/health system research, allowing innovative strategic approaches to be adapted to country-specific needs. In 2015, the WHO Global TB Program developed a global action framework for tuberculosis research,[3] the objective of which was to foster cutting-edge tuberculosis research to contribute to the elimination of the tuberculosis epidemic, at the national and international levels. A key output at the country level is to create a national tuberculosis research network, pursuing the development of a national tuberculosis research plan that could be integrated into larger national tuberculosis control efforts. To assist countries, the WHO Global TB Program has developed a toolkit[4] for defining and incorporating national tuberculosis research plans that target country-specific needs and resources that will help eliminate the global tuberculosis burden. By 2015, national tuberculosis research plans had been established in several high- and medium-burden countries, including Brazil, Ethiopia, Indonesia, Russia, South Africa, and Vietnam, all of which agreed to serve as pathfinder countries.[5]

In January of 2017, taking into account the fact that the actions carried out at the global level were failing to meet the milestones set in the End TB strategy, given the benefits gained per dollar spent on those actions, the United Nations General Assembly announced the first-ever high-level meeting on the fight against tuberculosis, to be held in 2018.[6] In addition, the WHO and the Russian Federation decided to hold the first WHO Global Ministerial Conference on Ending TB (November 16-17, 2017) to promote action and commitments.[6] Brazil, Russia, India, China, and South Africa, collectively known as the BRICS countries, bear 49% of the worldwide burden of tuberculosis and more than 60% of the multidrug-resistant tuberculosis burden.[1,7] The BRICS national tuberculosis program managers and academic leaders established the BRICS TB Research Network in September of 2017, at a meeting held in the city of Rio de Janeiro, Brazil, where all of the BRICS countries made commitments to combating tuberculosis and to developing a tuberculosis research agenda.[8]

At the WHO Global Ministerial Conference on Ending TB, in November of 2017, the Moscow Declaration to End TB

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was approved.[9] The declaration focused on the following essential building blocks, aimed at achieving revolutionary commitments for 2018 and beyond: advancing the tuberculosis response within the SDG agenda; ensuring sufficient and sustainable financing; pursuing science, research, and innovation; and developing a multisectoral accountability framework. The participants agreed to prepare and follow up on the United Nations General Assembly High-Level Meeting on Tuberculosis in 2018.

BRAZILIAN TUBERCULOSIS RESEARCH NETWORK

The *Rede Brasileira de Pesquisas em Tuberculose* (REDE-TB, Brazilian Tuberculosis Research Network) was created by an interdisciplinary group of Brazilian researchers with the common goal of promoting interaction among government, academia, health service providers, civil society, and industry on the development and implementation of new technologies and strategies to improve tuberculosis control throughout the country.[10] At this writing, the REDE-TB had 320 members working at 65 institutions across 16 of the 27 Federal Units of Brazil (comprising 26 states and the Federal District of Brasília). When the REDE-TB was created, in 2001, it already comprised researchers from different regions of the country, who carried out investigations along a continuum that linked upstream fundamental research to discovery and new tool development, as well as to operational/implementation, epidemiology, and health system research. The innovation consisted of strategies to achieve the following objectives:

a) to identify leaders in different areas/disciplines who were willing to coordinate connecting points (coordination areas), with a view to acting on different research platforms, upon which each subject can act on and champion processes whose key mission is to control tuberculosis
b) to identify gaps and partnerships, as well as to facilitate actions at the national, state (or provincial), and municipal levels
c) to focus on the ability of researchers and organizations to promote internal innovations in parallel with the incorporation of externally produced scientific and technological knowledge
d) to promote development and innovation in health, which should result not only from the important inputs to the health system, such as drugs/medications, vaccines, diagnostic reagents, and equipment, but also from concepts and innovative practices to improve health, equity, and public health care systems

Over the last 16 years, the REDE-TB coordinators have endeavored to attain several goals and have been working closely with the National Tuberculosis Program (Brazilian Ministry of Health).

THE ROLE OF THE REDE-TB IN IMPLEMENTING THE WHO END TB STRATEGY AT THE GLOBAL LEVEL

In 2009, the WHO invited the REDE-TB to join the Global Task Force TB Research Movement.[11] In 2006, the WHO reintroduced research as a recommended global tuberculosis control tool.[12] However, research was not incorporated into tuberculosis control programs in high-burden countries. The REDE-TB has taken an active part in the ongoing debates among key stakeholders and has contributed to the development of the first WHO document related to operational research.[13] In November of 2014, after research had been established as one of the three pillars in the WHO End TB strategy, Global TB Research Task Force debates prompted the WHO to hold up the REDE-TB platform as an example of how to establish links among the National Tuberculosis Program, researchers, the public health care system, the industrial sector, and civil society, in order to prioritize and conduct studies of strategic importance at the national level.

In June of 2015, the REDE-TB participated in the development of Global Action Framework for TB Research[3] and of the toolkit[4] for defining and incorporating a national tuberculosis research plan targeting country-specific needs. In addition, because the REDE-TB and the National Tuberculosis Program (Brazilian Ministry of Health) launched the National Tuberculosis Research Agenda, Brazil was invited to serve as a pathfinder country to incorporate the third pillar of the WHO End TB strategy. In December of 2015, the REDE-TB, in collaboration with the National Tuberculosis Program (Brazilian Ministry of Health) and the Oswaldo Cruz Foundation, organized the first Brazil-China workshop on tuberculosis research, in the city of Rio de Janeiro, initiating the interaction on tuberculosis research among BRICS countries, focusing on the WHO End TB strategy. In October of 2016, the REDE-TB and National Tuberculosis Program (Brazilian Ministry of Health) entered into discussions with other BRICS countries on how to improve their collaborations to leverage the third pillar of the WHO End TB strategy. In June of 2017, the REDE-TB, the National Tuberculosis Program (Brazilian Ministry of Health) and the WHO Global TB Program held a meeting in Geneva, Switzerland, involving representatives of other national tuberculosis programs and of academia from BRICS countries,[14] in order to identify the next steps in the creation of a BRICS TB Research Network. In September of 2017, the REDE-TB, representing academia, participated in the first meeting of the BRICS TB Research Network, held in the city of Rio de Janeiro. The meeting established that network following the resolution passed in the 6th Meeting of BRICS Health Ministers, held in New Delhi, India, on December 16, 2016. At that meeting, a Term of Reference was created and the following objectives were categorized as priorities: identifying strategies to accelerate clinical and implementation research; promoting multisectoral collaboration to drive research in the context of the SDGs; and promoting efforts and opportunities for mobilizing funding for tuberculosis research at the international level.[15] In November of 2017, the REDE-TB participated in the second meeting of the BRICS TB Research Network, held in

Moscow, Russia. At that meeting, the following topics were addressed: key representation in government, academia, the industrial sector, and civil society, to assist in the implementation of the BRICS TB Research Network; the most promising means of optimizing the interaction among the BRICS countries; and existing technologies, vaccine production capabilities, drugs, diagnostic tests, and innovative activities in health management among the BRICS countries. Also in November of 2017, the REDE-TB participated in the first BRICS Science and Technology Meeting, focusing on antimicrobial resistance, held in Moscow. At that meeting, the REDE-TB presented the BRICS proposal to cope with drug-resistant TB within the global antimicrobial resistance agenda.

THE ROLE OF THE REDE-TB IN IMPLEMENTING THE END TB STRATEGY AT THE NATIONAL LEVEL

In 2004, the REDE-TB helped the creation of the first non-governmental organization to combat tuberculosis in Rio de Janeiro and, in November of that year, played an active role in the creation of the Brazilian Partnership against TB, linked to the STOP TB Partnership. To this day, the REDE-TB continues to be the academic representative to the Executive Committee of the Brazilian Partnership against TB.[10,16] In addition, REDE-TB researchers led more than 80% of the tuberculosis research projects conducted in Brazil in the last decade.[17]

Since 2007, under new National Tuberculosis Program (Brazilian Ministry of Health) management, a higher level of interaction in research has taken place between the REDE-TB and the Brazilian government. Representatives of the REDE-TB came to participate in the National Technical Advisory Committee of the National Tuberculosis Program (Brazilian Ministry of Health). In 2007, the REDE-TB joined the Executive Secretariat of the Global Fund to Fight AIDS, Tuberculosis, and Malaria and helped the creation of the concept of metropolitan councils to combat tuberculosis.

In 2013, in response to a request by the WHO, the Global Task Force for TB Research, the REDE-TB, the Brazilian National Tuberculosis Program, and the Department of Science and Technology (Brazilian Ministry of Health) created the first national roadmap for tuberculosis research, at a meeting held in the city of São Paulo. The most relevant areas of tuberculosis research in Brazil were identified in order to develop the National Tuberculosis Research Agenda to comply with the third pillar of the WHO End TB strategy, which was under discussion at the WHO at that time. Also in 2013, the U.S. National Institute of Allergy and Infectious Diseases (of the National Institutes of Health) requested the help of the REDE-TB in identifying clinical sites in Brazil to carry out cohorts of tuberculosis cases and their close contacts, as part of the international Regional Prospective Observational Research in Tuberculosis (RePORT) project. The aim of the RePORT project, undertaken in partnership with India, South Africa, and China, was to collect clinical and biochemical data for later use in studies related to basic and translational research. Sites in the cities of Rio de Janeiro, Manaus, and Salvador have initiated the RePORT project with joint funding from the National Institute of Allergy and Infectious Diseases and the NMH Department of Science and Technology/ Department of Science, Technology, and Strategic Resources. Subsequently, a number of multi-country projects have been launched under the auspices of the RePORT International project, which represents a consortium of regional cohorts.[18]

In late 2015, the REDE-TB, in collaboration with the MoH—National Tuberculosis Program (Brazilian Ministry of Health) and the Oswaldo Cruz Foundation, consolidated the National Tuberculosis Research Agenda, to be adopted by public policy makers and funding bodies.[19] The research priorities were developed through the use of multiple research platforms (covering the spectrum from basic science to health system research). In 2016, the REDE-TB and the National Tuberculosis Program (Brazilian Ministry of Health) carried out a national electronic survey to review the National Tuberculosis Research Agenda. Of the 73 research priorities identified in the National Tuberculosis Research Agenda, 21 were selected (3 from each of the seven research platforms).[20] In that same year, the REDE-TB presented a preliminary national tuberculosis research plan at a public hearing at the Brazilian National House of Representatives, where the creation of the BRICS TB Research Network was discussed.[21] Also in 2016, the REDE-TB submitted a preliminary national tuberculosis research plan (including a budget for the 2017-2021 period) to the National Tuberculosis Program (Brazilian Ministry of Health) and the Brazilian Ministry of Science and Technology.[22]

In 2017, a research agenda for social protection was defined at the first Workshop on Research in Social Protection for the Control of Tuberculosis, held in the city of Brasília. The REDE-TB, together with the WHO Global TB Program, the National Tuberculosis Program (Brazilian Ministry of Health), and the Faculty of Epidemiology and Population Health at London School of Hygiene and Tropical Medicine, has discussed the national research proposal to cover the following topics: identifying determinants of tuberculosis patient access to social protection in Brazil, at the structural and individual level; investigating how different models of health care delivery can increase access to social protection and treatment for tuberculosis patients and their families; and establishing a platform to link biomedical and social protection research.[23] The REDE-TB was invited to participate in the development of the Brazilian National Plan for Eliminating Tuberculosis, which focuses on a number of principles, challenges, and objectives:

a) For the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) and the Brazilian National Health Council, the priority is to provide

quality care, with little involvement in the development of domestic products (medicines, vaccines, and diagnostic tests).

b) Few professionals coming out of universities are available to work within the national health industry.

c) Leaders in academia and researchers in the health arena are averse to interacting with industry.

d) There are difficulties with the regulatory system of Brazil (e.g., the National Research Ethics Committee and the National Health Oversight Agency) in launching and carrying out national projects in collaboration with international organizations.

e) Academia and the public health care system have not prioritized quality system management, few public clinical facilities and laboratories having been certified by the Brazilian National Institute of Metrology.

f) There is a high (12-billion-dollar) annual trade deficit in the health sector, due to low international competitiveness and limited national private sector investment in biotechnology.

In June 2017, during the 15th National Exposition of Successful Experiences in the Epidemiology, Prevention, and Control of Diseases meeting, held in Brasília, the National Plan for Eliminating Tuberculosis was launched. The REDE-TB coordinators actively organized the various stages, such as public consultations and meetings, in the development of the plan proposed by the Brazilian Ministry of Health. The National Plan for Eliminating Tuberculosis is based on the three pillars of the WHO End TB strategy, and the experience of the REDE-TB was used in order to foster interaction between the third pillar and the two other pillars. The established objective of the plan is the elimination of tuberculosis as a public health problem by 2035, to be achieved in four phases, with intermediate milestones in 2020, 2025, and 2030. The plan also has the objective of extirpating catastrophic household expenditures resulting from the disease, by 2020. In addition, the reductions envisioned in the numbers of tuberculosis-related deaths are 35%, 75%, and 90% by 2020, 2025, and 2030, respectively, with corresponding reductions in the incidence of the disease of 20%, 50%, and 80%, respectively. In June of 2017, the REDE-TB was invited to represent academia at the first meeting of the Congressional Working Group of Representatives to monitor the National Plan for Eliminating Tuberculosis launched by the Brazilian Ministry of Health.[24] In July of 2017, the REDE-TB and the National Tuberculosis Program (Brazilian Ministry of Health) organized the VI National Workshop on Tuberculosis Research, in the city of Rio de Janeiro. The main aims of the workshop were to promote the creation of a National Tuberculosis Research Committee, incorporating the third pillar of the WHO End TB strategy into the National Plan for Eliminating Tuberculosis; to optimize the implementation of the National Tuberculosis Research Agenda, facilitating its execution and monitoring; and to identify strategies that encourage key actors in tuberculosis research and tuberculosis program managers to participate in the inclusion of the third pillar of the WHO End TB strategy (research) and to interact effectively with those working on the first and second pillars.[25] In July of 2017, the REDE-TB presented the National Tuberculosis Research Plan to the Brazilian National Health Council.[26] In August of the same year, the REDE-TB and the National Tuberculosis Program (Brazilian Ministry of Health) helped the creation of the National Committee for Community-Based Monitoring of Tuberculosis, in order to foster interaction between researchers and civil society. In November of that year, in response to a request from the Congressional Working Group of Representatives to monitor the National Plan for Tuberculosis Elimination, the REDE-TB suggested the following actions, considered strategic for the implementation of the National Plan for Eliminating Tuberculosis:

a) the creation of a interministerial commission on science, technology, and innovation in tuberculosis to coordinate national efforts related to scientific and technological development and innovation, as well as to analyze the clinical, epidemiological, and budgetary impact of the incorporation of new technologies into the SUS

b) the development of public policies that facilitate interaction between the industrial sector and universities/research institutes, aimed at the development of new technologies, at the national level, and their validation in the health care system, in order to avoid the importation of technologies and decrease the trade deficit in the health sector

c) the promotion, together with government agencies, supported by the Parliamentary Front Against Tuberculosis in the Americas, the national health industry, and the BRICS TB Research Network, of the allocation of specific financial resources for tuberculosis research in areas related to the three pillars of the WHO End TB strategy, at the national and international levels

d) the building of capacity for research on tuberculosis within the health care system, fostering this research in undergraduate courses and graduate courses (master's and doctoral programs)

e) the development of innovative local information systems for epidemiological surveillance, enabling the registration, follow-up, and analysis of tuberculosis patients and their contacts, including the collection of basic information, as well as data on treatment, examinations, and hospitalizations

f) the active participation of universities and research institutes in the Brazilian National Tuberculosis Control Program, in the evaluation of new health technologies incorporated into the SUS, and in monitoring the goals and process indicators proposed in the National Plan for Tuberculosis Elimination, underscoring the need to conduct operational and implementation research, through quantitative and qualitative studies, on tuberculosis/HIV coinfection, multidrug-resistant tuberculosis, tuberculosis among prisoners, and tuberculosis among homeless people, as well as tuberculosis associated with mental disorders, alcohol use, and the use of other drugs

g) the development of integrated research projects in the social protection and biomedical aspects

of tuberculosis infection, taking human values into account

FINAL REMARKS

The REDE-TB represents a novel form of collaboration, in which the synergy of its complementary aspects facilitates the transfer of knowledge among academia, the government, civil society, and the national industrial sector to the community. A model that integrates and links efforts, using multisectoral approaches, has been used by the WHO to develop the third pillar of its End TB strategy and played a key role in the creation of the BRICS TB Research Network, as well as in encouraging the Brazilian Government to include tuberculosis in the national political health agenda.

REFERENCES

1. World Health Organization. Global tuberculosis report 2017. Geneva: WHO; 2017.
2. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al., WHO's new end TB strategy. Lancet. 2015;385(9979):1799-1801. https://doi.org/10.1016/S0140-6736(15)60570-0
3. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2015 [cited 2017 Nov 24]. A global action framework for TB research in support of the third pillar of WHO's end TB strategy; [about 2 screens]. Available from: http://www.who.int/tb/publications/global-framework-research/en/
4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2015 [cited 2017 Nov 24]. A Toolkit for Developing A National TB Research Plan, in support of the third pillar of the End TB Strategy; [about 2 screens]. Available from: http://www.who.int/tb/publications/TB_research_toolkit/en/
5. World Health Organization [homepage on the Internet]. Geneva: WHO; c2016 [cited 2017 Nov 24]. Global Tuberculosis Report 2016 [about 2 screens]. Available in http://www.who.int/tb/publications/global_report/en/
6. United Nations [homepage on the Internet]. New York (NY): United Nations [cited 2017 Nov 24]. Global health and foreign policy: health employment and economic growth. [about 9 screens]. Available from: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/71/159
7. Lavrov S. BRICS: a new generation forum with a global reach. University of Toronto [article on the Internet]. 2016 Oct 20 [cited 2017 Nov 24]; BRICS Information Centre [about 3 screens]. Available from: http://www.brics.utoronto.ca/newsdesk/delhi/lavrov.html
8. Raviglione M, Uplekar M, Weil D, Kasaeva T. Tuberculosis makes it onto the international political agenda for health…finally. Lancet Glob Health. 2018;6(1):e20-e21. https://doi.org/10.1016/S2214-109X(17)30449-7
9. World Health Organization [homepage on the Internet]. Geneva: WHO; c2016 [cited 2017 Nov 24]. Moscow Declaration to End TB [about 2 screens]. Available from: http://www.who.int/tb/features_archive/Online_Consultation_MinisterialConferenceDeclaration/en/
10. Kritski A, Ruffino-Netto A, Trajman A, Villa TCS, Lapa e Silva JR, Haddad DJ, et al. Brazilian Tuberculosis Research Network - REDE-TB. An Inst Hig Med Trop. 2016;15(Suppl 1):S35-S44.
11. Lienhardt C, Espinal M, Pai M, Maher D, Raviglione MC. What research is needed to stop TB? Introducing the TB Research Movement. PLoS Med. 8(11): e1001135. https://doi.org/10.1371/journal.pmed.1001135
12. World Health Organization. STOP TB Partnership. The Global Plan to Stop TB 2006-2015. Geneva: World Health Organization; 2006.
13. World Health Organization [homepage on the Internet]. Geneva: WHO; [cited 2017 Nov 24]. Priorities in Operational Research to Improve Tuberculosis Care and Control. [Adobe Acrobat document, 133p.]. Available from: http://www.stoptb.org/assets/documents/resources/publications/technical/StopTB%20Guide.pdf
14. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Strategic Advisory Group and Technical for Tuberculosis (STAG-TB); [about 2 screens]. http://www.redetb.org/index.php/262-grupo-consultivo-estrategico-e-tecnico-para-a-tuberculose-stag-tb
15. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Establishment of the Research Network on Tuberculosis, countries belonging to the BRICS: Brazil, Russia, India, China and South Africa; [about 4 screens] Available from: http://www.redetb.org/index.php/296-estabelecimento-da-rede-de-pesquisa-em-tuberculose-dos-paises-pertencentes-ao-brics-brasil-russia-india-china-e-africa-do-sul
16. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Brazilian Partnership Against Tuberculosis elects new coordination; about 3 screens]. Available from: http://www.redetb.org/index.php/299-parceria-brasileira-contra-a-tuberculose-elege-nova-coordenacao
17. Vasconcellos AG, Morel CM. Enabling policy planning and innovation management through patent information and co-authorship network analyses: a study of tuberculosis in Brazil. PLoS One. 2012;7(10):e45569. https://doi.org/10.1371/journal.pone.0045569
18. Hamilton CD, Swaminathan S, Christopher DJ, Ellner J, Gupta A, Sterling TR, et al. RePORT International: Advancing Tuberculosis Biomarker Research Through Global Collaboration. Clin Infect Dis. 2015;61Suppl 3:S155-9. https://doi.org/10.1093/cid/civ611
19. Kritski A, Barreira D, Junqueira-Kipnis AP, Moraes MO, Campos MM, Degrave WM, et al. Brazilian Response to Global End TB Strategy : The National Tuberculosis Research Agenda. Rev Soc Bras Med Trop. 2016;49(1):135-45. https://doi.org/10.1590/0037-8682-0330-2015
20. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Linhas de Pesquisas em Tuberculose Priorizadas em 2016. [Adobe Acrobat document, 3p.]. Available from. http://www.redetb.org/attachments/article/239/Linhas%20Pesquisas%20em%20TB%20Priorizadas%20Dez%202016.pdf
21. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Public hearing debate national plan to end tuberculosis; [about 3 screens]. Available from: http://www.redetb.org/index.php/238-audiencia-publica-debate-plano-nacional-pelo-fim-da-tuberculose
22. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. National TB Research Plan—RedeTB Proposal—2016 Dec 16. [Adobe Acrobat document, 38p.]. Available from: http://www.redetb.org/attachments/article/250/National%20TB%20Research%20Plan%20-Rede%20TB%20Proposal%20-%20Dec%2016%20-%202016.pdf
23. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Research in social protection for tuberculosis control is international debate topic; [about 2 screens]. Available from: http://www.redetb.org/index.php/253-pesquisa-em-protecao-social-para-controle-da-tuberculose-e-tema-de-debate-internacional
24. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. Commission on Social Security and Family House of Representatives installs Working Group to monitor the National Plan For Tuberculosis End; [about 2 screens]. Available from: http://www.redetb.org/index.php/259-comissao-de-seguridade-social-e-familia-da-camara-dos-deputados-instala-grupo-de-trabalho-para-o-acompanhamento-do-plano-nacional-pelo-fim-da-tuberculose
25. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. VI Workshop Nacional da Rede TB. Rio de Janeiro, junho de 2017; [about 15 screens]. Available from: http://www.redetb.org/index.php/noticias/workshop-rede-tb-2017
26. REDE-TB [homepage on the Internet]. São Paulo: REDE-TB; [cited 2017 Nov 24]. CIASPP document presents strategies against Tuberculosis; [about 3 screens]. Available from: http://www.redetb.org/index.php/290-comissao-intersetorial-de-atencao-a-saude-de-pessoas-com-patologias-ciaspp-em

J Bras Pneumol. 2018;44(2):82-82
http://dx.doi.org/10.1590/S1806-37562017000000450

Tuberculosis: where are we?

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Tuberculosis is the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent, ranking above HIV/AIDS. The BRICS countries (i.e., Brazil, Russia, India, China, and South Africa) account for 53% of all tuberculosis cases in the world. In 2016, there were an estimated 1.3 million tuberculosis deaths among HIV-negative individuals and an additional 374,000 deaths among HIV-positive individuals. An estimated 10.4 million people (adults, 90%; males, 65%; and people living with HIV, 10%) fell ill with tuberculosis (i.e., were incident cases) in 2016. Drug-resistant tuberculosis is a persistent threat, a total of 490,000 cases of multidrug-resistant tuberculosis having occurred in 2016, with an additional 110,000 cases of rifampin-resistant, isoniazid-susceptible tuberculosis.[1]

The World Health Assembly, convened annually by the World Health Organization, passed a resolution approving with full support the new post-2015 Global TB Strategy with its ambitious targets. The strategy is aimed at ending the global tuberculosis epidemic, with targets to reduce tuberculosis deaths by 90% and to cut new cases by 90% between 2015 and 2035.[1]

It has been estimated that two thirds of all incident tuberculosis cases worldwide are notified to national tuberculosis control programs and reported to the World Health Organization; strengthening and expansion of the existing network of diagnostic facilities are required in order to guarantee universal access to early and accurate diagnosis of tuberculosis.[2]

An accurate diagnosis of active tuberculosis is a prerequisite for any successful tuberculosis control program: at the individual level, a patient who has tuberculosis and goes undiagnosed remains infectious to others, being at risk of dying, whereas a patient who does not have tuberculosis and is misdiagnosed as having tuberculosis is unnecessarily exposed to potentially toxic drugs, and scarce public health resources are wasted.[3] In addition, only a fraction of the estimated cases of multidrug-resistant tuberculosis have a laboratory-confirmed diagnosis. Adequate capacity to diagnose all cases of drug-resistant tuberculosis is essential to make further progress in global tuberculosis care and control.[2] Therefore, the tuberculosis control strategy should ensure provision of services for early diagnosis and proper treatment of all forms of tuberculosis affecting people of all ages.[2,4] New, safer, affordable, and more effective drugs allowing treatment regimens that are shorter in duration and easier to administer are key to improving treatment outcomes of drug-resistant tuberculosis.[5]

A search of the recent literature reveals one review focusing on tuberculosis treatment and presenting current evidence on this fundamental aspect of tuberculosis control,[6] as well as a worldwide survey of the current use and acceptability of novel diagnostic tests for active tuberculosis.[7] In addition to contributing to individual case management, such studies contribute to developing updated local guidelines and local health care policies, especially in countries with a significant burden of the disease, such as Brazil.

REFERENCES

1. World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization; 2017.
2. World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2013.
3. Drobniewski F, Nikolayevskyy V, Balabanova Y, Bang D, Papaventsis D. Diagnosis of tuberculosis and drug resistance: what can new tools bring us? Int J Tuberc Lung Dis. 2012;16(7):860-70. https://doi.org/10.5588/ijtld.12.0180
4. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):e1-e33. https://doi.org/10.1093/cid/ciw694
5. World Health Organization. Treatment of tuberculosis: guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). Geneva: World Health Organization; 2017.
6. Rabahi MF, Silva Júnior JLRD, Ferreira ACG, Tannus-Silva DGS, Conde MB. Tuberculosis treatment. J Bras Pneumol. 2017;43(6):472-486. https://doi.org/10.1590/s1806-37562016000000388
7. Amicosante M, D'Ambrosio L, Munoz M, Mello FCQ, Tebruegge M, Chegou NN, et al. Current use and acceptability of novel diagnostic tests for active tuberculosis: a worldwide survey. J Bras Pneumol. 2017;43(5):380-392. https://doi.org/10.1590/s1806-37562017000000219

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ISSN 1806-3713

J Bras Pneumol. 2018;44(2):83-83
http://dx.doi.org/10.1590/S1806-37562018000000003

Lymph node calcifications

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A 61-year-old female presented with a 5-year history of dry cough and progressive dyspnea. A chest CT revealed small nodules and dense striae in the posterior regions of the upper lung lobes, as well as extensive lymph node calcifications, several of them predominantly in the periphery of the lymph nodes, with an "eggshell" appearance, affecting multiple mediastinal, hilar, and cervical lymph nodes. (Figure 1).

DISCUSSION

Lymph node calcifications most often result from prior granulomatous infections, especially tuberculosis and histoplasmosis. Other, less common, causes are sarcoidosis, silicosis, amyloidosis, and calcifications secondary to the treatment of lymphomas (radiation therapy or chemotherapy). However, the patient in question had lymph node calcifications with characteristics that made them more specific. The calcifications involved lymph nodes of multiple chains, including some that presented eggshell calcifications.

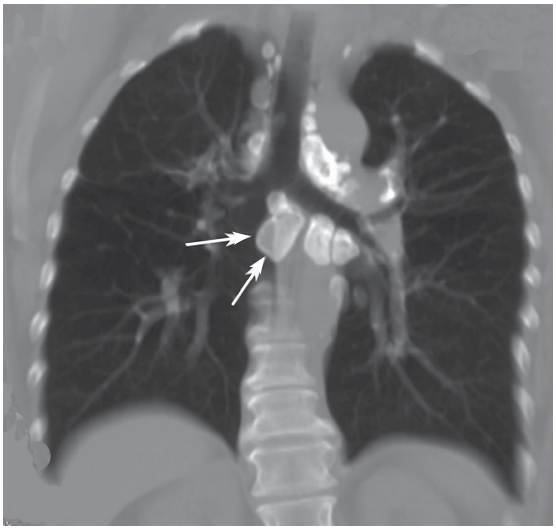

Figure 1. Chest CT with a mediastinal window and coronal reconstruction, showing calcifications affecting lymph nodes of several mediastinal and hilar chains. Note that several of them present calcifications predominantly in their periphery—"eggshell" calcifications (arrows).

When calcifications affecting multiple chains are observed, two diseases top the list of differential diagnoses: silicosis and sarcoidosis. Differentiation by imaging can be very difficult, because both diseases can present with small nodules, conglomerated masses, and areas of emphysema. It is therefore fundamental to investigate the clinical history of exposure to silica dust, given that most patients with silicosis have engaged in professional activities related to such exposure. Although our patient was a female and almost all cases of silicosis occur in male patients, she reported that she had been working at a lapidary, processing semiprecious stones, for 25 years. A diagnosis of silicosis was therefore made.

Silicosis is a chronic fibrotic lung disease caused by prolonged exposure to dust containing free silica. The diagnosis of silicosis is based on the combination of a history of exposure to silica and characteristic findings on imaging tests. Mining, quarrying, drilling (wells, tunnels, and galleries), ceramics work, marble work, sandblasting, and artisanal work with semiprecious stones are all common professional activities in Brazil.

The classic radiological findings are small nodules, typically located in the posterior and upper lung regions, which can be disseminated through the lungs. The nodules can agglomerate, forming conglomerate masses. The most common lymph node involvement occurs in the form of calcifications in multiple lymph node chains. The past and present occupation of the patient is decisive for the final diagnosis of silicosis.

RECOMMENDED READING

1. Fraser RS, Müller NL, Colman NC, Pare PD, editors. Diagnosis of Diseases of the Chest. 4th ed. Philadelphia: WB Saunders Company; 1999.

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J Bras Pneumol. 2018;44(2):84-84
http://dx.doi.org/10.1590/S1806-37562018000000088

Inclusion and exclusion criteria in research studies: definitions and why they matter

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PRACTICAL SCENARIO

A cross-sectional multicenter study evaluated self-reported adherence to inhaled therapies among patients with COPD in Latin America.[1] Inclusion and exclusion criteria for the study are shown in Chart 1. The authors found that self-reported adherence was low in 20% of the patients, intermediate in 29%, and high in 51%; and that poor adherence was associated with more exacerbations in the past year, a lower smoking history, and a lower level of education. The authors concluded that suboptimal adherence to inhaled therapies among COPD patients was common and that interventions to improve adherence are warranted.

BACKGROUND

Establishing inclusion and exclusion criteria for study participants is a standard, required practice when designing high-quality research protocols. Inclusion criteria are defined as the key features of the target population that the investigators will use to answer their research question.[2] Typical inclusion criteria include demographic, clinical, and geographic characteristics. In contrast, exclusion criteria are defined as features of the potential study participants who meet the inclusion criteria but present with additional characteristics that could interfere with the success of the study or increase their risk for an unfavorable outcome. Common exclusion criteria include characteristics of eligible individuals that make them highly likely to be lost to follow-up, miss scheduled appointments to collect data, provide inaccurate data, have comorbidities that could bias the results of the study, or increase their risk for adverse events (most relevant in studies testing interventions).

It is very important that investigators not only define the appropriate inclusion and exclusion criteria when designing a study but also evaluate how those decisions will impact the external validity of the results of the study. Common errors regarding inclusion and exclusion criteria include the following: using the same variable to define both inclusion and exclusion criteria (for example, in a study including only men, listing being a female as an exclusion criterion); selecting variables as inclusion criteria that are not related to answering the research question; and not describing key variables in the inclusion criteria that are needed to make a statement about the external validity of the study results.

IMPACT OF THE INCLUSION AND EXCLUSION CRITERIA ON THE EXTERNAL VALIDITY OF THE STUDY

In our example, the investigators described the inclusion criteria related to demographic characteristics (age ≥ 40 years of age and male or female gender), clinical characteristics (diagnosis of COPD, stable disease, outpatient, and current or former smoker); and exclusion criteria related to comorbidities that could bias the results (sleep apnea, other chronic respiratory diseases, and acute or chronic conditions that could limit the ability of the patient to participate in the study). On the basis of these inclusion and exclusion criteria, we can make a judgment regarding their impact on the external validity of the results. Making those judgments requires in-depth knowledge of the area of research, as well as of in what direction each criterion could affect the external validity of the study. As an example, the authors excluded patients with comorbidities, and it is therefore possible that the levels of nonadherence reported would not be generalizable to COPD patients with comorbidities, who most likely would show higher levels of nonadherence due to their more complex medication regimens.

Chart 1. Inclusion and exclusion criteria for a cross-sectional multicenter study of patients with COPD in Latin America.[1]

Inclusion criteria	Exclusion criteria
• Adults ≥40 years of age • Diagnosis of COPD at least for 1 year • At least one spirometry in the last year with a post-bronchodilator FEV_1/FVC < 0.70 • Current or former smokers (> 10 pack-years) • Stable disease (no recent exacerbation)	• Diagnosis of sleep apnea or any other chronic respiratory disease • Any acute or chronic condition that would limit the ability of the patient to participate in the study • Refusal to give informed consent

REFERENCES

1. Montes de Oca M, Menezes A, Wehrmeister FC, Lopez Varela MV, Casas A, Ugalde L, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: The LASSYC study. PLoS One. 2017;12(11):e0186777. https://doi.org/10.1371/journal.pone.0186777
2. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing Clinical Research. 3rd ed, Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

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ISSN 1806-3713

J Bras Pneumol. 2018;44(2):85-92
http://dx.doi.org/10.1590/S1806-37562016000000312

ORIGINAL ARTICLE

Sequential analysis as a tool for detection of amikacin ototoxicity in the treatment of multidrug-resistant tuberculosis

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Submitted: 31 October 2016.
Accepted: 18 June 2017.

Study carried out at the Ambulatório de Pesquisa Germano Gerhardt, Centro de Referência Professor Hélio Fraga, Escola Nacional de Saúde Pública Sérgio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: To investigate early detection of amikacin-induced ototoxicity in a population treated for multidrug-resistant tuberculosis (MDR-TB), by means of three different **tests:** pure-tone audiometry (PTA); high-frequency audiometry (HFA); and distortion-product otoacoustic emission (DPOAE) testing. **Methods:** This was a longitudinal prospective cohort study involving patients aged 18-69 years with a diagnosis of MDR-TB who had to receive amikacin for six months as part of their antituberculosis drug regimen for the first time. Hearing was assessed before treatment initiation and at two and six months after treatment initiation. Sequential statistics were used to analyze the results. **Results:** We included 61 patients, but the final population consisted of 10 patients (7 men and 3 women) because of sequential analysis. Comparison of the test results obtained at two and six months after treatment initiation with those obtained at baseline revealed that HFA at two months and PTA at six months detected hearing threshold shifts consistent with ototoxicity. However, DPOAE testing did not detect such shifts. **Conclusions:** The statistical method used in this study makes it possible to conclude that, over the six-month period, amikacin-associated hearing threshold shifts were detected by HFA and PTA, and that DPOAE testing was not efficient in detecting such shifts.

Keywords: Tuberculosis; Hearing loss; Aminoglycosides/toxicity.

INTRODUCTION

Worldwide, tuberculosis is the leading cause of death among infectious diseases and is associated with population clusters, poor housing and food conditions, alcohol abuse, tobacco abuse, and other comorbidities, such as HIV infection and diabetes mellitus, all of which contribute to the dissemination of the disease.[1-3]

The increase in the number of reported cases of multidrug-resistant tuberculosis (MDR-TB) is considered by the World Health Organization a worldwide threat to tuberculosis control. In 2014, the estimated global prevalence of MDR-TB was 3.3% for new cases and 20% for previously treated tuberculosis cases.[2] In Brazil, the incidence rate ranges from 11.0 to 68.4/100,000 population among the states, with the lowest and highest rates being observed in the states of Goiás and Amazonas, respectively. Rio de Janeiro has an incidence rate of 60.9/100,000 population and is the state with the highest mortality rate in the country (5.0 deaths/100,000 population). In 2013 in Brazil, a national system known as the *Sistema de Informação de Tratamentos Especiais de Tuberculose* (System of Information on Special Treatment for Tuberculosis) was implemented, and, since then, it has been possible to classify and monitor cases of drug-resistant tuberculosis. The complexity of clinical management of MDR-TB is explained by the high treatment default rates.[3]

The disappearance of symptoms at the beginning of treatment contributes to default and to the emergence of strains that are resistant to various drugs.[4,5] With the increase in the number of cases of MDR-TB, it becomes necessary to adopt second-line treatment regimens, with the use of aminoglycosides.[5]

Aminoglycosides are cost-effective and are widely used in patients with MDR-TB treated in low- and medium-income countries.[6,7] These drugs have ototoxicity as an important adverse effect,[8] and their toxicity predominantly affects one portion of the inner ear: the hair cells in the cochlea and labyrinth.[9,10] Data on the incidence of this event in humans remain controversial.[10,11] Incidence rates range from 7% to 90%,[8,11-22] and, according to Brumett et al.,[9] the discrepancy between the clinical evidence and laboratory findings of ototoxicity is due to two primary issues. The first is the fact that aminoglycosides initially affect higher frequencies (above 8 kHz), outside the range of human speech perception. The second issue is related to the different study models and different criteria established for ototoxicity.

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Financial support: None.

Adequate monitoring of patients on aminoglycosides is essential in order to detect hearing impairment affecting the human speech frequency range and thereby prevent psychosocial changes associated with difficulty in communication. The choice of a test for an appropriate hearing assessment is essential,[10,12,13,15,17,18,20] as is the choice of a data analysis method.

The objective of the present study was to investigate early detection of amikacin ototoxicity in patients treated for MDR-TB, by means of three different tests: pure-tone audiometry (PTA); high-frequency audiometry (HFA); and distortion-product otoacoustic emission (DPOAE) testing.

METHODS

This was a longitudinal prospective cohort study. We included patients aged 18-69 years with a diagnosis of pulmonary MDR-TB who were treated at the Professor Hélio Fraga Referral Center, located in the city of Rio de Janeiro, Brazil, and had to receive amikacin as part of their antituberculosis drug regimen for the first time.

We excluded patients with a history of exposure to high sound pressure levels during the study, those who were receiving other ototoxic drugs, and those who, at any time during the study, had results consistent with impairment of the outer or middle ear. Impairment was assessed by otoscopic examination of the external auditory meatus and immittance testing. The data obtained from these tests were not included in the analysis of the present study. We included patients who had a normal, type A tympanogram curve exclusively and who participated in an initial interview after giving written informed consent. Data collection was carried out between January 2015 and January 2016.

Hearing assessment consisted of the following tests: DPOAE testing; PTA; and HFA. The tests were performed before initiation of antituberculosis treatment (M_0); at two months after treatment initiation (M_2)—time at which the weekly dose of amikacin is reduced; and at six months after treatment initiation (M_6)—time of completion of amikacin therapy. The baseline assessment served as a reference for the others.

Hearing tests

All tests were performed in a calibrated sound-treated booth in accordance with the Brazilian Federal Council for Speech Therapy (ISO 8253-1 standard).

PTA and HFA

PTA and HFA were performed as described by Katz.[10] In PTA, air conduction was measured at 0.25 kHz, 0.5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz. Bone conduction was measured at 0.5 kHz to 4 kHz. Speech recognition thresholds were determined in all tests in order to confirm the hearing thresholds at speech frequencies. In HFA, responses were measured at 9 kHz, 10 kHz, 11.2 kHz, 12.5 kHz, 14 kHz, and 16 kHz. Ototoxicity was defined (on the basis of air-conduction thresholds) as a 20-dB increase in threshold at any single frequency or a 10-dB increase in threshold at two or more adjacent frequencies for PTA results, as well as a 10-dB increase in threshold at one or more frequencies between 9 kHz and 14 kHz.[23,24]

The equipment used was a Madsen Itera II A audiometer (GN Otometrics A/S, Taastrup, Denmark) with TDH-39 headphones (Telephonics Corporation, Farmingdale, NY, USA). The results were expressed as dB hearing level.

DPOAE testing

In DPOAE testing, simultaneous stimulation with two pure tones (f_1/f_2) was presented. These frequencies were expressed at a ratio of 1.22 ($f_1/f_2 = 1.22$). DPOAE responses were recorded at $2f_1/f_2$. The intensity ratios used were 65 dB/55 dB sound pressure level (SPL).[25,26] The frequencies tested were 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, and 6 kHz.[5,11] DPOAE responses with values greater than or equal to 6 dB above the noise level at each frequency were considered present. The maximum noise level permitted for analysis of responses was 6 dB SPL.[25,26] Testing was performed in the acoustic booth in order to attain the maximum reduction in recorded noise levels.

The criterion used for assessing cochlear damage by testing DPOAEs was the same as that described by Reavis et al.,[24] according to which DPOAE amplitude reductions of 4 dB or more at two or more adjacent frequencies, on the basis of results obtained at M_0, are considered an ototoxic drug effect.

The equipment used was an adult probe (ILO 292 USB II module; Otodynamics Ltd., Hatfield, UK) connected to a laptop (Hewlett-Packard Brasil, Barueri, Brazil).

Statistical analysis

Results were assessed by sequential analysis. This method meets the methodological rigor that ensures reproducibility, validity, and reliability, providing time and consumable savings. This is due to the fact that the sample size required for decision making is a random variable, in contrast with statistical tests commonly used in health care. Decisions are made immediately after each piece of information is obtained over the course of the study, that is, the H_0 hypothesis is rejected or accepted or the experiment continues with a larger number of parameters. The experiment ends with the H_0 hypothesis being accepted or rejected, thus reducing the number of observations required. In order to determine decision regions, we proposed the following hypothesis: H_0, there is no hearing loss; and H_1, there is hearing loss. With α errors set to 5% and β errors set to 10% and assuming $p_0 = 1\%$[27] and p_1 (the probability of people exposed to amikacin developing hearing loss),[28] and considering the reference range established for each test, we have

the following: for PTA, p_1 = 18%[12]; b) for HFA, p_1 = 67%[13]; and c) for DPOAE testing, p_1 = 78%.[24] For each calculation, a plot was constructed with H_0 rejection and acceptance lines, with the y axis representing "*s*" and the x axis representing "*n* – *s*". On the basis of these parameters, decision lines were calculated using the following formulas:

$$R = \frac{\log \frac{1-\beta}{\alpha}}{\log \frac{p_1}{p_0}} + (n-s) \times \frac{\log \frac{1-p_0}{1-p_1}}{\log \frac{p_1}{p_0}}$$

$$A = \frac{\log \frac{\beta}{1-\alpha}}{\log \frac{p_1}{p_0}} + (n-s) \times \frac{\log \frac{1-p_0}{1-p_1}}{\log \frac{p_1}{p_0}}$$

where R represents the H_0 rejection line and A represents the H_0 acceptance line.[29,30] The ears were assessed separately to check for damage to each cochlea.

The reference values used in each test were obtained from studies in which aminoglycoside-induced hearing impairment was assessed with the same test and technique, as well as with the same criteria for defining hearing loss.[24,27]

The study was approved by the Research Ethics Committee of the Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro (Protocol no. 75676/12).

RESULTS

Sixty-one patients were included on the basis of the inclusion criteria. Our final analysis population comprised 10 patients because sample size was determined using sequential analysis. This population consisted of 7 men (70%), with a mean age of 45.4 years, and 3 women (30%), with a mean age of 49.0 years. All had MDR-TB and used amikacin for six months as part of their drug regimen.

Regarding otological history, there were self-reports only of previous sensorineural hearing loss (in 1, 10%) and dizziness (in 1, 10%; Table 1).

There were no concomitant diseases (HIV, diabetes mellitus, or systemic arterial hypertension). Among habits and dependences, we found that 8 patients (80%) reported alcohol dependence, 2 (20%) reported frequent use of illicit drugs, and 7 (70%) reported smoking dependence, 2 of whom described themselves as former smokers (Table 1).

When comparing the test response values obtained at M_2 and M_6 with those obtained at M_0, we found that, on the basis of PTA, none of the patients had hearing threshold shifts consistent with ototoxicity criteria at M_2. However, at M_6, we found threshold shifts consistent with ototoxicity in 20% and 30% of the sample, respectively, in the right and left ears. On the basis of HFA, we found hearing threshold shifts in 50% and 60% of the patients, respectively, in the right and left ears at M_2, whereas, at M_6, these were found in 70% of the patients in both ears. On the basis of DPOAEs, we found impairment only in the right ear in 20% of the patients at M_2; however, no impairment was observed in the patients at M_6.

Table1. Characteristics of the study population.

	Male		Female	
	n	%	n	%
History of ototoxic drugs				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
History of tinnitus				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
History of hypoacusis				
Yes	1	14.3	0	0.0
No	6	85.7	3	100.0
History of dizziness				
Yes	0	0.0	1	33.3
No	7	100.0	2	66.7
History of exposure to noise				
Yes	2	28.6	2	66.7
No	5	71.4	1	33.3
Otologic surgery				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
HIV positive				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
Diabetes mellitus				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
Arterial hypertension				
Yes	0	0.0	0	0.0
No	7	100.0	3	100.0
Smoking				
Yes	5	71.4	2	66.7
No	2	28.6	1	33.3
Alcoholism				
Yes	7	100.0	1	33.3
No	0	0.0	2	66.7
Ilicit drug use				
Yes	2	28.6	0	0.0
No	5	71.4	3	100.0
Level of education				
Illiterate	1	14.3	1	33.3
Elementary school	3	42.9	2	66.7
High school	2	28.6	0	0.0
College	1	14.3	0	0.0

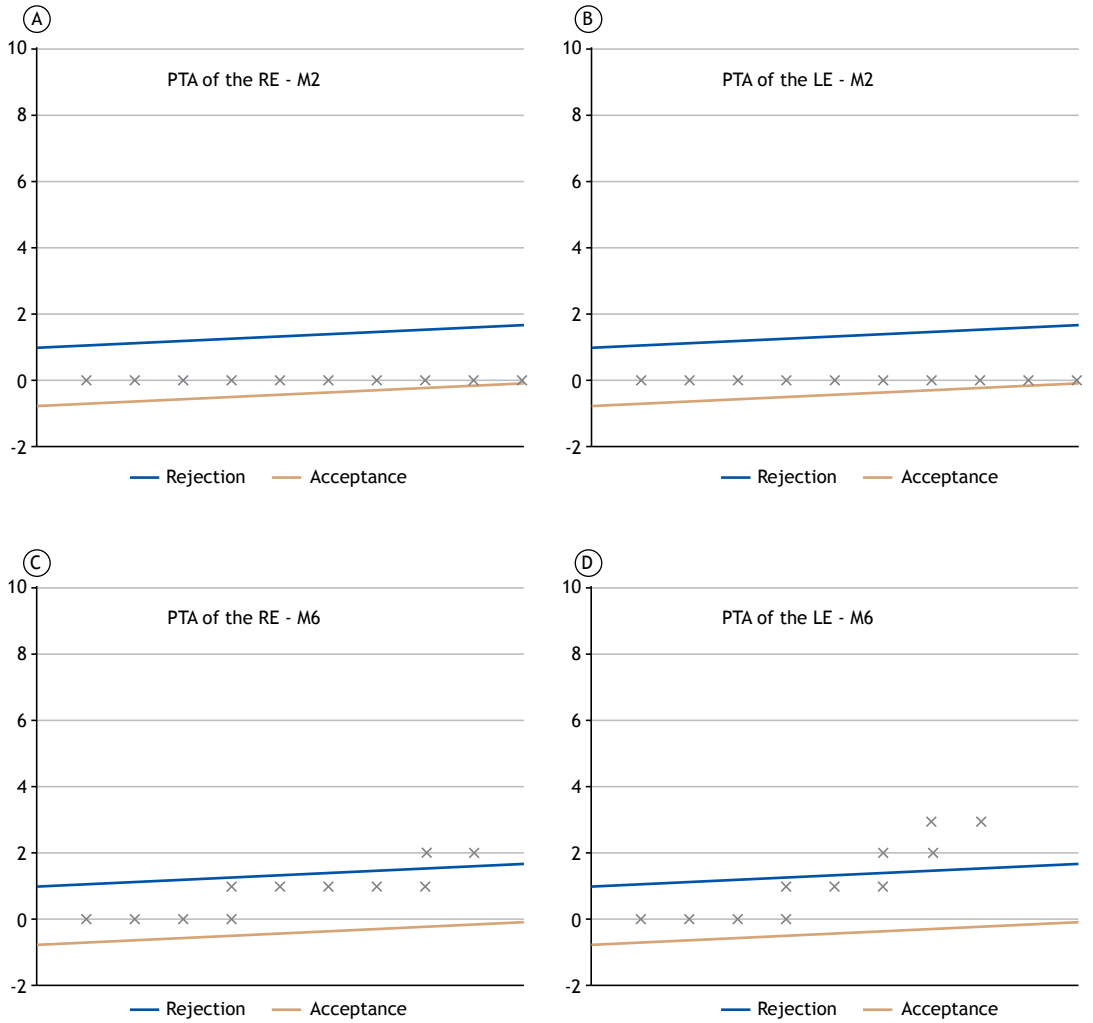

Figure 1. Sequential analysis of pure-tone audiometry (PTA) results for the right ear (RE) and the left ear (LE) at two months of treatment (M2; in A and B) and at six months of treatment (M6; in C and D).

The results were analyzed by comparing the results obtained at M_0 (baseline) with those obtained at M_2 (time at which the dose of amikacin is reduced) and those obtained at M_6 (time of completion of amikacin therapy). When considering the criteria for determining ototoxicity on the basis of PTA, we found, over the period of monitoring of auditory function, an association between amikacin use and hearing threshold shifts consistent with ototoxicity at M_6 (Figure 1). On the basis of HFA, we found an association between hearing threshold shifts and amikacin use already at M_2 (Figure 2). On the basis of DPOAE testing, H_0 was accepted already at M_2, that is, amikacin use was not associated with hearing impairment. Over the period of monitoring of auditory function, we found an increase in DPOAEs from M_2 onward (Figure 3).

DISCUSSION

Aminoglycoside-induced hearing impairment can consist of permanent hearing loss or tinnitus secondary to degeneration of cochlear sensory hair cells.[5,9] Dizziness or imbalance can occur as a result of damage to the sensory structures of the vestibular system. Damage to cochlear hair cells occurs as a result of oxidative stress, which begins in the basal portion of the cochlea.[28]

Aminoglycosides are included in MDR-TB treatment regimens and are initially used for at least six months.[31] In the present study, all patients were treated with the ototoxic drug amikacin. This drug is known to be cochleotoxic.[8,21] The incidence of hearing loss varies greatly and may depend on genetic factors, individual susceptibility, the type of assessment used, and the criteria established to define hearing loss.[10] Early detection of ototoxicity enables changes to be made to the drug regimen in order to stabilize damage to the structures of the ear and prevent further damage to them, thus reducing the chance of impaired psychosocial relationships due to impaired communication.[10]

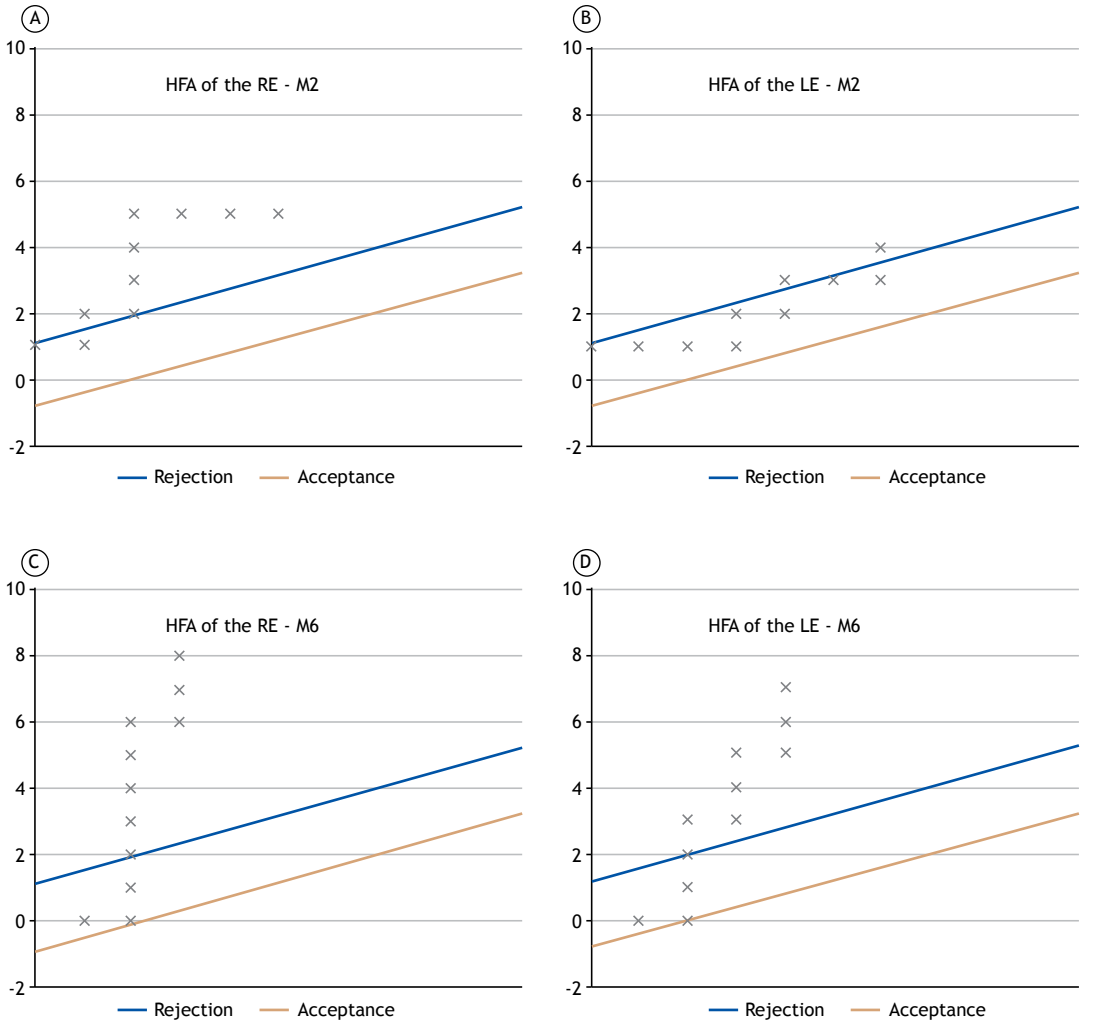

Figure 2. Sequential analysis of high-frequency audiometry (HFA) results for the right ear (RE) and the left ear (LE) at two months of treatment (M2; in A and B) and at six months of treatment (M6; in C and D).

PTA is the hearing test that is most widely used in clinical practice because it analyzes the frequency range responsible for discrimination of sounds familiar to human beings, including speech.[11] Ototoxicity was found in 20% of our sample, which is in agreement with findings in the literature.[13] PTA proved to be an appropriate test for monitoring and detecting amikacin ototoxic effect over the six-month period. H_0 was rejected at M_6 for both ears, confirming the association between amikacin use and hearing loss. However, early detection should be routine in order to prevent damage to this region.[5,13-15]

When assessing the HFA results, we found an association between amikacin use and hearing threshold shifts already at M_2, and this association persisted and was more accurately observed at M_6. The proportions found in the present study are, once again, in agreement with data reported in the literature[5,13-15] and can be explained by the frequency range assessed.[14] HFA is increasingly being included in further hearing assessment,[5,9-11,13,22,24] but it is far from being considered a routine test, even in cases of auditory function monitoring,[10] because the equipment used in HFA is costly and the usefulness of HFA is limited by the lack of reference values. The variability of responses, even in individuals without a history of otologic complaints or otologic disease, makes it difficult to establish reference values for this test.[10] Thus, in cases of auditory function monitoring by HFA, the test responses should always be compared with the responses from an assessment performed before the exposure that may carry a risk of auditory function impairment.[5,10]

DPOAE testing is described as being able to detect ototoxicity as early as possible because it assesses outer hair cells.[13,14,22,23,26] It is considered a rapid, painless, objective, and reliable test. In the present study, DPOAE testing detected hearing impairment in 20% of the population only in the right ear at M_2, that is, 2 patients showed DPOAE amplitude reductions, and this finding did not persist at M_6. DPOAE testing is recommended by the American Speech-Language-Hearing Association[23] for auditory function monitoring. However, given that DPOAE testing results vary greatly, even in normal-hearing listeners, it is suggested that,

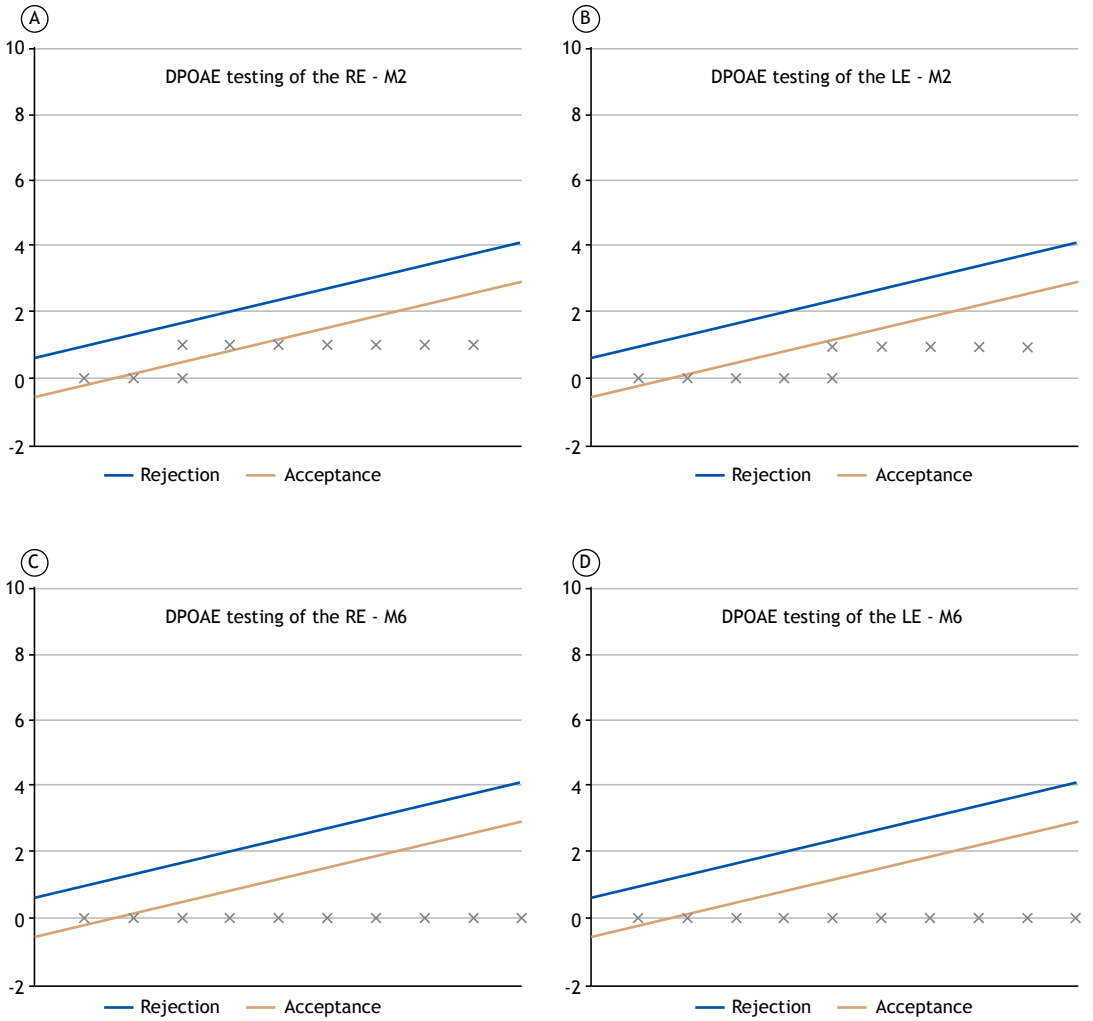

Figure 3. Sequential analysis of distortion-product otoacoustic emission (DPOAE) testing results for the right ear (RE) and the left ear (LE) at two months of treatment (M2; in A and B) and at six months of treatment (M6; in C and D).

when using DPOAE testing, test-retest comparison of responses should always be considered. The American Speech-Language-Hearing Association[23] has associated response variability with the different equipment used, the different parameters defining the presence or absence of OAE, the way probes are placed, or the statistical methods used in the different studies. Since no record has been found in the literature that can explain the increase in and persistence of DPOAEs during aminoglycoside therapy, it is possible that the variation found in the present study occurred because the probe was not properly placed during the test. In addition, the persistence of the amplitudes and even the slight increases recorded may have occurred because of the overall health status of patients with MDR-TB. In this case, the reference values used in the present study (i.e., the values obtained at M_0) could have been influenced by the overall health status of patients who were starting treatment and showed responses that would not correspond to their true hearing status; that is, the responses that served as reference were, at that point, inadequate. This would be an uncontrollable bias. In DPOAE testing, sounds are generated in the cochlea by healthy hair cells. Physiological changes may interfere with the responses,[11] and it is known that, in general, the health status of patients with MDR-TB is precarious before treatment. Another factor that should be considered when monitoring auditory function by DPOAE testing is the frequency range assessed by the test. DPOAE testing does not assess the frequency range in which aminoglycoside-induced hearing impairment begins. In animal model studies, an improvement in DPOAE responses was observed over a period of time after the use of ototoxic agents. This improvement in responses was followed by a recorded decrease in responses. The authors explain that areas adjacent to those that were damaged by the drug may at first respond in an attempt to compensate for the damage to a specific area of the cochlea.[11,28,32]

The establishment of causality is one of the central components of studies in health care. Determining how causality functions in a representative way in a given population is a challenge for researchers. Establishing the level of statistical significance of a given event has been presented as evidence of a causal relationship; likewise, the absence of a causal relationship leads to rejection of the hypotheses tested.[29] Sequential analysis allowed us to find a causal relationship between amikacin use and hearing threshold shifts in the high-frequency range, demonstrating that it is possible to use this method also in health care.

The limitations of the present study include the facts that cognitive function was not systematically assessed in the patients who attended the interviews, that the strategy of directly observed treatment was not used, and that patient serum levels of amikacin were not determined over the study period.

The statistical method used in this study makes it possible to conclude that, over the six-month period, amikacin-associated hearing threshold shifts were detected by HFA and PTA, and that DPOAE testing was not efficient in detecting such shifts.

ACKNOWLEDGMENTS

We are grateful to the patients and staff at the Professor Hélio Fraga Referral Center. We are especially grateful to Dr. Margareth Dalcolmo and nurse Suzanne Leite.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Especial Tuberculose. Boletim Epidemiológico [serial on the Internet]. 2012 Mar [cited 2016 Oct 1];43 Mar. [Adobe Acrobat document, 12p.]. Available from: http://antigo.ses.rs.gov.br/upload/1337634001_Tuberculose-Boletim%20Epidemio.pdf
2. World Health Organization [homepage on the Internet]. Geneva: WHO; c2015 [cited 2016 Oct 1]. Global Tuberculosis Report 2015, 20th ed. 2015. [Adobe Acrobat document, 204p.]. Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Detectar, tratar e curar: desafios e estratégias brasileiras frente à tuberculose. Boletim Epidemiológico [serial on the Internet]. 2015 [cited 2016 Oct 1];46(9). [Adobe Acrobat document, 19p.]. Available from: http://u.saude.gov.br/images/pdf/2015/marco/25/Boletim-tuberculose-2015.pdf
4. Vasconcelos KA, Lima MA, Frota S, Ruffino Netto A, Kritski AL. Audiometric evaluation of patients treated for pulmonary tuberculosis. J Bras Pneumol 2012;38(1):81-7. https://doi.org/10.1590/S1806-37132012000100012
5. Dalcolmo MP, Andrade MK, Picon PD. Multiresistant tuberculosis in Brazil: history and control [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:34-42. https://doi.org/10.1590/S0034-89102007000800006
6. Dalcolmo MP. Tratamento da Tuberculose Sensível e Resistente. Pulmão RJ. 2012;21(1):55-9.
7. Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol. 2011;2011:937861. https://doi.org/10.1155/2011/937861
8. Wu WJ, Sha SH, Schacht J. Recents advances in understanding aminoglycoside ototoxicity and its prevention. Audiol Neurootol. 2002;7(3):171-4. https://doi.org/10.1159/000058305
9. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989;33(6):797-800. https://doi.org/10.1128/AAC.33.6.797
10. Katz J. Avaliação dos Limiares por Via Aérea. In: Katz J, editor. Tratado de Audiologia Clínica. 4th ed. São Paulo: Manole, 1999. p.97-108.
11. Dulon D, Aran JM, Zajic G, Schacht J. Comparative uptake of gentamicin, netilmicin, and amikacin in the guinea pig cochlea and vestibule. Antimicrob Agents Chemother. 1986;30(1):96-100. https://doi.org/10.1128/AAC.30.1.96
12. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5. https://doi.org/10.1186/1472-6815-7-5
13. Fausti AS, Frey RH, Henry JA, Olson DJ, Schaffer HI. High-frequency testing techniques and instrumentation for early detection of ototoxicity. J Rehabil Res Dev. 1993;30(3):333-41.
14. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis. 2002;6(7):622-7.
15. Lima ML, Lessa F, Aguiar-Santos AM, Medeiros Z Hearing impairment in patients with tuberculosis from Northeast Brazil. Rev Inst Med Trop Sao Paulo. 2006;48(2):99-102. https://doi.org/10.1590/S0036-46652006000200008
16. Carmo LC, Silveira JA, Marone SA, D'Ottaviano FG, Zagati LL, Lins EM. Audiological study of an elderly Brazilian population. Rev Bras Otorrinolaringol. 2008;74(3):342-9. https://doi.org/10.1590/S0034-72992008000300006
17. Fernandez M, Morata TC. Auditory and extra-auditory effects of occupational exposure to noise and vibration [Article in Portuguese]. Rev Bras Otorrinolaringol. 2002;68(5):705-13. http://dx.doi.org/10.1590/S0034-72992002000500017
18. Schacht J, Talaska AE, Rybak LP. Cisplatin and aminoglycoside antibiotics: hearing loss and its prevention. Anat Rec (Hoboken). 2012;295(11):1837-50. https://doi.org/10.1002/ar.22578
19. Karlsmose B, Lauritzen T, Engberg M, Parving A. A five-year longitudinal study of hearing in a Danish rural population aged 31-50 years. British J Audiol. 2000;34(1):47-55. https://doi.org/10.3109/03005364000000117
20. Melchionda V, Wyatt H, Capocci S, Garcia Medina R, Solamalai A, Katiri S, et al. Amikacin treatment for multidrug resistant tuberculosis: how much monitoring is required? Eur Respir J. 2013;42(4):1148-50. https://doi.org/10.1183/09031936.00184312
21. Geyer LB, Menna Barreto SS, Weigert LL, Teixeira AR. High frequency hearing thresholds and product distortion otoacoustic emissions in cystic fibrosis patients. Braz J Otorhinolaryngol. 2015;81(6):589-97. https://doi.org/10.1016/j.bjorl.2015.08.011
22. Konrad-Martin D, Helt WJ, Reavis KM, Gordon JS, Coleman LL, Bratt GW, et al. Ototoxicity: Early Detection and Monitoring. ASHA Lead. 2005;10:1-14. https://doi.org/10.1044/leader.FTR1.10072005.1
23. American Speech-Language-Hearing Association (ASHA) [homepage on the Internet]. Rockville (MD): ASHA [cited 2016 Oct 1]. Guidelines. Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy; [about 32 screens]. Available from: http://www.asha.org/policy/gl1994-00003.htm
24. Reavis KM, McMillan G, Austin D, Gallun F, Fausti SA, Gordon JS, et al. Distortion-product otoacoustic emission test performance for ototoxicity monitoring. Ear Hear. 2011;32(1):61-74.
25. Gorga MP, Neely ST, Ohlrich B, Hoover B, Redner J, Peters J From laboratory to clinic: a large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss. Ear Hear. 1997;18(6):440-55. https://doi.org/10.1097/00003446-199712000-00003
26. Ribeiro L, Sousa C, Sousa A, Ferreira C, Duarte R, Faria E, et al. Evaluation of hearing in patients with multiresistant tuberculosis [Article in Portuguese]. Acta Med Port. 2015;28(1):87-91. https://

doi.org/10.20344/amp.5783

27. Instituto Brasileiro de Geografia e Estatística (IBGE). Coordenação de Trabalho e Rendimento. Pesquisa nacional de saúde 2013–Ciclos de vida: Brasil e grandes regiões. Rio de Janeiro: IBGE; 2015.
28. Cardinaal RM, de Groot JC, Huizing EH, Veldman JE, Smoorenburg GF. Histological effects of co-administration of an ACTH((4-9)) analogue, ORG 2766, on cisplatin ototoxicity in the albino guinea pig. Hear Res. 2000;144(1-2):157-67. https://doi.org/10.1016/S0378-5955(00)00061-7
29. Berquó ES, Barbosa V. Nota sobre a aplicação da análise sequencial na rotina de laboratório de uma campanha de erradicação de malária. Avaliação da capacidade diagnóstica de microscopistas. Arq Fac Hig Saude Pub Univ Sao Paulo. 1958;12(2):129-34. https://doi.org/10.11606/issn.2358-792X.v12i2p129-134
30. Berquó ES, Souza JM, Gotlieb SL. Bioestatística. São Paulo: EPU; 1981.
31. Brasil. Ministério da Saúde. Biblioteca Virtual em Saúde [homepage on the Internet]. Brasília: Ministério da Saúde [cited 2016 Oct 1]. Manual de recomendações para o controle da tuberculose no Brasil, 2011. [Adobe Acrobat document, 298p.]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil.pdf
32. Petersen L, Rogers C. Aminoglycoside-induced hearing deficits – a review of cochlear ototoxicity, S Afr Family Pract. 2015;57:2:77-82. https://doi.org/10.1080/20786190.2014.1002220

J Bras Pneumol. 2018;44(2):93-98
http://dx.doi.org/10.1590/S1806-37562016000000378

Clinical aspects in patients with pulmonary infection caused by mycobacteria of the *Mycobacterium abscessus* complex, in the Brazilian Amazon

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Submitted: 12 December 2016.
Accepted: 16 October 2017.

Study carried out at the Ambulatório de Micobactérias Não Tuberculosas, Hospital Universitário João de Barros Barreto – HUJBB – Belém (PA) and in the Laboratório de Biologia Molecular, Seção de Bacteriologia e Micologia, Instituto Evandro Chagas, Ananindeua (PA) Brasil.

ABSTRACT

Objective: To describe the clinical manifestations of patients with pulmonary infection caused by mycobacteria of the *Mycobacterium abscessus* complex (MABSC), and to compare these manifestations with those of patients infected with other nontuberculous mycobacteria (NTM). **Methods:** This was a retrospective cohort study involving 43 patients divided into two groups: the MABSC group, consisting of patients with pulmonary infection caused by MABSC (n = 17); and the NTM group, consisting of patients with pulmonary infection caused by NTM other than MABSC (n = 26). Patients were previously treated with a regimen of rifampin, isoniazid, pyrazinamide, and ethambutol before the diagnosis of NTM was confirmed by two culture-positive sputum samples. The nucleotide sequences of the *hsp65*, *16S rRNA*, and/or *rpoB* genes were analyzed to identify the mycobacteria. Data were collected on demographic, clinical, and radiological characteristics, as well as on treatment responses and outcomes. **Results:** Loss of appetite was the only clinical manifestation that was significantly more common in the MABSC group than in the NTM group (p = 0.0306). The chance of having to use a second treatment regimen was almost 12 times higher in the MABSC group than in the NTM group. Treatment success was significantly higher in the NTM group than in the MABSC group (83.2% vs. 17.6%; p < 0.0001). The chance of recurrence was approximately 37 times higher in the MABSC group than in the NTM group. **Conclusions:** In the study sample, treatment response of pulmonary disease caused by MABSC was less favorable than that of pulmonary disease caused by other NTM.

Keywords: Nontuberculous mycobacteria/classification; Nontuberculous mycobacteria/drug effects; Lung diseases.

INTRODUCTION

Nontuberculous mycobacteria (NTM) comprise a group of microorganisms that differ from *Mycobacterium tuberculosis* and *M. leprae*. There are currently more than 100 documented species of slowly or rapidly growing pathogenic or nonpathogenic NTM, many of which are environmental saprophytes and some of which are more related to opportunistic infections in immunocompromised individuals.[1] The number of cases of NTM pulmonary infection has been increasing worldwide, and the most commonly involved pathogens are *M. kansasii*, *M. abscessus*, and the members of the *M. avium complex* (MAC). The *M. abscessus* complex (MABSC) is characterized by rapidly growing mycobacteria in culture, represented by the subspecies *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii*[2]; the hallmark of this complex is the presence of genes conferring resistance to macrolides, the most widely described of these genes being the *erm* gene, except in the case of *M. abscessus* subsp. *Massiliense*, and this hinders treatment response in infected patients.[3] In cases of MABSC pulmonary infection, protocols involve the use of macrolides (clarithromycin or azithromycin), aminoglycosides (amikacin), and there are regimens that include cefoxitin, imipenem, and tigecycline.[4] Therefore, regimens can include up to two

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Financial support: None.

parenteral agents (amikacin, imipenem, tigecycline, or cefoxitin) for a long time (1 year). The profile of patients most affected by MABSC mycobacteria is not different from that of patients affected by other mycobacteria, the majority of whom are middle-aged women with structural lung changes (bronchiectasis).[5] Regarding the epidemiology of NTM in Brazil, there are regional differences in the prevalence of the species involved. In a recent survey evaluating the incidence of cases of NTM among patients misdiagnosed with pulmonary tuberculosis, it was observed that 8% of those patients were infected with NTM in the Brazilian states of Bahia, Piauí, and Pará; in the Brazilian state of São Paulo, which accounted for most cases, 20% of the patients diagnosed with tuberculosis actually were infected with NTM.[6,7] Since Brazil is a country of continental dimensions, demographic differences should be taken into account, and the lack of studies in this area in Brazil warrants further investigation for understanding the natural history of such patients in a regional context.

METHODS

This was a descriptive, analytical, retrospective cohort study using data on all patients diagnosed with NTM pulmonary infection who were followed between 2003 and 2013 at the NTM infection outpatient clinic of the *Hospital Universitário João de Barros Barreto* (HUJBB, João de Barros Barreto University Hospital), which is a referral center for the treatment of patients with multidrug-resistant tuberculosis and patients with NTM infection in the Brazilian state of Pará. The sample was selected by convenience. The study project was approved by the Research Ethics Committee of the HUJBB (CAAE: 44731115.6.3001.0017). Data were collected from patient charts and questionnaires that had been completed in monthly medical visits. Cases were reviewed starting at six months after treatment initiation, by using records from properly completed forms, including clinical evaluation data, bacteriological data (culture results), and radiological data (radiological records). The inclusion criteria were having a clinical, radiological, and biochemical diagnosis of NTM pulmonary infection—the last of the three being confirmed by two culture-positive sputum samples, in accordance with the American Thoracic Society (ATS) criteria—and having given written informed consent. We excluded cases in which there was concurrent isolation of *M. tuberculosis*. The identification of the mycobacterial species and subspecies involved, which was performed in the Molecular Biology Laboratory of the Evandro Chagas Institute, was based on the analysis of the nucleotide sequences of the *hsp65*, *16S rRNA*, and/or *rpoB* genes, as appropriate. The participants were divided into two groups: the MABSC group, consisting of 17 individuals with pulmonary infection caused by MABSC; and the NTM group, consisting of 26 individuals with pulmonary infection caused by NTM other than MABSC. The variables studied were categorized as demographic, clinical, and radiological (posteroanterior chest X-ray and/or HRCT of the chest).

Treatment responses were categorized after the use of the regimens available at the institution. The first regimen consisted of clarithromycin (500 mg p.o.; 12/12 h), ethambutol (1,200 mg; 24/24 h), and rifampin (600 mg p.o.; 24/24 h). The second regimen consisted of adding amikacin (500 mg i.m.; 3 times/week) or streptomycin (1 g i.m.; 3 times/week) to the first regimen. The third regimen consisted of adding imipenem (500 mg i.v.; 6/6 h) to the second regimen. To assess outcomes, we took into account clinical improvement, as recorded on patient charts, and culture results, which were classified as culture conversion to negative, persistence of positivity (positive cultures for at least six months after treatment initiation), and positivity after initial conversion to negative (positive cultures for two consecutive months after initial conversion to negative). Radiological improvement as seen on chest X-ray or HRCT of the chest after treatment was the criterion defining cure until 2007 (prior to the 2007 ATS protocols). Sociodemographic and clinical characteristics were expressed as means and standard deviations, as medians and interquartile ranges, or as absolute and relative frequencies, as appropriate. The proportion of cases observed in each group, according to the NTM species isolated, was assessed by the chi-square test or G-test, whereas associations among categorical variables were examined by the chi-square test (or G-test), complemented by analysis of adjusted residuals, when necessary. The magnitude of association between outcome and condition was measured by the odds ratio. Differences among means were tested with the Student's t-test. All tests were performed with BioEstat 5.48, and results with $p \leq 0.05$ were considered significant.

RESULTS

Of the 43 patients included in the study, 17 (39.5%) belonged to the MABSC group and 26 (60.5%) belonged to the NTM group. The mean age of the patients in the MABSC and NTM groups was 62.4 ± 13.7 years (range, 39-94 years) and 56.2 ± 14.6 years (range, 23-81 years), respectively, with the difference not being significant ($p = 0.1715$), and similar proportions of men (23.5% vs. 34.6%) and women (76.5% vs. 65.4%) were found in the two groups ($p = 0.6640$).

With the exception of loss of appetite, which was significantly more common in the MABSC group than in the NTM group ($p = 0.0306$), all other reported symptoms occurred in similar proportions in the groups ($p > 0.05$). The patients in the two groups had similar proportions of comorbidities at the time of diagnosis of the infection, and no significant associations were found between comorbidities and infection. There was a greater proportion of active smokers among the patients in the NTM group than among those in the MABSC group, and there was a greater proportion of

passive smokers in the MABSC group than in the NTM group ($p < 0.01$ for both; Table 1).

Table 2 shows the radiological findings at the time of diagnosis of NTM pulmonary disease, by study group. There were no statistically significant differences between the two groups regarding any of the study variables.

In the study sample, the chance of treatment nonadherence was 10 times higher in the MABSC group than in the NTM group (OR = 10.0; 95% CI: 1.2-86.9). Regarding treatment response, the proportion of patients who did not respond to the first treatment regimen was significantly greater in the MABSC group than in the NTM group ($p = 0.0007$), and, in the former group, 7 of the patients (41.2%) had to use the second treatment regimen and 4 (23.5%) had to use the third treatment regimen. In the NTM group, however, 20 of the 22 patients who completed the first treatment regimen (83.2%) experienced cure, and only 2 (9.0%) had to start the second treatment regimen (Table 3). Therefore, the chance of having to use a second treatment regimen was found to be almost 12 times higher in the MABSC group than in the NTM group (OR

Table 1. Patient distribution for comorbidities and lifestyle habits, by study group. Belém, Brazil, 2015.[a]

Variable	Group		p*
	MABSC (n = 17)	NTM (n = 26)	
Comorbidities			
Absence	3 (17.7)	6 (23.1)	0.3283
Diabetes	1 (5.9)	0 (0.0)	
COPD and/or asthma and/or GERD	2 (11.7)	4 (15.4)	
HIV infection	0 (0.0)	4 (15.4)	
Isolated bronchiectasis	6 (35.3)	7 (26.9)	
Associated bronchiectasis	5 (29.4)	5 (19.2)	
Smoking			
No	4 (23.5)	6 (23.1)	0.0017
Active	3 (17.7)	18 (69.2)†	
Passive	8 (47.1)†	2 (7.7)	
Both	2 (11.7)	0 (0.0)	

MABSC: *Mycobacterium abscessus* complex; NTM: mycobacteria other than *M. tuberculosis* and MABSC; and GERD: gastroesophageal reflux disease. [a]Values expressed as n (%). *Chi-square test or G-test, as appropriate, and analysis of adjusted residuals, when necessary. †Cell with statistical significance.

Table 2. Pretreatment HRCT findings, by study group. Belém, Brazil, 2015.[a]

Variable	Group		p*
	MABSC (n = 17)	NTM (n = 26)	
Pulmonary involvement			
Absent	1 (5.9)	0 (0.0)	
Unilateral	4 (23.5)	7 (26.9)	0.4772
Bilateral	12 (70.6)	19 (73.1)	
Cavitation			
Absent	8 (47.1)	11 (42.3)	0.7369
Single	4 (23.5)	9 (34.6)	
Multiple	5 (29.4)	6 (23.1)	
Distribution of cavitation			
Unilobar	7 (77.8)	10 (66.7)	0.2555
Bilobar	0 (0.0)	3 (20.0)	
Multilobar	2 (22.2)	2 (13.3)	
Bronchiectasis			
Absent	1 (5.9)	4 (15.4)	0.3376
Present	11 (64.7)	11 (42.3)	
Present (subsequent NTM infection)	5 (29.4)	11 (42.3)	
Radiological presentation			
Fibrocavitary	7 (41.2)	14 (53.8)	0.6163
Nodular bronchiectasis	10 (58.8)	12 (46.2)	

MABSC: *Mycobacterium abscessus* complex; and NTM: mycobacteria other than *M. tuberculosis* and MABSC. [a]Values expressed as n (%). *Chi-square test or G-test, as appropriate.

Table 3. Treatment regimens used and patient outcomes observed, by study group. Belém, Brazil, 2015.

Variable	Group[a]		p*	OR (95% CI)
	MABSC (n = 17)	NTM (n = 26)		
Regimen used[b]				
1st regimen	6 (35.3)	20 (91.0)‡		1.0
2nd regimen	7 (41.2)†	2 (9.0)	0.0007	11.70 (1.9-71.8)
3rd regimen	4 (23.5)†	0 (0.0)		-
Primary outcome[c] (after 1st regimen)				
Clinical improvement and cure	3 (17.6)	20 (83.2)†	< 0.0001	1.00
Dropout	3 (17.6)	2 (8.4)		10.00 (1.2-86.9)
Treatment failure	11 (64.8)†	2 (8.4)		36.70 (5.3-253.8)
Secondary outcome				
Clinical improvement and cure	10 (91.0)	2 (100)	0.3917	1.0
Death	1 (9.0)	0 (0.0)		-

MABSC: *Mycobacterium abscessus* complex; NTM: mycobacteria other than *M. tuberculosis* mycobacteria and MABSC; 1st regimen: rifampin, ethambutol, and clarithromycin; 2nd regimen: 1st regimen plus amikacin or streptomycin; and 3rd regimen: 2nd regimen plus imipenem. [a]Values expressed as n (%). [b]The value of n is different in the NTM group because of two deaths and two dropouts for which there was no information on primary outcome. [c]The value of n is different in the NTM group because of two deaths of unknown cause. *G-test and analysis of adjusted residuals, when necessary. †Cell with statistical significance.

= 11.70; 95% CI: 1.9-71.8). We emphasize that none of the patients in the NTM group had to use the third treatment regimen (second treatment regimen plus imipenem). Regarding primary outcomes, there was a significantly higher frequency of recurrence in the MABSC group than in the NTM group ($p < 0.0001$), and the chance of recurrence was approximately 37 times higher in the MABSC group than in the NTM group (OR = 36,7; 95% CI: 5.3-253.8). In contrast, an evaluation of cases of clinical improvement and cure after completion of the first treatment regimen showed that the proportion of these cases was significantly greater in the NTM group than in the MABSC group ($p < 0.0001$). These data suggest that pulmonary disease caused by MABSC is more aggressive and has a worse prognosis than pulmonary disease caused by other NTM (Table 3). We emphasize that there were 2 deaths of unknown cause (not related to NTM infection) in the NTM group, and, therefore, these patients were excluded from the comparisons. Regarding secondary outcomes—obtained after the use of the second regimen or after administration of the third regimen—91.0% (10/11) of the patients in the MABSC experienced clinical improvement and cure, and 9.0% (1/11) died; the patient who died was among the patients who used imipenem (third regimen). One of the patients discharged after the use of the third regimen required surgical treatment. Of the patients in the NTM group who received the second treatment regimen (n = 2), all (100%) achieved treatment success. However, there were no statistically significant differences regarding these outcomes between the groups evaluated ($p = 0.3917$).

DISCUSSION

In view of the increasing number of cases of NTM infection, several studies have been conducted to analyze the condition and its epidemiology.[8-10] Of the 43 patients included in the present study, 39.5% had MABSC infection and 60.5% had pulmonary disease caused by other NTM, the most prevalent of which were MAC mycobacteria. The prevalence of pulmonary disease caused by MAC and by MABSC found in our study is in line with that reported in recent surveys conducted in the United States, where MABSC infection is second only to MAC infection, accounting for 2.6-13.0% of all cases of NTM pulmonary infection, with an annual prevalence of < 1/100,000 population.[4] Regarding pulmonary disease caused by MABSC subspecies, our results were similar to those reporting that the proportion of cases of *M. abscessus* subsp. *abscessus* would be similar to that of cases of *M. abscessus* subsp. *massiliense*, whereas *M. abscessus* subsp. *bolletii* is rarely identified.[4,11,12] Conditions predisposing to disease include previous treatment for pulmonary tuberculosis and structural pulmonary changes, represented here by bronchiectasis.[9,13,14] In a study comparing clinical variables between patients with pulmonary disease caused by *M. abscessus* subsp. *massiliense* and those with pulmonary disease caused by *M. abscessus* subsp. *abscessus*, no significant differences were found,[15] which is in contrast with the findings of the present study, in which loss of appetite was more common among those infected with MABSC mycobacteria. Regarding multiple treatments with the rifampin-isoniazid-pyrazinamide-ethambutol (RHZE) regimen for tuberculosis in patients infected with NTM, this is due to the fact that identification of mycobacteria in cultures is not mandatory in Brazil. Therefore, patients who received previous treatments for pulmonary tuberculosis experienced a higher frequency of asthenia, and this frequency was significantly (3-4 times) higher in those improperly treated with the RHZE regimen ($p = 0.0491$). In the Amazon, the great distances and the few centers equipped for the follow-up of patients infected with NTM are factors

that result in a delay in appropriate diagnosis and treatment of these patients.[16]

Although our study found no association between bronchiectasis and the study groups, bronchiectasis was the most prevalent comorbidity in both groups, proving the strong association between NTM infection and bronchiectasis. In a retrospective observational study that included 107 patients with pulmonary disease caused by MABSC, bronchiectasis and cavitation were found in 98% and 44% of the patients, respectively.[17] In that study, the nodular bronchiectasis form was associated with patients without previous treatment for pulmonary tuberculosis ($p = 0.0325$), which may be due to the fact that physicians associate cavitation with pulmonary tuberculosis and therefore request sputum smear microscopy for AFB early, whereas the presence of nodules and/or bronchiectasis requires a more thorough etiological investigation, demanding specialized evaluation.[18] Regarding the treatment of MABSC pulmonary infections, high-level resistance to the drugs in the RHZE regimen has been extensively described. In addition, resistance mechanisms similar to those of macrolide and aminoglycoside resistance are of note, impairing treatment response in this group of patients and worsening their prognosis.[19] The results of the present analysis show that the proportion of cases that did not respond to the first treatment regimen and required a second or third regimen was almost 12 times higher in the MABSC group than in the NTM group. Chief among the factors complicating this patient follow-up phase is the lack of susceptibility testing, which, because of technical and institutional limitations, was not performed; the result was that most regimens were initiated on the basis of few existing clinical protocols or of consultation with experienced specialists, as recommended in the ATS document itself, and therefore relying on a low level of evidence.[20] We observed that, in the NTM group, none of the patients had to use the third regimen containing imipenem, which may be explained by the fact that MAC has a different susceptibility pattern, showing susceptibility to regimens containing macrolides and antituberculosis drugs, which is well established, including in the ATS consensus statement.[20] New publications, subsequent to those of the ATS, recommend the use of intermittent therapy administered thrice weekly in an attempt to increase patient adherence,[10] because of the long treatment time and the possible side effects of the drugs; in our study sample, the chance of treatment nonadherence was 10 times higher in the MABSC group than in the NTM group. The patients in the NTM group, which was comprised mostly of individuals infected with MAC, achieved treatment success after the use of the second regimen, confirming literature findings that prognosis is better in cases of pulmonary disease caused by MAC or other NTM than in those of pulmonary disease caused by MABSC.[21] In cases of infection with *M. massiliense*—which, according to the literature, appear to exhibit a susceptibility pattern when treated with regimens containing macrolides—the chance of having to use a second treatment regimen is 10 times higher than it is in cases of infection with other NTM (95% CI: 1.4-74.5).[21]

MAC organisms are the most relevant slowly growing mycobacteria, and, according to recently published data, individuals infected with these mycobacteria have a better prognosis and a survival of 13 years.[20,21] In our study sample, the cure rate achieved with the first treatment regimen (clarithromycin, ethambutol, and rifampin) was high (83.2%) among the patients in the NTM group (which was mostly comprised of individuals infected with MAC), of whom only 2 (9.0%) had to start the second regimen, and the difference between the two groups was significant. The results of the present study, despite the technical limitations due to the lack of susceptibility testing, as well as the limitations due to the study's retrospective design and the fact that is was conducted in a referral hospital, which may have introduced selection and information bias, are in line with those of most published studies on the course of illness in patients with pulmonary disease caused by MABSC.[22-24] The unfavorable outcomes of long-term treatments with several prescribed regimens, together with important adverse effects, demonstrate the urgent need for a laboratory network that can identify NTM species and perform early susceptibility testing, so as to enable that specific standardized protocols be evaluated and instituted.

REFERENCES

1. Nunes-Costa D, Talarico S, Dalcolmo M, Correia-Neves M, Empadinhas N. The looming tide of nontuberculous mycobacterial infection in Portugal and Brazil. Tuberculosis (Edinb). 2016;96:107-19. https://doi.org/10.1016/j.tube.2015.09.006
2. Nie W, Duan H, Huang H, Lu Y, Bi D, Chu N. Species identification of Mycobacterium abscessus subsp. abscessus and Mycobacterium abscessus subsp. bolletii using rpoB and hsp65, and susceptibility testing to eight antibiotics. Int J Infect Dis. 2014;25:170-4. https://doi.org/10.1016/j.ijid.2014.02.014
3. Rubio M, March F, Garrigó M, Moreno C, Español M, Coll P. Inducible and Acquired Clarithromycin Resistance in the Mycobacterium abscessus Complex. PloS One. 2015;10(10):e0140166. https://doi.org/10.1371/journal.pone.0140166
4. Lee MR, Sheng WH, Hung CC, Yu CJ, Lee LN, Hsueh PR. Mycobacterium abscessus Complex Infections in Humans. Emerg Infect Dis. 2015;21(9):1638-46. https://doi.org/10.3201/2109.141634
5. Cândido PH, Nunes Lde S, Marques EA, Folescu TW, Coelho FS, de Moura VC, et al. Multidrug-resistant nontuberculous mycobacteria isolated from cystic fibrosis patients. J Clin Microbiol. 2014;58(8):2990-7. https://doi.org/10.1128/JCM.00549-14
6. Williams MM, Yakrus MA, Arduino MJ, Cooksey RC, Crane CB, Banerjee S, et al. Structural analysis of biofilm formation by rapidly and slowly growing nontuberculous mycobacteria. Appl Environ Microbiol. 2009;75(7):2091-8. https://doi.org/10.1128/AEM.00166-09
7. de Mello KG, Mello FC, Borga L, Rolla V, Duarte RS, Sampaio EP, et al. Clinical and therapeutic features of pulmonary nontuberculous mycobacterial disease, Brazil, 1993-2011. Emerg Infect Dis. 2013;19(3):393-9.
8. Ayres M, Ayres Junior M, Ayres DL, Santos AS. Bioestat 5.0 - Aplicações estatísticas nas áreas das ciências biomédicas. Belém: ONG Mamiraua; 2007.
9. Sousa S, Bandeira M, Carvalho PA, Duarte A, Jordao L.

Nontuberculous mycobacteria pathogenesis and biofilm assembly. Int J Mycobacteriol. 2015;4(1):36-43. https://doi.org/10.1016/j.ijmyco.2014.11.065

10. Mcshane PJ, Glassroth J. Pulmonary Disease Due To Nontuberculous Mycobacteria: Current State and New Insights. Chest. 2015;148(6):1517-1527. https://doi.org/10.1378/chest.15-0458
11. Adékambi T, Drancourt M. Mycobacterium bolletii respiratory infections. Emerg Infect Dis. 2009;15(2):302-5. https://doi.org/10.3201/eid1502.080837
12. Jeong BH, Kim SY, Jeon K, Huh HJ, Ki CS, Lee NY, et al. The First Korean Case of Nontuberculous Mycobacterial Lung Disease Caused by Mycobacterium abscessus Subspecies bolletii in a Patient with Bronchiectasis. Tuberc Respir Dis (Seoul). 2014;76(1):30-3. https://doi.org/10.4046/trd.2014.76.1.30
13. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med. 2015;36(1):13-34. https://doi.org/10.1016/j.ccm.2014.10.002
14. Thomson R, Tolson C, Carter R, Coulter C, Huygens F, Hargreaves M. Isolation of nontuberculous mycobacteria (NTM) from household water and shower aerosols in patients with pulmonary disease caused by NTM. J Clin Microbiol. 2013;51(9):3006-11. https://doi.org/10.1128/JCM.00899-13
15. Harada T, Akiyama Y, Kurashima A, Nagai H, Tsuyuguchi K, Fujii T, et al. Clinical and microbiological differences between Mycobacterium abscessus and Mycobacterium massiliense lung diseases. J Clin Microbiol. 2012;50(11):3556-61. https://doi.org/10.1128/JCM.01175-12
16. Jarrand J, Levin A, Zhang L, Huitt G, Mitchell JD, Daley CL. Clinical and microbiologic outcomes in patients receiving treatment for Mycobacterium abscessus pulmonary disease. Clin Infect Dis. 2011;52(5):565-71. https://doi.org/10.1093/cid/ciq237
17. Chung MJ, Lee KS, Koh WJ, Lee JH, Kim TS, Kwon OJ, et al. Thin-section CT findings of nontuberculous mycobacterial pulmonary diseases: comparison between Mycobacterium avium-intracellulare complex and Mycobacterium abscessus infection. J Korean Med Sci. 2005;20(5):777-83. https://doi.org/10.3346/jkms.2005.20.5.777
18. Chu H, Li B, Zhao L, Huang D, Xu J, Zhang J, et al. Tree-in-bud pattern of chest CT images for diagnosis of Mycobacterium abscessus. Int J Clin Exp Med. 2015; 8(10):18705-12. eCollection 2015.
19. Philley JV, Griffith DE. Treatment of slowly growing mycobacteria. Clin Chest Med. 2015;36(1):79-90. https://doi.org/10.1016/j.ccm.2014.10.005
20. Maurer FP, Castelberg C, Quiblier C, Böttger EC, Somosközi A. Erm(41)-dependent inducible resistance to azithromycin and clarithromycin in clinical isolates of Mycobacterium abscessus. J Antimicrob Chemother. 2014;69(6):1559-63. https://doi.org/10.1093/jac/dku007
21. Shin SJ, Choi GE, Cho SN, Woo SY, Jeong BH, Jeon K, et al. Mycobacterial genotypes are associated with clinical manifestation and progression of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense. Clin Infect Dis. 2013;57(1):32-9. https://doi.org/10.1093/cid/cit172
22. Olivier KN, Shaw PA, Glaser TS, Bhattacharyya D, Fleshner M, Brewer CC, et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. Ann Am Thorac Soc. 2014;11(1):30-5. https://doi.org/10.1513/AnnalsATS.201307-231OC
23. Plotinsky RN, Talbot E, von Reyn CF. Proposed definitions for epidemiologic and clinical studies of Mycobacterium avium complex pulmonary disease. PloS One. 2013;8(11):e77385. https://doi.org/10.1371/journal.pone.0077385
24. Kotilainen H, Valtonen V, Tukiainen P, Poussa T, Eskola J, Järvinen A. Clinical findings in relation to mortality in non-tuberculous mycobacterial infections: patients with Mycobacterium avium complex have better survival than patients with other mycobacteria. Eur J Clin Microbiol Infect Dis. 2015;34(9):1909-18. https://doi.org/10.1007/s10096-015-2432-8

J Bras Pneumol. 2018;44(2):99-105
http://dx.doi.org/10.1590/S1806-37562017000000161

ORIGINAL ARTICLE

Impact of smoking on sputum culture conversion and pulmonary tuberculosis treatment outcomes in Brazil: a retrospective cohort study

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Submitted: 12 May 2017.
Accepted: 15 October 2017.

Study carried out at the Ambulatório de Tuberculose, Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: To evaluate the impact of smoking on pulmonary tuberculosis (PTB) treatment outcomes and the two-month conversion rates for *Mycobacterium tuberculosis* sputum cultures among patients with culture-confirmed PTB in an area with a moderate incidence of tuberculosis in Brazil. **Methods:** This was a retrospective cohort study of PTB patients diagnosed and treated at the Thoracic Diseases Institute of the Federal University of Rio de Janeiro between 2004 and 2012. **Results:** Of the 298 patients diagnosed with PTB during the study period, 174 were included in the outcome analysis: 97 (55.7%) were never-smokers, 31 (17.8%) were former smokers, and 46 (26.5%) were current smokers. Smoking was associated with a delay in sputum culture conversion at the end of the second month of TB treatment (relative risk = 3.58 [95% CI: 1.3-9.86]; p = 0.01), as well as with poor treatment outcomes (relative risk = 6.29 [95% CI: 1.57-25.21]; p = 0.009). The association between smoking and a positive culture in the second month of treatment was statistically significant among the current smokers (p = 0.027). **Conclusions:** In our sample, the probability of a delay in sputum culture conversion was higher in current smokers than in never-smokers, as was the probability of a poor treatment outcome.

Keywords: Tuberculosis; Treatment outcome; Smoking.

INTRODUCTION

According to the World Health Organization, 10.4 million people developed tuberculosis and 1.4 million people died from tuberculosis in 2015.[1] In order to change this reality, the major goal of the World Health Organization strategy since 2015 has been to eradicate the global epidemic of tuberculosis by 2035, reducing the number of cases and deaths by 90% and 95%, respectively.[2] To that end, a treatment success rate of 90% remains the primary goal.[2] However, delays in the diagnosis of pulmonary tuberculosis (PTB) and the large proportion of patients who do not adequately complete treatment remain barriers to achieving these goals.[3] In addition, clinical variables and comorbidities, such as diabetes, HIV infection, alcohol abuse, and the extent of the disease on chest X-rays, can also affect the infectivity, diagnosis, and prognosis of these patients.[4,5] In this context, smoking has been associated not only with a two-fold higher risk of development of active tuberculosis but also with poor treatment outcomes.[6-8]

The smoking epidemic remains one of the greatest global public health threats, with more than 5 million annual deaths being directly associated with tobacco use.[9] Approximately 80% of more than 1 billion smokers worldwide live in low- to middle-income countries, where PTB is not controlled and is highly prevalent.[10] In 2013, the estimated prevalence of smoking in Brazil among individuals aged 15 years or older was 16.1%.[11] This is significant, given that Brazil is one of the 20 countries with the highest absolute numbers of tuberculosis cases worldwide and is also the country with the highest number of cases in Latin America (84,000 estimated new cases in 2015, representing an estimated incidence of 41/100,000 population).[1] In addition, two studies in Brazil demonstrated an association between smoking and delayed culture conversion in PTB patients, although the effects of smoking on treatment outcomes were not analyzed.[12,13] *Mycobacterium tuberculosis* sputum culture conversion at 2 months is an important marker for cure and an important primary outcome marker in most (if not all) clinical trials in PTB.[14,15] However, smoking, a possible confounding variable, has not been evaluated or considered even in recent clinical trials of new tuberculosis treatment regimens.[16-18]

Recently, a consensus statement on the treatment of PTB issued by the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America suggested that smokers with cavitation

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Financial support: This study received financial support from the International Clinical, Operational, and Health Services Research and Training Award (ICOHRTA, Grant no. 5 U2R TW006883-10) and the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq-UNIVERSAL, National Council for Scientific and Technological Development-UNIVERSAL, Grant no. 477582/2011-7).

on baseline chest X-ray or culture positivity at 2 months could be considered for extended tuberculosis treatment.[19] This suggestion is based on scientific evidence demonstrating a high risk of PTB recurrence in these patients.[20,21] According to data obtained from the Brazilian National Tuberculosis Control Program, the only comorbidity that should be regarded as a reason for extended PTB treatment is HIV infection.[22] Therefore, the objective of the present study was to evaluate the impact of smoking on *M. tuberculosis* sputum culture conversion rates at 2 months and on PTB treatment outcomes among patients with culture-confirmed PTB in an area with a moderate incidence of tuberculosis in Brazil.

METHODS

This was a retrospective cohort study carried out at the Tuberculosis Outpatient Clinic of the *Instituto de Doenças de Tórax da Universidade Federal do Rio de Janeiro* (IDT/UFRJ, Federal University of Rio de Janeiro Thoracic Diseases Institute), a referral center for the diagnosis and treatment of and clinical research on tuberculosis (formerly known as site 29, Hopkins-Brazil, of the Tuberculosis Clinical Trials Consortium of the Centers for Disease Control and Prevention) in the city of Rio de Janeiro, Brazil, involving patients with PTB between 2004 and 2012. The incidence rate of tuberculosis in Rio de Janeiro during the study period ranged from 83.7/100,000 population in 2004 to 69/100,000 population in 2012.[23]

Data collection, definitions, and subject selection

As part of the routine of the Tuberculosis Outpatient Clinic of theIDT/UFRJ, data regarding demographic aspects, cavitation on chest X-ray, and comorbidities were recorded in the patient medical charts. As for comorbidities, patients were assessed for diabetes mellitus (DM) on the basis of laboratory testing and a history of diagnosis of or treatment for DM. Patients were also assessed for smoking status and consumption, as well as for alcohol use (Cut down, Annoyed, Guilty, and Eye-opener questionnaire, known by the acronym CAGE). In addition, HIV serology testing was offered to all tuberculosis patients. Symptomatic subjects and/or those with abnormal chest X-rays were, on the first visit, instructed to provide two unsupervised sputum samples for AFB smear microscopy (Ziehl-Neelsen staining) and *M. tuberculosis* culture (Löwenstein-Jensen medium). Symptomatic subjects with abnormal chest X-rays who were unable to provide spontaneous sputum underwent sputum induction with hypertonic saline solution. Sputum samples, whether spontaneous or induced, were obtained at admission (baseline) and at eight weeks after treatment initiation for further smear microscopy and culture. Antimicrobial susceptibility testing was carried out on the baseline samples. Tuberculosis treatment is routinely administered under direct supervision to all patients at the Tuberculosis Outpatient Clinic of the IDT/UFRJ, and these patients are followed for 12 months after completion of the tuberculosis treatment.

The medical chart numbers of the patients with a diagnosis of PTB who were admitted to the Tuberculosis Outpatient Clinic of the IDT/UFRJ between October 1, 2004 and December 31, 2012 were obtained from the outpatient clinic database. A data collection instrument was created specifically for the present study, having been pre-tested and modified during a pilot study conducted in March 2012 and involving 15 medical charts (data not shown). The following data were obtained by medical chart review: smear microscopy and *M. tuberculosis* culture results; chest X-ray findings; demographic data (gender and age); level of education; alcohol consumption; HIV status; and comorbidities (cancer, immunosuppression, liver disease, and renal failure). Patients were categorized by their self-reported smoking status as smokers (current or former smokers) and nonsmokers. Current smokers were defined as subjects who were smoking at the time of diagnosis of PTB or who had quit smoking within 12 months prior to diagnosis and had smoked at least 100 cigarettes during their lifetime.[24] Former smokers were defined as those who had quit smoking more than 12 months prior to diagnosis of PTB. Subjects who reported never having smoked were defined as nonsmokers. Smoking history was expressed in pack-years. A diagnosis of DM was established if the subject had a history of DM and was on insulin and/or an oral hypoglycemic agent or had been diagnosed with DM during PTB treatment (on the basis of two or more fasting blood glucose levels ≥ 126 mg/dL on different days or a glycosylated hemoglobin level ≥ 6.5%). Sputum culture conversion was defined as culture negativity at 2 months. Treatment outcomes were categorized as treatment success (cure or treatment completion) or poor treatment outcomes (death, treatment default, or treatment failure). Recurrence was defined as a new PTB episode confirmed by culture positivity for *M. tuberculosis* within 12 months after treatment completion.[25] Subjects with culture positivity for *M. tuberculosis* and aged ≥ 18 years were included in the study.

For the outcome analysis, patient exclusion criteria were as follows: being pregnant during treatment; testing positive for HIV serology; data required for evaluation being missing; having an antimicrobial susceptibility test result that showed *M. tuberculosis* strains resistant to any drug in the standard regimen; and having received different treatments from the standard regimen: rifampin and isoniazid for 6 months, as well as pyrazinamide and ethambutol in the first 2 months, as recommended by the Brazilian National Tuberculosis Control Program.

Statistical analysis

The results were analyzed with IBM SPSS Statistics software, version 21.0 (IBM Corporation, Armonk, NY, USA), and Stata software, version 11.0 (StataCorp LP, College Station, TX, USA). The exposure variable was

smoking, and the nonexposure variable was absence of a smoking history. The confounding variables considered in our study were DM, cavitation on chest X-ray, and alcohol abuse. The outcome variables evaluated were culture positivity for *M. tuberculosis* at 2 months (yes or no), PTB treatment outcome (poor or treatment success), and PTB recurrence (yes or no). Relative risks (RRs) and 95% confidence intervals were calculated for each outcome. Dichotomous variables were analyzed with the chi-square test and Fisher's exact test, with a level of significance set at 5%. Continuous variables were analyzed with the Kruskal-Wallis test for independent samples, and logistic regression was used for the multivariate analysis.

Ethics

The Research Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro approved the present study on March 15, 2012 (Memorandum no. 391/12; Protocol no. 137/11).

RESULTS

Of the 298 patients with a diagnosis of PTB who were enrolled in the outpatient clinic database during the study period, 12 were ineligible for inclusion (culture negativity for *M. tuberculosis*). In addition, 41 subjects were excluded because they tested positive for HIV serology (n = 8) or had baseline resistance to rifampin, isoniazid, pyrazinamide, or ethambutol (n = 33). Those who did not receive the standard treatment regimen because they were participating in a clinical trial testing new drugs were also excluded (n = 71). Of the remaining 174 patients diagnosed with PTB, 77 (44.3%) were in the exposure group (31 former smokers and 46 current smokers) and 97 (55.7%) were in the control group (nonexposure; Figure 1).

The patients included in the study were predominantly male, with a median age of 35 years (interquartile range: 35-49 years), and the presence of cavitation on baseline chest X-ray was highly prevalent (Table 1). The prevalence of DM was 17% among all subjects (30/174). Current smokers had fewer years of schooling and showed a lower prevalence of DM than did nonsmokers. The prevalence of alcohol abuse was higher among those with a (previous or current) history of smoking. There was no significant difference among nonsmokers, former smokers, and current smokers with respect to the presence of cavitation on baseline chest X-ray.

Two-month culture results were available for 137 subjects, and the prevalence of culture positivity at 2 months was 25.5% (35/137). DM and smoking were significantly associated with this outcome in the univariate analysis (RR = 2.59 [95% CI: 0.98-6.89]; p = 0.05; and RR = 2.87 [95% CI: 1.25-6.59]; p = 0.01, respectively). However, in the multivariate model, only smoking remained significantly associated with culture positivity at 2 months (RR = 3.58 [95% CI: 1.30-9.86]; p = 0.01; Table 2). Thus, the likelihood of culture positivity at 2 months was greater among current smokers than among nonsmokers (p = 0.02; Figure 2). In addition, we identified a dose-response relationship between tobacco consumption and culture positivity at 2 months. The proportion of tobacco consumption was similar between former smokers and current smokers (p = 0.6).

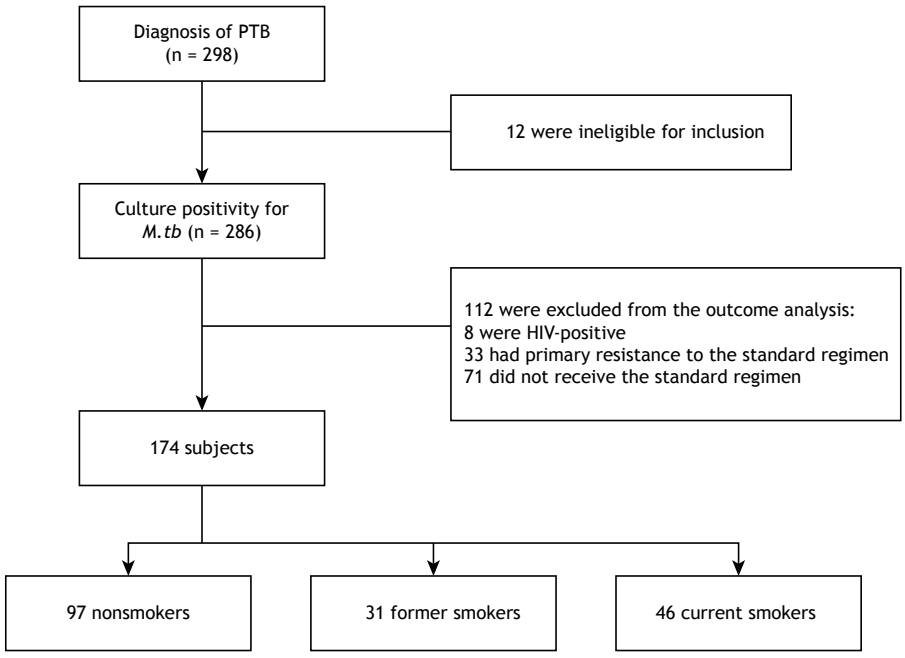

Figure 1. Pulmonary tuberculosis (PTB) patient evaluation flowchart. *M.tb: Mycobacterium tuberculosis.*

Treatment outcomes were available for 164 patients: treatment success was observed in 146—cure, in 26; and treatment completion, in 120—and a poor outcome was observed in 18—failure, in 5; death, in 4; and default, in 9. Thus, the treatment success rate was 89%. There was 1 case of recurrence within 1 year after treatment completion. Smoking was the only independent factor associated with a poor treatment outcome (RR = 6.29 [95% CI: 1.57-25.21]; p = 0.009; Table 3). Current smokers were more likely to have a poor treatment outcome than were former smokers and nonsmokers (p = 0.04 and p = 0.002, respectively; Figure 3).

DISCUSSION

The clinical characteristics of our study sample were representative of what is expected for PTB patients. The male predominance, the median age of 35 years, few years of schooling, and the rate of alcohol abuse above 20% of the sample are comparable to what has been previously reported in other studies.[8,12,13] Notably, the prevalence of DM among the PTB patients was higher than that found in the general population of Brazil in 2014 (17% vs. 7.6%).[26] Although a descriptive study in Brazil found a DM prevalence of 8%, our findings were similar to those of descriptive studies conducted in China and in India (16.2% and 14%, respectively).[27-29] The prevalence of smoking among the PTB patients was also higher (44.3%) than that in the general Brazilian population (15%).[11] Likewise, our data were consistent with the smoking prevalence of 44% found in South Africa, another middle-income country with a high number of tuberculosis cases.[30] The presence of cavitation on baseline chest X-ray was highly prevalent, but this finding was similar between the exposure and nonexposure groups.

In our study, the prevalence of alcohol abuse was higher among former smokers and current smokers than among nonsmokers. A higher prevalence of alcohol abuse among individuals with a (previous or current) history of smoking than among those who were nonsmokers has also been reported previously.[8,21] Because alcohol abuse is a confounding variable for PTB treatment outcomes, it is commonly analyzed together

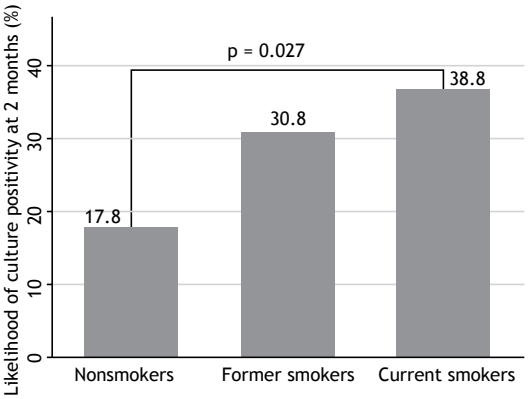

Figure 2. Smoking status and culture positivity at 2 months.

Table 1. Characteristics of pulmonary tuberculosis patients (n = 174).[a]

Characteristic	Total sample (N = 174)	Nonsmokers (n = 97)	Former smokers (n = 31)	p*	Current smokers (n = 46)	p**
Male gender	114 (66)	52 (54)	25 (71)	0.09	37 (80)	0.002
Age, years	35 [25-49]	30 [24-41]	51 [34-57]	< 0.001	40 [25-52]	0.2
Schooling, years[b¤]						
≤ 7	43 (25)	21 (22)	7 (23)	0.9	15 (32)	0.1
8-10	65 (38)	31 (33)	13 (43)	0.3	21 (46)	0.2
> 10	62 (36)	42 (45)	10 (33)	0.2	10 (22)	0.008
Diabetes mellitus	30 (17)	13 (46)	10 (32)	0.1	7 (15)	< 0.001
Alcohol abuse[c]	48 (29)	13 (13)	11 (35)	0.006	24 (52)	< 0.001
Cavitation on baseline CXR[c]	118 (69)	65 (67)	18 (58)	0.3	35 (76)	0.2

CXR: chest X-ray.¤ [a]Values expressed as n (%) or as median [interquartile range]. [b]Information not available for 4 patients. [c]Information not available for 7 patients. *Nonsmokers vs. former smokers. **Nonsmokers vs. current smokers.

Table 2. Predictors of culture positivity at 2 months (n = 137).

Predictor	Univariate analysis[a]	p	Multivariate analysis[a]	p
Male gender	1.06 (0.46-2.46)	0.884	0.96 (0.35-2.66)	0.941
Age	1.02 (0.99-1.05)	0.166	1.01 (0.97-1.04)	0.701
>10 years of schooling	1.69 (0.76-3.76)	0.200	2.32 (0.91-5.91)	0.077
Diabetes mellitus	2.59 (0.98-6.89)	0.056	2.33 (0.76-7.14)	0.140
Other comorbidities[b]	1.28(0.50-3.28)	0.607	1.39 (0.49-3.88)	0.535
Alcohol abuse	0.73 (0.29-1.80)	0.494	0.47 (0.16-1.34)	0.157
Cavitation	1.80(0.70-4.60)	0.220	1.79 (0.66-4.85)	0.253
Smoking	2.87 (1.25-6.59)	0.013	3.58 (1.30-9.86)	0.014

[a]Values expressed as relative risk (95% CI). [b]Cancer, immunosuppression, liver disease, and renal failure.

Table 3. Predictors of poor treatment outcome[a] (n = 164).

Predictor	Univariate analysis[b]	p	Multivariate analysis[b]	p
Male gender	1.14 (0.37-3.47)	0.821	0.97 (0.28-3.39)	0.967
Age	0.98 (0.95-1.02)	0.426	0.97 (0.92-1.01)	0.169
>10 years of schooling	0.8 (0.26-2.43)	0.691	1.04 (0.29-3.68)	0.957
Diabetes mellitus	0.7 (0.15-3.27)	0.646	0.84 (0.15-4.61)	0.841
Other comorbidities[c]	0.55 (0.12-2.54)	0.441	0.85 (0.16-4.41)	0.846
Alcohol abuse	1.16 (0.38-3.56)	0.795	0.68 (0.19-2.41)	0.546
Cavitation	0.42 (0.15-1.20)	0.105	0.37 (0.12-1.13)	0.081
Smoking	3.75 (1.15-12.22)	0.028	6.29 (1.57-25.21)	0.009

[a]Death, treatment failure, or default. [b]Values expressed as relative risk (95% CI). [c]Cancer, immunosuppression, liver disease, and renal failure.

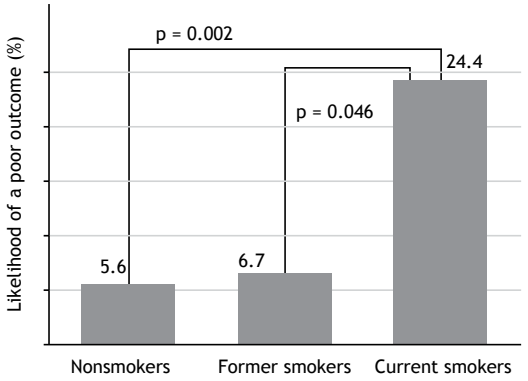

Figure 3. Smoking status and poor tuberculosis treatment outcomes.

with smoking. Like in other studies, multivariate analysis in our study demonstrated that smoking (rather than alcohol abuse) was the variable associated with a poor PTB treatment outcome.[21,31,32]

In our study sample, only smoking was independently associated with delayed 2-month *M. tuberculosis* culture conversion. , The association between smoking and delayed *M. tuberculosis* culture conversion among PTB patients was also observed in China and in Spain,[21,33] which suggests that smoking could be evaluated as a predictive variable in future studies, affecting culture conversion and PTB treatment failure. Thus, this may also be an important aspect for consideration in future publications on the treatment of tuberculosis, given that the rate of *M. tuberculosis* culture conversion is one of the most commonly used predictors of outcomes in clinical trials in PTB.[14] In addition, Maciel et al. demonstrated that smoking more than 20 cigarettes per day was independently associated with delayed 2-month culture conversion.[13] Similarly, we also observed a dose-response relationship between these two variables.

Some studies have demonstrated an association between smoking and a poor PTB treatment outcome.[8,21,31] The association between smoking and treatment default has already been described as being independent of alcohol or illicit drug use.[34] Thus, this association may be related to the psychosocial aspect of smoking, because smoking predominates in males and in disadvantaged populations, which are factors associated with poor treatment adherence. Chiang et al.[31] demonstrated that high tobacco consumption (> 20 cigarettes per day) was significantly associated with a lower likelihood of achieving a positive treatment outcome. The functional damage seen in human alveolar macrophages of smokers after *M. tuberculosis* infection could contribute to the delayed culture conversion and poor treatment outcomes observed.[35]

In our sample, current smoking was associated with culture positivity at 2 months and with a poor treatment outcome. Delayed culture conversion is relevant when we consider the tuberculosis transmission process and because it is a risk factor for recurrence.[14,36] Therefore, the results of the present study support the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America suggestion that, among smokers, the presence of cavitation on baseline chest X-ray or culture positivity at 2 months could result in extended tuberculosis treatment.[19] In addition, current smokers in our sample were defined as subjects who were smoking at the time of diagnosis of PTB or who had quit smoking within 12 months prior to diagnosis. Therefore, they continued smoking despite their PTB-related symptoms, which could be interpreted as high tobacco dependence and greater difficulty in quitting smoking.

The present study has limitations. Smoking status was self-reported by the patient during the clinical interview and was not assessed by cotinine levels. Nevertheless, a recent study suggested that self-reporting is an accurate way of determining patient smoking status.[37] In addition, the classification of current smoking among new PTB cases could consider smoking at the time of onset of PTB symptoms, in order to prevent misclassification of current smokers as former smokers.[30] Thus, it is possible that we classified more patients as current smokers than as former smokers, given that we used a cutoff of 12 months of abstinence to define former smokers. Further limitations of the study were that glucose levels were not determined for all PTB patients because of operational difficulties and that the sample size was limited. However, the present study is unique in that it evaluates the impact of smoking in a sample of PTB patients with culture positivity for *M. tuberculosis* in the country with the highest number of tuberculosis cases in Latin America.

All patients were treated under direct supervision with a standard treatment regimen and using data collected in accordance with good clinical practices.

In conclusion, smoking was independently associated with delayed 2-month culture conversion and with a poor treatment outcome. These findings suggest that current smoking in PTB patients could be considered as an additional variable for extending PTB treatment to 9 months in Brazil. Prospective studies with larger sample sizes are needed to confirm our findings.

ACKNOWLEDGMENTS

The authors thank the professionals and patients at the Tuberculosis Outpatient Clinic of the IDT/UFRJ.

REFERENCES

1. World Health Organization (WHO). Global tuberculosis report 2016. Geneva: WHO; 2016
2. World Health Organization (WHO). The End TB Strategy 2015. Geneva: WHO; 2015.
3. Dye C, Watt CJ, Bleed D. Low access to a highly effective therapy: a challenge for international tuberculosis control. Bull World Health Organ. 2002;80(6):437-44.
4. Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R, et al. The HIV-associated tuberculosis epidemic–when will we act? Lancet. 2010;375(9729):1906-19. https://doi.org/10.1016/S0140-6736(10)60409-6
5. Baghaei P, Marjani M, Javanmard P, Tabarsi P, Masjedi MR. Diabetes mellitus and tuberculosis facts and controversies. J Diabetes Metab Disord. 2013;12(1):58. https://doi.org/10.1186/2251-6581-12-58
6. Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. Am J Respir Crit Care Med. 2009;180(5):475-80. https://doi.org/10.1164/rccm.200904-0549OC
7. Chiang CY, Slama K, Enarson DA. Associations between tobacco and tuberculosis. Int J Tuberc Lung Dis. 2007;11(3):258-62.
8. Bonacci RA, Cruz-Hervert LP, García-García L, Reynales-Shigematsu LM, Ferreyra-Reyes L, Bobadilla-del-Valle M, et al. Impact of cigarette smoking on rates and clinical prognosis of pulmonary tuberculosis in Southern Mexico. J Infect. 2013;66(4):303-12. https://doi.org/10.1016/j.jinf.2012.09.005
9. World Health Organization [homepage on the Internet]. Geneva: WHO [updated 2016 Jun; cited 2017 Feb 1]. Tobacco Fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs339/en/
10. Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murray MB. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. Int J Epidemiol. 2011;40(2):417-28. https://doi.org/10.1093/ije/dyq238
11. Instituto Brasileiro de Geografia e Estatística (IBGE) [homepage on the Internet]. Rio de Janeiro: IBGE [cited 2017 Feb 1]. Pesquisa Nacional de Saúde 2013. [Adobe Acrobat document, 181p.]. Available from: http://biblioteca.ibge.gov.br/visualizacao/livros/liv91110.pdf
12. Nijenbandring de Boer R, Oliveira e Souza Filho JB, Cobelens F, Ramalho Dde P, Campino Miranda PF, Logo Kd, et. al. Delayed culture conversion due to cigarette smoking in active pulmonary tuberculosis patients. Tuberculosis (Edinb). 2014;94(1):87-91. https://doi.org/10.1016/j.tube.2013.10.005
13. Maciel EL, Brioschi AP, Peres RL, Guidoni LM, Ribeiro FK, Hadad DJ, et al. Smoking and 2-month culture conversion during anti-tuberculosis treatment. Int J Tuberc Lung Dis. 2013;17(2):225-8. https://doi.org/10.5588/ijtld.12.0426
14. Mitchison DA. Assessment of new sterilizing drugs for treating pulmonary tuberculosis by culture at 2 months. Am Rev Respir Dis. 1993;147(4):1062-3. https://doi.org/10.1164/ajrccm/147.4.1062
15. Wallis RS, Doherty TM, Onyebujoh P, Vahedi M, Laang H, Olesen O, et al. Biomarkers for tuberculosis disease activity, cure, and relapse. Lancet Infect Dis. 2009;9(3):162-72. https://doi.org/10.1016/S1473-3099(09)70042-8
16. Diancon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. Am J Respir Crit Care Med. 2015;191(8):943-53. https://doi.org/10.1164/rccm.201410-1801OC
17. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588-98. https://doi.org/10.1056/NEJMoa1315817
18. Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008;12(2):128-38.
19. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. https://doi.org/10.1093/cid/ciw376
20. Yen YF, Yen MY, Lin YS, Lin YP, Shih HC, Li LH, et al. Smoking increases risk of recurrence after successful anti-tuberculosis treatment: a population-based study. Int J Tuberc Lung. 2014;18(4):492-8. https://doi.org/10.5588/ijtld.13.0694
21. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, et al. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J. 2015;45(3):738-45. https://doi.org/10.1183/09031936.00114214
22. Brasil. Ministério da Saúde. Portal da Saúde [homepage on the Internet]. Brasília: o Ministério [cited 2017 Feb 1]. Manual de recomendações para o controle da tuberculose no Brasil 2011. [Adobe Acrobat document, 298p.]. Available from: : http://portalarquivos.saude.gov.br/images/pdf/2015/junho/30/MANUAL-DE-RECOMENDACOES-PARA-O-CONTROLE-DA-TUBERCULOSE-NO-BRASIL.pdf
23. Secretaria Estadual de Saúde do Estado do Rio de Janeiro [homepage on the Internet]. Rio de Janeiro: a Secretaria [cited 2017 Feb 1]. Principais indicadores da tuberculose no estado do Rio de Janeiro, 2013 [about 23 screens]. Available from: http://www.riocomsaude.rj.gov.br/Publico/MostrarArquivo.aspx?C=QXgbrHtoUtA%3D
24. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults–United States, 1992, and changes in the definition of current cigarette smoking. MMWR Morb Mortal Wkly Rep. 1994;43(19):342-6.
25. World Health Organization (WHO). Definitions and reporting framework for tuberculosis–2013 revision. Geneva: WHO; 2013.
26. World Health Organization (WHO). Global status report on noncommunicable diseases 2014. Geneva: WHO; 2014.
27. Khanna A, Lohya S, Sharath BN, Harries AD. Characteristics and treatment response in patients with tuberculosis and diabetes mellitus in New Delhi, India. Public Health Action. 2013;3(Suppl 1):S48-50. https://doi.org/10.5588/pha.13.0025
28. Hongguang C, Min L, Shiwen J, Fanghui G, Shaoping H, Tiejie G, et al. Impact of diabetes on clinical presentation and treatment outcome of pulmonary tuberculosis in Beijing. Epidemiol Infect. 2015;143(1):150-6. https://doi.org/10.1017/S095026881400079X
29. Augusto CJ, Carvalho Wda S, Gonçalves AD, Ceccato Md, Miranda SS. Characteristics of tuberculosis in the state of Minas Gerais, Brazil: 2002-2009. J Bras Pneumol. 2013;39(3):357-64. https://doi.org/10.1590/S1806-37132013000300013
30. Lam C, Martinson N, Hepp L, Ambrose B, Msandiwa R, Wong ML, et al. Prevalence of tobacco smoking in adults with tuberculosis in South Africa. Int J Tuberc Lung Dis. 2013;17(10):1354-7. https://doi.org/10.5588/ijtld.13.0016
31. Chiang YC, Lin YM, Lee JA, Lee CN, Chen HY. Tobacco consumption is a reversible risk factor associated with reduced successful treatment outcomes of anti-tuberculosis therapy. Int J Infect Dis. 2012;16(2):e130-5 https://doi.org/10.1016/j.ijid.2011.10.007
32. Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Gloub JE, et al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bull World Health Organ. 2015;93(6):390-9. https://doi.org/10.2471/BLT.14.147439
33. Gullón Blanco JA, Suárez Toste I, Lecuona Fernández M, Galindo

Morales R, Fernández Alvarez R, Rubinos Cuadrado G, et al. Tobacco smoking and sputum smear conversion in pulmonary tuberculosis [Article in Spanish]. Med Clin (Barc). 2007;128(15):565-8. https://doi.org/10.1157/13101612

34. Cherkaoui I, Sabouni R, Ghali I, Kizub D, Billioux AC, Bennani K, et al. Treatment default amongst patients with tuberculosis in urban Morocco: predicting and explaining default and post-default sputum smear and drug susceptibility results. PLoS One. 2014;9(4):e93574. https://doi.org/10.1371/journal.pone.0093574
35. O'Leary SM, Coleman MM, Chew WM, Morrow C, McLaughlin AM, Gleeson LE, et al. Cigarette smoking impairs human pulmonary immunity to Mycobacterium tuberculosis. Am J Respir Crit Care Med. 2014;190(12):1430-6. https://doi.org/10.1164/rccm.201407-1385OC
36. Godoy P, Caylà JA, Carmona G, Camps N, Álvarez J, Alsedà M, et al. Smoking in tuberculosis patients increases the risk of infection in their contacts. Int J Tuberc Lung Dis. 2013;17(6):771-6. https://doi.org/10.5588/ijtld.12.0696
37. Brunet L, Pai M, Davids V, Ling D, Paradis G, Lenders L, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. Eur Respir J. 2011;38(1):139-46. https://doi.org/10.1183/09031936.00137710

J Bras Pneumol. 2018;44(2):106-111
http://dx.doi.org/10.1590/S1806-37562017000000213

ORIGINAL ARTICLE

Nontuberculous mycobacterial lung disease in a high tuberculosis incidence setting in Brazil

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Submitted: 18 June 2017.
Accepted: 15 October 2017.

Study carried out in the Ambulatório de Referência de TBDR e MNT, Hospital Sanatório Partenon, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: The incidence of lung disease caused by nontuberculous mycobacteria (NTM) has been increasing worldwide. In Brazil, there are few studies about nontuberculous mycobacterial lung disease (NTMLD), and its prevalence is yet to be known. Our objective was to determine the specific etiology of the disease in the state of Rio Grande do Sul, Brazil, as well as the frequency and diversity of NTM species in our sample of patients. **Methods:** This is a retrospective analysis of the medical records of patients diagnosed with NTMLD treated in a referral center located in the city of Porto Alegre, Brazil, between 2003 and 2013. **Results:** Our sample comprised 100 patients. The most prevalent NTM species were *Mycobacterium avium* complex (MAC), in 35% of the cases; *M. kansasii*, in 17%; and *M. abscessus*, in 12%. A total of 85 patients had received previous treatment for tuberculosis. Associated conditions included structural abnormalities in the lungs, such as bronchiectasis, in 23% of the cases; COPD, in 17%; and immunosuppressive conditions, such as AIDS, in 24%. **Conclusions:** MAC and *M. kansasii* were the most prevalent species involved in NTMLD in the state, similarly to what occurs in other regions of Brazil. Data on regional epidemiology of NTMLD, its specific etiology, and associated conditions are essential to establish appropriate treatment, since each species requires specific regimens. Most patients with NTMLD had received previous tuberculosis treatment, which might lead to development of resistance and late diagnosis.

Keywords: Nontuberculous mycobacteria; Mycobacterium infections, nontuberculous; Lung diseases.

INTRODUCTION

Nontuberculous mycobacteria (NTM) consist of species of the genus *Mycobacterium*, but with distinct characteristics from those of the species of the *Mycobacterium tuberculosis* complex.[1] Since NTM are widespread in nature, it is believed that the source of infection in humans is the environment.[2] Infections caused by NTM are not considered a public health problem, and, therefore, reporting them is not mandatory, even though a few species are highly pathogenic and responsible for causing disease and death.[3]

The propensity of NTM to cause lung disease is greater in the presence of associated factors, such as COPD, previous tuberculosis, cystic fibrosis, bronchiectasis, HIV, and transplantation. It is known that pre-existing structural lung abnormalities and immunosuppressive conditions favor the development of NTM lung disease (NTMLD).[4]

Worldwide, NTM have been increasingly identified as causative agents of lung disease,[3] with high incidence and prevalence rates, including all regions in the USA (the annual prevalence significantly increased from 20 cases/100,000 population in 1997 to 47 cases/100,000 population in 2007, i.e., 8.2% per year), southwestern Ireland (mean incidence of 0.4/100,000 population), New Zealand (incidence of 1.92/100,000 population), and Canada (mean incidence of 6.7/100,000 population).[5-8]

At least 40 species of NTM are associated with lung disease,[9] the lungs being the most common site affected by NTM. The clinical diagnosis of NTMLD is complicated by symptom similarity with other lung diseases, especially tuberculosis. The wide variety and nonspecificity of symptoms caused by NTMLD, such as cough, hemoptysis, chest pain, fever, asthenia, weight loss, shortness of breath, and night sweats, hinders the diagnosis. NTMLD requires specific diagnosis to define the therapeutic regimen, given that different species of NTM require distinct therapies.[10-12]

In the state of Rio Grande do Sul, the southernmost Brazilian state, mycobacterial cultures are not performed as a routine procedure for the diagnosis of tuberculosis,

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Financial support: None.

ISSN 1806-3713

which further hinders the detection of NTM. Since there is no mandatory reporting of NTMLD cases and there are no studies on NTMLD in the state, the main objective of the present study was to determine the specific etiology of the disease in our state, as well as the frequency and diversity of NTM species.

METHODS

The present study involved patients attending the Tuberculosis/NTM Outpatient Clinic in *Hospital Sanatório Partenon* (HSP), the referral institution for the treatment of multidrug-resistant tuberculosis and NTM-related diseases in the state of Rio Grande do Sul, Brazil. In accordance with the Brazilian Ministry of Health guidelines,[13] mycobacterial cultures should only be performed according to the following criteria: 1) patients who were diagnosed with tuberculosis who remain positive for AFB at the second month of treatment; 2) patients with previously treated tuberculosis and a positive result for AFB; 3) patients who are contacts of people diagnosed with drug-resistant tuberculosis; and 4) patients taking part of specific population groups considered at risk, such as health professionals, homeless people, those deprived of liberty, indigenous populations, and people living with HIV. Patients with suspected NTMLD in the state of Rio Grande do Sul are sent to the HSP Outpatient Clinic for evaluation, diagnosis, treatment, and follow-up.

To demonstrate the clinical profile of patients with NTMLD, a retrospective review of the clinical medical records from the HSP Outpatient Clinic regarding tuberculosis and NTMLD was performed. The study population consisted of all patients who presented with pulmonary symptoms, had radiological findings consistent with mycobacterial disease, had an NTM-positive respiratory culture, and were treated at the HSP Outpatient Clinic between 2003 and 2013.

In accordance with an official statement by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA),[11] the diagnosis of NTMLD should be based on respiratory symptoms, image findings (e.g., nodular or cavitary opacities on X-rays or multifocal bronchiectasis and multiple small nodules), and a positive culture for NTM in two or more sputum specimens or in one BAL fluid specimen. Lung biopsy followed by a positive tissue culture is another way to confirm the diagnosis.[11]

Cure was defined when a patient presented with 12 consecutive negative cultures collected every month (bacteriological cure). In cases of absence of expectoration, cure was clinically and radiologically diagnosed after 18 months of treatment (clinical cure).[11] Patients were followed up for 2 years after the end of treatment for the identification of relapse prior to defining the outcome as definitive cure. Since there is no reliable antibiotic regimen to provide cure for *M. abscessus* lung disease, the disease is considered to be controlled when no exacerbations are observed for 2 years.[11]

Demographic, clinical, and epidemiological data, including associated diseases, treatment outcome, and previous tuberculosis treatment, were obtained from medical records. Patients with extrapulmonary mycobacteriosis and patients younger than 18 years of age were excluded from the study.

The identification of NTM species is performed by the association of phenotypic and molecular tests. After growth on a solid medium, colonies are tested for phenotypic differentiation between *M. tuberculosis* complex and NTM. The molecular identification is performed by PCR-restriction enzyme analysis, which is based on the amplification of a 441-bp fragment of the *hsp65* gene and subsequent digestion with two restriction enzymes (*BstEII* and *HaeIII*).[14,15]

The descriptive analysis was expressed as mean ± SD or proportion. The study was approved by the Research Ethics Committee of the *Escola de Saúde Pública/Secretária de Saúde* - ESP/SES/RS (CAAE no. 18656413.1.3001.5312).

RESULTS

Our sample comprised 100 patients who met the inclusion criteria. The mean age of the patients was 54.6 years, and 24 patients had positive HIV results. Most (64%) of the patients reported pulmonary and systemic signs and symptoms of the disease, including cough, hemoptysis, chest pain, fever, anorexia, weight loss, shortness of breath, and night sweats (Table 1).

The most common associated conditions were HIV, in 24% of the patients; bronchiectasis, in 23%; and COPD, in 17%. No associated disease was identified in 23% of the patients (Table 2). In our sample, at least 42 patients presented with structural abnormalities of the lungs. A total of 85 patients had received previous treatment for tuberculosis, based on a positive AFB smear (Table 1).

A total of 74 patients met the criteria for NTMLD in accordance with the ATS/IDSA[11] statement (Table 1). We were able to identify an increase in the number of patients with NTMLD disease from 2007 to 2013 (Figure 1).

Among all of the species of NTM identified, three were the most prevalent (in 64% of the cases): *M. avium* complex (MAC), in 35 patients; *M. kansasii*, in 17; and *M. abscessus*, in 12. Among MAC species, 26 were identified as *M. avium*, and 9 were identified as *M. intracellulare*. Rapidly growing mycobacteria were identified in only 16 patients: *M. abscessus*, in 12; and *M. fortuitum*, in 4. However, we were unable to identify the NTM species in 26 patients (Table 3). In addition, we were also unable to determine the most prevalent NTM species with regard to the HIV status of the patients, because the species were unidentified in 15 of the 24 patients diagnosed with HIV.

The cure rate of the patients who met the ATS/IDSA criteria[11] was 60.7% and 73.3% in those infected with MAC and *M. kansasii*, respectively. In addition,

M. abscessus lung disease was considered controlled in 70.0% of those cases. Of the 17 patients diagnosed with *M. kansasii* infection, 13 (76.4%) received a treatment regimen with rifampin, isoniazid, and ethambutol, whereas 67.7% of the patients infected with MAC were treated with a regimen with rifampin, ethambutol, and clarithromycin, and 41.6% of those infected with *M. abscessus* were treated with a regimen containing amikacin, clarithromycin, and imipenem.

DISCUSSION

The increasing number of cases and the diversity of species found in the present study demonstrate that NTMLD requires more attention. In fact, the real prevalence of NTMLD is possibly underestimated, since there is no mandatory reporting of cases of NTM disease in Brazil. Moreover, the vast majority of routine laboratories do not perform cultures for mycobacteria but only the evaluation of AFB direct smears.

The increase in the number of cases of NTMLD from 2007 to 2013 might be related to an increasing awareness on the part of physicians regarding this issue, increasing the number of cases diagnosed; improved laboratory capacity; a higher number of people living with structural abnormalities in the lung or immunosuppressive conditions; and increased life expectancy.[3,11]

Brazil has a high prevalence of tuberculosis—30.9 cases/100.000 population in 2015[16]—which is highly contagious. Therefore, it is recommended that patients with AFB in sputum should be treated regardless of culture identification of the *M. tuberculosis* complex. Moreover, tuberculosis can result in pulmonary sequelae; therefore, patients who had tuberculosis show a higher risk of developing NTMLD.[17] In the present study, most patients (85%) had had a prior treatment for tuberculosis. Similar results were also found in the state of Rio de Janeiro (in 58% of the cases).[17] A limitation of the present study is that we were unable to identify whether NTMLD was due to tuberculosis sequelae because those patients who had been treated for tuberculosis had no culture confirmation.

Structural abnormalities, such as bronchiectasis, COPD, and cystic fibrosis, are considered risk factors

Table 1. Clinical and demographic characteristics of the patients with nontuberculous mycobacterial lung disease (N = 100).[a]

Characteristic	Result
Male gender	51 (51)
HIV positive	24 (24)
Age according to HIV status, years	
HIV positive	43.6 ± 11.9
HIV negative	56.2 ± 15.3
Not informed	64.1 ± 16.3
Symptoms	
Lung	17 (17)
Systemic	8 (8)
Lung and systemic	64 (64)
Not specified	11 (11)
Previous tuberculosis treatment	85 (85)
Met the criteria for NTMLD[b]	74 (74)

NTMLD: nontuberculous mycobacterial lung disease. [a]Values expressed as n (%) or mean ± SD. [b]In accordance with Griffith et al.[11]

Table 2. Main coexisting medical conditions in the patients with nontuberculous mycobacterial lung disease (N = 100).[a]

Coexisting condition	Patient
AIDS	24
None	23
Bronchiectasis	22
COPD	17
Cancer	6
Hepatitis B or C	6
Diabetes mellitus	4
Tuberculosis	2
Systemic lupus erythematosus	1
Transplant	1
Silicosis	1
Cystic fibrosis	1
Congenital immunosuppression	1

[a]Patients may have more than one coexisting condition.

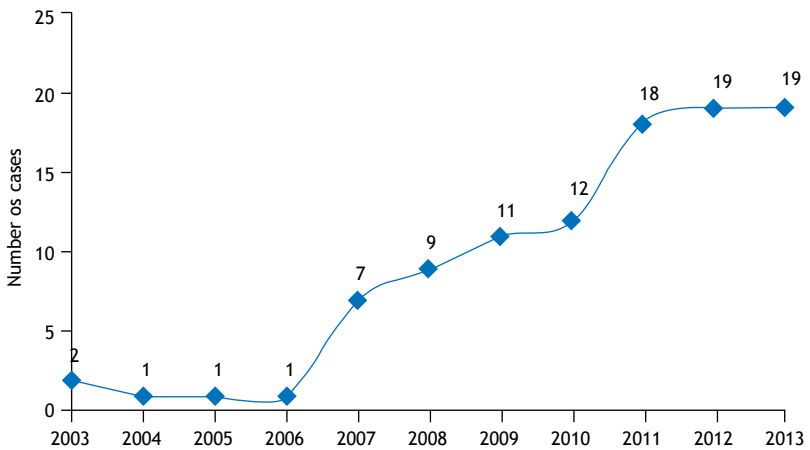

Figure 1. Number of nontuberculous mycobacterial lung disease cases per year (N = 100).

for the emergence of NTMLD. In the present study, these conditions were prevalent; however, in some cases of patients with bronchiectasis, we were unable to determine whether NTMLD was a sequel of the pre-existing lung condition or whether it was the initial illness.[4]

Disease triggered by mycobacteria is common in people with AIDS and low CD4 counts.[18] The state of Rio Grande do Sul has the second highest rate of HIV cases per capita (38.3 cases/100.000 population).[19] This might have contributed to the increase in NTMLD cases in this group of patients.

The results of the current study indicate that MAC was the most common NTM causing lung disease in the state. A higher prevalence of MAC was also found in studies carried out in other countries, such as the USA,[20] China,[21] and Australia.[22] In contrast, at the *Professor Hélio Fraga* Referral Center in the state of Rio de Janeiro, de Mello et al.[17] reported that 33.9% (59/174) of the patients with NTMLD were infected with *M. kansasii*.

In fact, Brazil exibits diversity in the prevalence of NTM species causing lung disease (Table 4).[17,23-25] The NTM species most commonly found in clinical samples in industrialized countries are MAC and *M. kansasii*.[26] Clinical and radiological signs of disease caused by *M. kansasii* are similar to those of post-primary tuberculosis,[27,28] and this species responds to antituberculosis treatment, leading to the late identification or the lack of a diagnosis of that species.[17] The most likely reason for the fact that NTMLD caused by MAC was more prevalent in the state of Rio Grande do Sul than in the state of Rio de Janeiro is the higher number of HIV-positive patients in the former state (24% vs. 9.8%).[17] Distinct study populations and methods limit the comparability of estimates.

The diagnostic criteria established by ATS/IDSA in 2007 for NTMLD[11] are the most used for therapeutic decision making and were met by 74% of the patients in the present study. Those criteria could not be wholly applied, because our sample included HIV-positive patients with low CD4 counts and severe respiratory symptoms, requiring immediate therapeutic intervention; in addition, there were symptomatic cases with radiologic findings in which we were unable to obtain a second sputum sample for the identification of the mycobacteria because of scarce sputum production. Also, some patients who were already on treatment were referred from other institutions without that identification.

Regarding cure, in addition to other factors, therapeutic success depends on the species that cause the lung disease: in our study, patients who

Table 3. Nontuberculous mycobacterium species identified in the patients with nontuberculous mycobacterial lung disease according to their HIV status (N = 100).

Species	HIV +	HIV −	HIV?	n
M. avium	15	6	5	26
M. intracellulare	7	0	2	9
M. kansasii	12	3	2	17
M. abscessus	7	0	5	12
M. fortuitum	4	0	0	4
M. gordonae	2	0	1	3
M. simiae	1	0	0	1
M. szulgai	2	0	0	2
Unidentified NTM	8	15	3	26

NTM: nontuberculous mycobacteria; and HIV?: HIV status not informed.

Table 4. Clinical and epidemiological studies about nontuberculous mycobacterial lung disease in Brazil.

Author	Brazilian state	Period	Patient, n	Male gender, %	Mean age, years	Predominant species	Met the criteria for NTMLD[a,b]
Matos et al.[23]	Bahia	1998-2003	19	68.4	48.8	*M. chelonae*/*M. abscessus*/ MAC/*M. kansasii*	14 (74.4)
Fusco da Costa et al.[25]	Pará	2010-2011	38	27.6	52	*M. massiliense*/*M. avium*/*M. intracellulare*	29 (76.3)
Lima et al.[24]	Rondônia	2008-2010	45	64.5	50	*M. abscessus*/*M. avium*/*M. fortuitum*	19 (46.7)
de Mello et al.[17]	Rio de Janeiro	1993-2011	174	72.1	55	*M. kansasii*/MAC/*M. abscessus*	101 (58)
Present study	Rio Grande do Sul	2003-2013	100	51.0	54.6	MAC/*M. kansasii*/*M. abscessus*	74 (74.0)

NTMLD: nontuberculous mycobacterial lung disease; and MAC: *Mycobacterium avium* complex.
[a]Values expressed as n (%). [b]In accordance with Griffith et al.[11]

met the ATS/IDSA criteria and were infected with MAC had a cure rate of 60.7%. Since rifampin started to be included in regimens, *M. kansasii* has become one of the most treatable causes of NTMLD.[3] In the present study, the cure rate of those infected with *M. kansasii* was 73.3%. The study by de Mello et al.[17] presented similar results for MAC (57.8%) and *M. kansasii* (71.4%) infections. The patients infected with *M. abscessus* met stability criteria in 70% of the cases. Lung disease caused by *M. abscessus* is difficult to treat; in some cases, complete cure of the disease cannot be achieved, and, therefore, clinical improvement is a more viable target, which is considered a favorable outcome for these patients.[11] In our sample, approximately 80% of rapidly growing mycobacteria isolates were identified as *M. abscessus*.

Another limitation of our study, which is an obstacle in the treatment of NTMLD, was the impossibility of performing susceptibility tests, which would help select the most appropriate treatment regimen for our patients.[11] Molecular identification of NTM species and susceptibility testing were not performed in our center, and the samples had to be sent to the Brazilian referral center in Rio de Janeiro. The molecular identification results were available at least two months later.

In Brazil, there are few studies about NTMLD, making it difficult to know its prevalence in the country. Most studies deal with NTM isolates, not with the prevalence of the disease. Table 4 shows a review of studies regarding NTMLD published in Brazil. Despite the shortage of data, MAC, *M. kansasii*, and *M. abscessus* are the most prevalent species in all studies available.

The lack of differentiation between *M. tuberculosis* and NTM makes the problem even more complicated. It is essential to know the specific etiology of the lung disease and its associated conditions in order to establish the appropriate treatment, considering the fact that each species requires a specific treatment regimen. Therefore, it is essential that culture, molecular identification, and susceptibility testing should be performed for all suspected NTMLD cases and that the reporting of NTMLD be mandatory so that the patients can be properly treated and the actual prevalence of the disease can be determined in Brazil.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the *Hospital Sanatório Partenon* and the *Instituto de Pesquisas Biológicas*, *Laboratório Central de Saúde Pública do Rio Grande do Sul*.

REFERENCES

1. Tortoli E. Impact of genotypic studies on mycobacterial taxonomy: the new mycobacteria of the 1990s. Clin Microbiol Rev. 2003;16(2):319-54. https://doi.org/10.1128/CMR.16.2.319-354.2003
2. Halstrom S, Price P, Thomson R. Review: Environmental mycobacteria as a cause of human infection. Int J Mycobacteriol. 2015;4(2):81-91. https://doi.org/10.1016/j.ijmyco.2015.03.002
3. Weiss CH, Glassroth J. Pulmonary disease caused by nontuberculous mycobacteria. Expert Rev Respir Med. 2012;6(6):597-612; quiz 613. https://doi.org/10.1586/ers.12.58
4. Sexton P, Harrison AC. Susceptibility to nontuberculous mycobacterial lung disease. Eur Respir J. 2008;31(6):1322-33 https://doi.org/10.1183/09031936.00140007
5. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881-6. https://doi.org/10.1164/rccm.201111-2016OC
6. Kennedy MP, O'Connor TM, Ryan C, Sheehan S, Cryan B, Bredin C. Nontuberculous mycobacteria: incidence in Southwest Ireland from 1987 to 2000. Respir Med. 2003;97(3):257-63. https://doi.org/10.1053/rmed.2003.1431
7. Freeman J, Morris A, Blackmore T, Hammer D, Munroe S, McKnight L. Incidence of nontuberculous mycobacterial disease in New Zealand. N Z Med J. 2007;120(1256):U2580.
8. Hernández-Garduño E, Rodrigues M, Elwood RK. The incidence of pulmonary non-tuberculous mycobacteria in British Columbia, Canada. Int J Tuberc Lung Dis. 2009;13(9):1086-93.
9. Daley CL, Griffith DE. Pulmonary non-tuberculous mycobacterial infections. Int J Tuberc Lung Dis. 2010;14(6):665-71.
10. Shenai S, Rodrigues C, Mehta A. Time to identify and define non-tuberculous mycobacteria in a tuberculosis-endemic region. Int J Tuberc Lung Dis. 2010;14(8):1001-8.
11. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416. https://doi.org/10.1164/rccm.200604-571ST
12. Wildner LM, Bazzo ML, Liedke SC, Nogueira CL, Segat G, Senna SG, et al. Mycobacteria mobility shift assay: a method for the rapid identification of Mycobacterium tuberculosis and nontuberculous mycobacteria. Mem Inst Oswaldo Cruz. 2014;109(3):356-61. https://doi.org/10.1590/0074-0276130458
13. Brasil. Ministério da Saúde [homepage on the Internet]. Brasília: o Ministério; 2016c [cited 2018 Jan 16]. Saúde de A a Z—Orientações para profissionais de saúde [about 6 screens]. Available from: http://portalms.saude.gov.br/saude-de-a-z/tuberculose/orientacoes-para-profissionais-de-saude
14. Taylor TB, Patterson C, Hale Y, Safranek WW. Routine use of PCR-restriction fragment length polymorphism analysis for identification of mycobacteria in liquid media. J Clin Microbiol. 1997;35(1):79-85.
15. Brunello F, Ligozzi M, Cristelli E, Bonora S, Tortoli E, Fontana R. Identification of 54 mycobacterial species by PCR-restriction fragment length polymorphism analysis of the hsp65 gene. J Clin Microbiol. 2001;39(8):2799-806. https://doi.org/10.1128/JCM.39.8.2799-2806.2001
16. Brasil. Ministério da Saúde. Secretária de Vigilância à Saúde. Perspectivas brasileiras para o fim da tuberculose como problema de saúde pública. Brasília: o Ministério. Boletim Epidemiológico. 2016;47(13):1-15.
17. de Mello KG, Mello FC, Borga L, Rolla V, Duarte RS, Sampaio EP, et al. Clinical and therapeutic features of pulmonary nontuberculous mycobacterial disease, Brazil, 1993-2011. Emerg Infect Dis. 2013;19(3):393-9.
18. Haas MK, Daley CL. Semin Respir Crit Care Med. 2016;37(2):230-42. https://doi.org/10.1055/s-0036-1572559
19. Brasil. Ministério da Saúde. Secretária de Vigilância à Saúde. AIDS e DSTs. Boletim Epidemiológico. 2015; Ano IV(1).
20. Prevots DR, Shaw PA, Strickland D, Jackson LA, Raebel MA, Blosky MA, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med. 2010;182(7):970-6. https://doi.org/10.1164/rccm.201002-0310OC
21. Jing H, Wang H, Wang Y, Deng Y, Li X, Liu Z, et al. Prevalence of nontuberculous mycobacteria infection, China, 2004-2009. Emerg Infect Dis. 2012;18(3):527-8. https://doi.org/10.3201/eid1803.110175
22. O'Brien DP, Currie BJ, Krause VL. Nontuberculous mycobacterial disease in northern Australia: a case series and review of the literature. Clin Infect Dis. 2000;31(4):958-67. https://doi.org/10.1086/318136
23. Matos ED, Santana MA, de Santana MC, Mamede P, de Lira Bezerra B, Panão ED, et al. Nontuberculosis mycobacteria at a multiresistant tuberculosis reference center in Bahia: clinical epidemiological aspects. Braz J Infect Dis. 2004;8(4):296-304. https://doi.org/10.1590/S1413-86702004000400005

24. Lima CA, Gomes HM, Oelemann MA, Ramos JP, Caldas PC, Campos CE, et al. Nontuberculous mycobacteria in respiratory samples from patients with pulmonary tuberculosis in the state of Rondônia, Brazil. Mem Inst Oswaldo Cruz. 2013;108(4):457-62. https://doi.org/10.1590/S0074-0276108042013010
25. Fusco da Costa AR, Falkinham JO 3rd, Lopes ML, Barretto AR, Felicio JS, Sales LH, et al. Occurrence of nontuberculous mycobacterial pulmonary infection in an endemic area of tuberculosis. PLoS Negl Trop Dis. 2013;7(7):e2340. https://doi.org/10.1371/journal.pntd.0002340
26. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med. 2015;36(1):13-34. https://doi.org/10.1016/j.ccm.2014.10.002
27. Christensen EE, Dietz GW, Ahn CH, Chapman JS, Murry RC, Anderson J, et al. Initial roentgenographic manifestations of pulmonary Mycobacterium tuberculosis, M kansasii, and M intracellularis infections. Chest. 1981;80(2):132-6. https://doi.org/10.1378/chest.80.2.132
28. Koh WJ, Kwon OJ, Lee KS. Nontuberculous mycobacterial pulmonary diseases in immunocompetent patients. Korean J Radiol. 2002;3(3):145-57. https://doi.org/10.3348/kjr.2002.3.3.145

J Bras Pneumol. 2018;44(2):112-117
http://dx.doi.org/10.1590/S1806-37562017000000201

ORIGINAL ARTICLE

Rapid molecular test for tuberculosis: impact of its routine use at a referral hospital

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Submitted: 15 June 2017.
Accepted: 7 December 2017.

Study carried out at the Octávio Mangabeira Specialized Hospital, Bahia State Health Department, Salvador (BA) Brazil.

ABSTRACT

Objective: To evaluate the impact of the use of the molecular test for *Mycobacterium tuberculosis* and its resistance to rifampin (Xpert MTB/RIF), under routine conditions, at a referral hospital in the Brazilian state of Bahia. **Methods:** This was a descriptive study using the database of the Mycobacteriology Laboratory of the Octávio Mangabeira Specialized Hospital, in the city of Salvador, and georeferencing software. We evaluated 3,877 sputum samples collected from symptomatic respiratory patients, under routine conditions, between June of 2014 and March of 2015. All of the samples were submitted to sputum smear microscopy and the Xpert MTB/RIF test. Patients were stratified by gender, age, and geolocation. **Results:** Among the 3,877 sputum samples evaluated, the Xpert MTB/RIF test detected *M. tuberculosis* in 678 (17.5%), of which 60 (8.8%) showed resistance to rifampin. The Xpert MTB/RIF test detected *M. tuberculosis* in 254 patients who tested negative for sputum smear microscopy, thus increasing the diagnostic power by 59.9%. **Conclusions:** The use of the Xpert MTB/RIF test, under routine conditions, significantly increased the detection of cases of tuberculosis among sputum smear-negative patients.

Keywords: Tuberculosis/diagnosis; Molecular diagnostic techniques; Sputum.

INTRODUCTION

In 2010, the World Health Organization endorsed the use of the Xpert MTB/RIF molecular test (Cepheid Inc., Sunnyvale, CA, USA) for the diagnosis of tuberculosis. The Xpert MTB/RIF test is a molecular test, based on polymerase chain reaction, which detects *Mycobacterium tuberculosis* DNA and, simultaneously, resistance to rifampin, within two hours.[1] Following the recommendation of the World Health Organization, many countries have incorporated this technology into the tuberculosis diagnostic routine, replacing sputum smear microscopy.[2] Although many studies have shown the high sensitivity and specificity of this test in the diagnosis of tuberculosis and in the detection of rifampin resistance,[3-8] it is relevant to evaluate its routine use in local programs, considering that many logistical and health system barriers can influence the impact of this test on patient care. In Brazil, limited access to health care and poor patient perception of the symptoms were identified as important factors for delayed diagnosis and consequently for a delay in the initiation of treatment.[9] Until July of 2014, the diagnosis of tuberculosis in Brazil was based on the clinical-radiological profile and on phenotypic tests (sputum smear microscopy and culture for mycobacteria).[10] However, the Brazilian scientific community had for some time emphasized the need for the incorporation of new diagnostic technologies into the Brazilian public health system, including genotypic tests for pulmonary and extrapulmonary tuberculosis.[11-13] A survey involving tuberculosis experts worldwide demonstrated the high acceptability of new rapid tests for the diagnosis of tuberculosis and the widespread use of the Xpert MTB/RIF test (reported by 46.7% of interviewees).[14]

A pragmatic clinical trial, conducted in two Brazilian cities (Rio de Janeiro and Manaus), showed the feasibility of the routine use of the Xpert MTB/RIF test in the National Tuberculosis Control Program in a country of continental dimensions and immense regional differences in the organization and quality of health care services. In that

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Financial support: None

ISSN 1806-3713

study, Durovni et al.[15] observed a 59% increase in the rate of cases with laboratory confirmation and a reduction in the time to treatment initiation (from 11 to 8 days). In addition, some studies conducted in Brazil have demonstrated that the Xpert MTB/RIF test is a cost-effective diagnostic strategy for tuberculosis.[16,17]

In September of 2013, the Xpert MTB/RIF test was approved by the National Committee for Health Technology Incorporation for use in the Brazilian Unified Health Care System.[18] The use of this test in Brazil was initiated by the Brazilian National Ministry of Health (NMH) in July of 2014, and the Rapid Molecular Testing Network for Tuberculosis was created. Since then, the National Tuberculosis Control Program has distributed 160 Xpert MTB/RIF systems throughout the country, priority being given to all state capitals and the Federal District of Brasília, as well as to host cities of prisons, border towns, and municipalities with more than 130 cases of tuberculosis per year.[19]

In 2014, 69,262 new cases of tuberculosis were reported in Brazil, with an incidence coefficient of 33.5 cases/100,000 population. Among all Brazilian states, Bahia ranks third in terms of the burden of tuberculosis, with 4,833 new cases reported in 2014 (32 cases/100,000 population).[20] The state of Bahia received 5 GeneXpert MTB/RIF systems from the NMH in 2014, 3 of which were allocated to the *Hospital Especializado Otávio Mangabeira* (HEOM, Octávio Mangabeira Specialized Hospital), located in the city of Salvador. In the context of operational research, the present study evaluated the impact of using the Xpert MTB/RIF test under routine conditions at a referral center for tuberculosis in Bahia.

METHODS

The research was conducted in the mycobacteriology laboratory of the HEOM, a tertiary referral hospital for tuberculosis and belonging to the state public network. The HEOM has hospital wards and an outpatient care clinic, serving patients from the capital and from the state at large. Due to the operational difficulties of making a diagnosis based on laboratory test results within the local primary care network, approximately 37% of tuberculosis cases in Salvador are diagnosed at the HEOM laboratory (State Tuberculosis Control Program, unpublished data). The HEOM laboratory makes Xpert MTB/RIF test results available on the day of collection, and there is a routine return flow of these results to the various hospital sectors.

This was a laboratory-based retrospective descriptive study, conducted in the context of operational research, under routine conditions. The information was obtained using the database of the HEOM mycobacteriology laboratory and stored in the Microsoft Excel program.

The sample consisted of patients who underwent the Xpert MTB/RIF test and sputum smear microscopy, from the same sputum sample, between June 10, 2014 and March 31, 2015. The study focused on the performance of the two different methodologies, carried out under routine laboratory conditions, following algorithms recommended by the NMH[19] in the scenario of a referral center in Bahia.

Tuberculosis cases were georeferenced as to their spatial distribution and demographic incidence. The objective was to process the data as geographic information, to support the planning and health management of the referral center in question. We used the geodetic reference system currently in use in Brazil, known as the Geocentric Reference System for the Americas 2000, which allows the direct use of the Global Navigation Satellite Systems technology. To generate the thematic map, we used the kernel method. On the map, the point intensity of certain phenomena is plotted across the study region.[21]

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as absolute and relative frequencies. The agreement between the results of the semiquantitative Xpert MTB/RIF test and sputum smear microscopy was calculated using weighted kappa statistics. Data were analyzed using the GraphPad Prism program, version 5.01 (GraphPad Inc., San Diego, CA, USA).

Ethical aspects

This study was approved by the Research Ethics Committee of the Bahia School of Medicine and Public Health of the Bahia Foundation for the Advancement of Science (Protocol no. 119/2008, addendum in 2011). Data confidentiality and anonymity of the patients were assured in the design and database handling.

RESULTS

During the study period (between June of 2014 and March of 2015), 19,117 tests (sputum smear microscopy, culture for mycobacteria, and the Xpert MTB/RIF test) were performed in the HEOM mycobacteriology laboratory for the diagnosis of suspected cases and follow-up of cases of tuberculosis. We identified 3,877 patients in whom the Xpert MTB/RIF test and sputum smear microscopy were performed simultaneously in the same sputum sample. The mean age of the study population was 41.5 ± 15.4 years, and males predominated (accounting for 67.1% of the sample).

Among the 3,877 patients evaluated, positive results on sputum smear microscopy and the Xpert MTB/RIF test were observed in 424 (10.9%) and 678 (17.5%), respectively (Table 1). The Xpert MTB/RIF test detected positivity for tuberculosis in 254 patients who tested negative on sputum smear microscopy, a diagnostic gain of 59.9%.

A positive result on the Xpert MTB/RIF test is available on its platform in four levels of semiquantitative detection: very low, low, medium, and high. However, the result of the sputum smear microscopy is categorized in the routine of the facility as negative, positive (1-9 bacilli/100 fields examined), 1+, 2+, or 3+. Table 2

shows the correlation between the semiquantitative Xpert MTB/RIF test results and the bacillary load in the sputum smear microscopy examination. All 424 sputum samples testing positive on sputum smear microscopy also tested positive on the Xpert MTB/RIF test. Of the 189 Xpert MTB/RIF test results classified as very low positivity, 175 (92.6%) tested negative on sputum smear microscopy. Of the 245 Xpert MTB/RIF test results classified as low positivity, 169 (68.9%) were categorized as 1+ on sputum smear microscopy. Of the 57 Xpert MTB/RIF test results classified as medium positivity, 54 (94.5%) were categorized as 1+ or 2+ on sputum smear microscopy. Of the 187 Xpert MTB/RIF test results classified as high positivity, 142 (75.9%) were categorized as 3+ on sputum smear microscopy. The statistical analysis showed a strong correlation between the semiquantitative Xpert MTB/RIF test results and the sputum smear microscopy results (weighted kappa = 0.82).

The reports of 175 cases in which the Xpert MTB/RIF test result was positive and the sputum smear microscopy result was negative were later reviewed in the Brazilian Case Registry Database. Of those 175 cases, 146 (83.4%) were new cases and 29 (16.6%) were identified as cases of retreatment (presence of one or more reports prior to the date of the two tests). Of the 29 cases of retreatment, 10 had positive cultures recorded, confirming active tuberculosis, records of the culture results being unavailable for the remaining 19. Among the 175 patients with positive results on the Xpert MTB/RIF test and negative results on sputum smear microscopy, there were 19 cases (10.9%) in which it was not possible to confirm the presence of active tuberculosis.

Among the 424 patients with positive sputum smear microscopy results, the Xpert MTB/RIF test result was classified as "undetectable", suggesting the presence of nontuberculous mycobacteria, in 9 (2.1%).

Of the 678 cases confirmed by the Xpert MTB/RIF test (new cases and cases of retreatment), 60 (8.8%) presented rifampin resistance (Table 3). Patients infected with rifampin-resistant strains were referred to the HEOM tertiary referral outpatient clinic for follow-up.

Analysis of the spatial distribution of the incidence of tuberculosis in the study population by subdistricts of the city of Salvador showed a higher concentration of cases in the eastern region of the city, in the subdistricts of Santo Antônio and São Caetano (Figure 1).

DISCUSSION

In the present study, conducted under routine laboratory conditions at a tertiary referral hospital for tuberculosis in Bahia, the Xpert MTB/RIF test detected 254 cases of tuberculosis that tested negative on sputum smear microscopy, representing a 59.9% gain in the rate of biologically confirmed diagnosis. Wide variability in the proportion of diagnostic gain was observed in several published studies comparing the two methods.[22-25] In a study conducted in Rwanda, in which both methods were applied in the same group of patients, Ngbonziza et al. found a 32.3% gain in diagnostic power,[22] whereas Cowan et al. reported a 69.0% diagnostic gain in a study conducted in Mozambique.[23] In a population of 401 HIV-infected individuals in Cambodia, Auld et al.[24] reported a diagnostic gain of only 26.0% attributed to the use of the Xpert MTB/RIF test. Evaluating routine program data in 18 countries, Ardizzoni et al.[25] observed that the use of the Xpert MTB/RIF test resulted in a mean relative diagnostic gain of 42.3% over the use of sputum smear microscopy. However, those authors pointed out the wide variation in the diagnostic gain,

Table 1. Distribution of Xpert MTB/RIF test and sputum smear microscopy results at Octávio Mangabeira Specialized Hospital, in the city of Salvador, Brazil, between June of 2014 and March of 2015 (N = 3,877).[a]

Result	Sputum smear microscopy	Xpert MTB/RIF test
Positive	424 (10.9)	678 (17.5)
Negative	3,453 (89.1)	3,199 (82.5)
Total	3,877 (100%)	3,877 (100%)

[a]Values expressed as n (%).

Table 3. Resistance to rifampin detected by the Xpert MTB/RIF test at Octávio Mangabeira Specialized Hospital, in the city of Salvador, Brazil, between June of 2014 and March of 2015 (N = 678).

Response to rifampin	n	%
Resistant	60	8.8
Sensitive	618	91.2
Total	678	100

Table 2. Correlation between the results of the semiquantitative Xpert MTB/RIF test and those of sputum smear microscopy (N = 678).[a,*]

Sputum smear microscopy	Xpert MTB/RIF test				
Results	Very low	Low	Medium	High	Total
Negative	175 (92.6)	76 (31)	3 (5.3)	0	254 (37.5)
Positive[b]	14 (7.4)	0	0	0	14 (2.0)
1+	0	169 (69)	15 (26.3)	0	184 (27.1)
2+	0	0	39 (68.4)	45 (24.1)	84 (12.4)
3+	0	0	0	142 (75.9)	142 (30.0)
Total	189 (100)	245 (100)	57 (100)	187 (100)	678 (100)

[a]Values expressed as n (%). [b]1-9 bacilli/100 fields). *Weighted kappa = 0.82 (strong agreement).

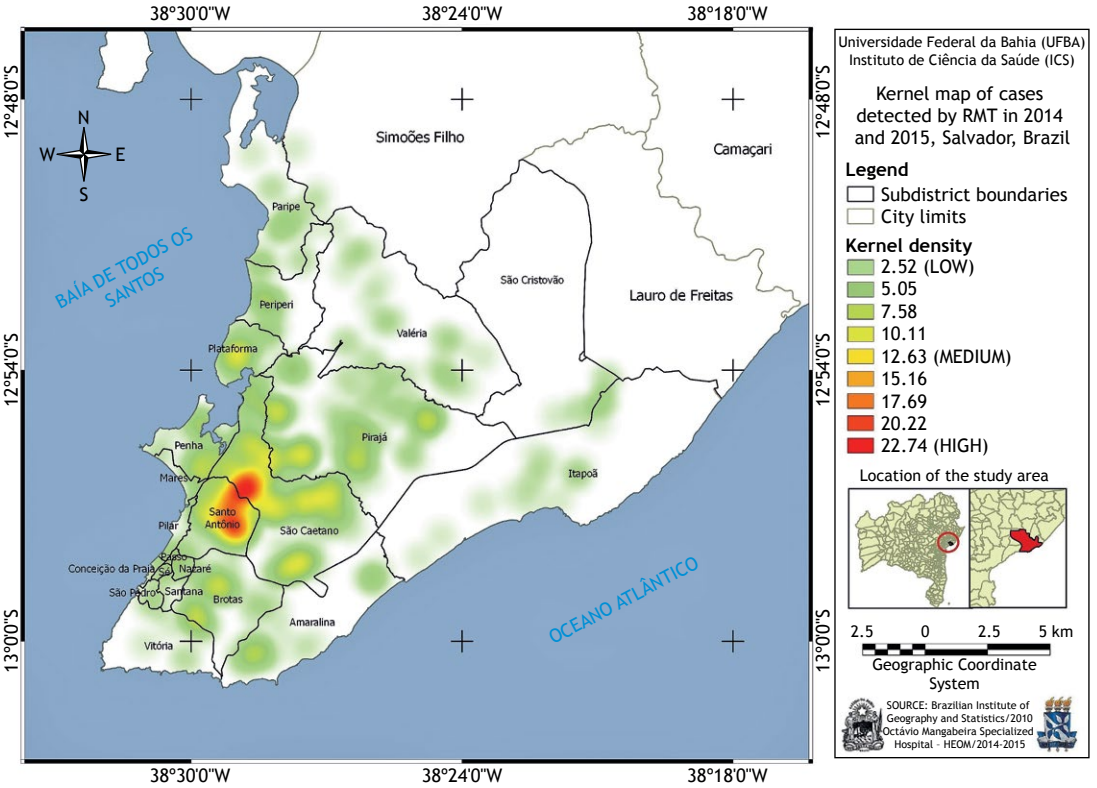

Figure 1. Map of the city of Salvador, Brazil, generated with the kernel method, indicating the spatial distribution of tuberculosis cases diagnosed by a rapid molecular test (RMT)—the Xpert MTB/RIF test—during the study period.

which ranged from 9.7% to 110%, among various countries.[25] Those differences were attributed to different epidemiological scenarios among the countries evaluated and the heterogeneity among the studies in terms of the methodologies used.

In a clinical trial conducted in two Brazilian cities where the incidence of tuberculosis is high (Rio de Janeiro and Manaus), during the trial period prior to the incorporation of the Xpert MTB/RIF test into the public health care system, Durovni et al.[15] reported that the use of the new test resulted in a 59% increase in rate of bacteriologically confirmed diagnosis. The authors compared baseline data (collected when diagnosis was performed using conventional sputum smear microscopy in two samples) with those collected after the Xpert MTB/RIF test had replaced sputum smear microscopy. Therefore, the methodology used differed from that used in the present study, in which the same group of patients performed concomitant tests (sputum smear microscopy and Xpert MTB/RIF). Although the present study was carried out under routine conditions and with a different methodology, our results corroborate those of Durovni et al.[15]

There are some potential explanations for the wide variability across studies in terms of the proportional diagnostic gain achieved with the Xpert MTB/RIF test in comparison with sputum smear microscopy. First, epidemiological contexts differ among regions, with heterogeneous rates of tuberculosis incidence. Another plausible explanation is that the sensitivity of sputum smear microscopy varies among laboratories and geographic locations, as well as that the quality of the results of the examination is highly dependent on the training of the professionals responsible. Therefore, in laboratories where the sensitivity of sputum smear microscopy is low, the relative diagnostic gain achieved with the Xpert MTB/RIF test might be artificially high. Our study was carried out at a tertiary referral center for tuberculosis, where the laboratory professionals are periodically trained by the NMH to perform sputum smear microscopy.

Although there have been few studies of the topic, the semiquantitative results of the Xpert MTB/RIF test estimate the bacterial load by measuring the real-time polymerase chain reaction threshold cycle. The bacterial load can be an elementary biomarker for evaluation of disease severity, risk of transmission, and therapeutic response.[26] In our study, we observed a strong correlation between the sputum smear microscopy results and those of the semiquantitative Xpert MTB/RIF test (weighted kappa = 0.82), similar to that observed in a multicenter study.[27] In the absence of culture results (as was the case for a considerable proportion of cases in the present study) or in the waiting period for the release of the test results, the Xpert MTB/RIF semiquantitative test result (especially in cases with low positivity) can be useful in the identification of cases of active tuberculosis in patients not previously

treated for tuberculosis with consistent clinical and radiological findings. In the present study, we found that 175 (92.6%) of the 189 Xpert MTB/RIF tests in which the results were classified as very low positivity were in samples that tested negative on sputum smear microscopy. It is likely that the quantification of the Xpert MTB/RIF test results represents an important tool in the early identification of the subset of potentially infectious patients, even before the culture result for mycobacteria is known. However, in cases of retreatment, these data should be interpreted with caution, and it is advisable to wait for the result of the culture before initiating treatment, because the Xpert MTB/RIF test could produce a false positive result.

Resistance to rifampin was observed in 8.8% of the cases evaluated in the present study. In the previously mentioned pragmatic clinical trial conducted in Brazil, Durovni et al.[15] found that rate to be 3.8% overall (3.3% among new cases and 7.5% among cases of retreatment). The greater proportion of cases of rifampin resistance found in our study can be explained by certain factors. First, there were methodological differences between the two studies, which also had different designs. Second, because our study was performed at a tertiary referral hospital for tuberculosis, it is possible that there was a selection bias, although our hospital also conducts tests for the primary care network. However, data from the NMH Rapid Molecular Testing Network for Tuberculosis monitoring during the first year of its implementation (between June of 2014 and May of 2015) showed higher proportions of rifampin resistance, similar to those found in our study, in Brazil as a whole and in the state of Bahia—in 4.6% and 7.2% of new cases, respectively, and in 13.9% and 17.7% of cases of retreatment, respectively.[28]

The Xpert MTB/RIF test has high specificity for the detection of rifampin resistance (98%), already well established in previous studies.[6,29] Trajman et al.[30] showed that the test has a high positive predictive value for rifampin resistance (90.2%), even in countries where the prevalence of drug-resistant tuberculosis is relatively low. Those authors also demonstrated that 82% of the rifampin-resistant cases detected by the Xpert MTB/RIF test were confirmed as cases of multidrug-resistant tuberculosis in a phenotypic sensitivity test.[30] Therefore, although our sample might not have been representative of the true proportion of resistance in the state, the detection of rifampin resistance in 8.8% of the cases indicates that the Xpert MTB/RIF test can facilitate the early identification of cases of multidrug-resistant tuberculosis in Brazil.

The highest density of cases detected in the georeferencing of the subdistricts of Santo Antônio and São Caetano, in the city of Salvador, can be attributed to the proximity of these regions to the HEOM. Another aspect to be considered is the fact that these two subdistricts are located in the historical center and São Caetano/Valéria health districts, respectively, which present high rates of tuberculosis incidence.

Our study has a number of limitations. Such limitations include the retrospective design, as well as the fact that the study was laboratory-based and was carried out at a tertiary referral hospital for tuberculosis. In addition, some weaknesses in data collection at the beginning of the implementation of the Xpert MTB/RIF test at the HEOM prevented us from adequately identifying new cases and cases of retreatment, constituting a limitation related to drawing comparisons with other studies. In settings with a high prevalence of tuberculosis, one of the major limitations of the Xpert MTB/RIF test is the possibility of a false-positive result in patients who have had active disease and been cured, because the genetic material can be detected in the sputum of such individuals. Another important limitation of our study is the small proportion of cultures performed, thus preventing us from resolving questions related to the presence or absence of active tuberculosis, especially in cases of retreatment. However, our review of the reports of the 175 cases with positive results on the Xpert MTB/RIF test and negative results on sputum smear microscopy, in the Brazilian Case Registry Database, showed that there were only 19 cases (10.9%) in which it was not possible to confirm active tuberculosis, which could theoretically correspond to the possibility of false-positive results on the Xpert MTB/RIF test. Especially in cases of retreatment, a positive result on the Xpert MTB/RIF test (which could represent a false-positive result) should be interpreted with caution and the importance of culturing mycobacteria should be emphasized in tuberculosis training for health professionals. Nevertheless, we should also draw attention to cases of positive sputum smear microscopy results and a result of "undetectable" on the Xpert MTB/RIF test in the same sputum sample (as occurred in 2.1% of our cases), which could represent the presence of nontuberculous mycobacteria, indicating the need to continue research with culture and species identification.

In conclusion, the introduction of the use of the Xpert MTB/RIF test under routine conditions contributed significantly to the increased detection of tuberculosis cases in patients with negative sputum smear microscopy results, thereby increasing the rate of treatment of active tuberculosis in patients not diagnosed by sputum smear microscopy.

REFERENCES

1. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. Geneva, Switzerland: World Health Organization, 2011.
2. World Health Organization. Global tuberculosis report 2014. Geneva, Switzerland: World Health Organization; 2014.
3. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010;363(11):1005-15. https://doi.org/10.1056/NEJMoa0907847

4. Lawn SD, Nicol MP. Xpert MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol. 2011;6(9):1067-82. Erratum in: Future Microbiol. 2012;7(8):1024. https://doi.org/10.2217/fmb.11.84
5. Chang K, Lu W, Wang J, Zhang K, Jia S, Li F, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect. 2012;64(6):580-8. https://doi.org/10.1016/j.jinf.2012.02.012
6. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011;377(9776):1495-505. https://doi.org/10.1016/S0140-6736(11)60438-8
7. Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, et al. A diagnostic accuracy study of Xpert MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One. 2012;7(9):e44626. https://doi.org/10.1371/journal.pone.0044626
8. Yoon C, Cattamanchi A, Davis JL, Worodria W, den Boon S, Kalema N, et al. Impact of Xpert MTB/RIF testing on tuberculosis management and outcomes in hospitalized patients in Uganda. PLoS One. 2012;7(11):e48599. https://doi.org/10.1371/journal.pone.0048599
9. Maior Mde L, Guerra RL, Cailleaux-Cezar M, Golub JE, Conde MB. Time from symptom onset to the initiation of treatment of pulmonary tuberculosis in a city with a high incidence of the disease. J Bras Pneumol 2012;38(2):202-9.
10. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin P de T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48. https://doi.org/10.1590/S1806-37132009001000011
11. Telles MA, Menezes A, Trajman A. Bottlenecks and recommendations for the incorporation of new technologies in the tuberculosis laboratory network in Brazil. J Bras Pneumol. 2012;38(6):766-70. https://doi.org/10.1590/S1806-37132012000600013
12. Furini AA, Pedro Hda S, Rodrigues JF, Montenegro LM, Machado RL, Franco C, et al. Detection of Mycobacterium tuberculosis complex by nested polymerase chain reaction in pulmonary and extrapulmonary specimens. J Bras Pneumol. 2013;39(6):711-8. https://doi.org/10.1590/S1806-37132013000600010
13. Barreto LB, Lourenço MC, Rolla VC, Veloso VG, Huf G. Use of amplified Mycobacterium tuberculosis direct test in respiratory samples from HIV-infected patients in Brazil. J Bras Pneumol. 2014;40(2):148-54. https://doi.org/10.1590/S1806-37132014000200008
14. Amicosante M, D'Ambrosio L, Munoz M, Mello FCQ, Tebruegge M, Chegou NN, et al. Current use and acceptability of novel diagnostic tests for active tuberculosis: a worldwide survey. J Bras Pneumol. 2017;43(5):380-392. https://doi.org/10.1590/s1806-37562017000000219
15. Durovni B, Saraceni V, Van Den Hof S, Trajman A, Cordeiro-Santos M, Cavalcante S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: a stepped-wedge cluster-randomized trial. PLoS Med. 2014;11(12):e1001766. https://doi.org/10.1371/journal.pmed.1001766
16. da Silva Antunes R, Pinto M, Trajman A. Patient cost for the diagnosis of tuberculosis in Brazil: comparison of Xpert MTB/RIF and smear microscopy. Int J Tuberc Lung Dis. 2014;18(5):547-51. https://doi.org/10.5588/ijtld.13.0637
17. Pinto M, Trajman A, Steffen R, Entringer AP. Cost analysis of nucleic acid amplification for diagnosing pulmonary tuberculosis, within the context of the Brazilian Unified Health Care System. J Bras Pneumol. 2015;41(6):536-8. https://doi.org/10.1590/s1806-37562015000004524
18. Brasil. Ministério da Saúde. Biblioteca Virtual em Saúde [homepage on the Internet]. Brasília: o Ministério; [cited 2016 Aug 22]. Portaria MS no. 48 de 10 de setembro de 2013. Available from: http://www.bvsms.saude.gov.br/bvs/saudelegis/sctie/2013/prt0048_10_09_2013.html
19. Brasil. Ministério da Saúde. Secretaria de Vigilância à Saúde. Recomendações sobre o diagnóstico da tuberculose por meio do teste rápido molecular para tuberculose: nota informativa no. 9. Brasília: Ministério da Saúde; 2014.
20. Bahia. Secretaria Estadual de Saúde. Superintendência de Vigilância em Saúde. Sistema de Informação de Agravos de Notificação [homepage on the Internet]. Salvador: a Secretaria [cited 2017 Aug 11]. Casos de tuberculose notificados no SINAN – Bahia. Available from: http://www3.saude.ba.gov.br/cgi/deftohtm.exe?sinan/tube.def
21. Oliveira EXG, Silveira Jr JC, Souza-Santos R, Pina MF, Portugal JL. Análise de dados espaciais. In: Santos S, Souza-Santos R, editors. Sistemas de informações geográficas e análise espacial na saúde pública. Brasília: Ministério da Saúde, Fundação Oswaldo Cruz; 2017.
22. Ngabonziza JC, Ssengooba W, Mutua F, Torrea G, Dushime A, Gasana M, et al. Diagnostic performance of smear microscopy and incremental yield of Xpert in detection of pulmonary tuberculosis in Rwanda. BMC Infect Dis. 2016;16(1):660. https://doi.org/10.1186/s12879-016-2009-x
23. Cowan J, Michel C, Manhiça I, Monivo C, Saize D, Creswell J, et al. Implementing rapid testing for tuberculosis in Mozambique. Bull World Health Organ. 2015;93(2):125-30. https://doi.org/10.2471/BLT.14.138560
24. Auld SC, Moore BK, Kyle RP, Eng B, Nong K, Pevzner ES, et al. Mixed impact of Xpert() MTB/RIF on tuberculosis diagnosis in Cambodia. Public Health Action. 2016;6(2):129-35. https://doi.org/10.5588/pha.16.0001
25. Ardizzoni E, Fajardo E, Saranchuk P, Casenghi M, Page AL, Varaine F, et al. Implementing the Xpert MTB/RIF Diagnostic Test for Tuberculosis and Rifampicin Resistance: Outcomes and Lessons Learned in 18 Countries PLoS One. 2015;10(12):e0144656. https://doi.org/10.1371/journal.pone.0144656
26. Opota O, Senn L, Prod'hom G, Mazza-Stalder J, Tissot F, Greub G, et al. Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country. Clin Microbiol Infect. 2016;22(7):613-9. https://doi.org/10.1016/j.cmi.2016.04.010
27. Blakemore R, Nabeta P, Davidow AL, Vadwai V, Tahirli R, Munsamy V, et al. A multisite assessment of the quantitative capabilities of the Xpert MTB/RIF assay. Am J Respir Crit Care Med. 2011;184(9):1076-84. https://doi.org/10.1164/rccm.201103-0536OC
28. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Rede de Teste Rápido para Tuberculose no Brasil – Primeiro ano de implantação. Brasília: Ministério da Saúde; 2015.
29. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2014;(1):CD009593. https://doi.org/10.1002/14651858.CD009593.pub3
30. Trajman A, Durovni B, Saraceni V, Cordeiro-Santos M, Cobelens F, Van den Hof S. High positive predictive value of Xpert in a low rifampicin resistance prevalence setting. Eur Respir J. 2014;44(6):1711-13. https://doi.org/10.1183/09031936.00115514

J Bras Pneumol. 2018;44(2):118-124
http://dx.doi.org/10.1590/S1806-37562017000000316

ORIGINAL ARTICLE

Predictors of mortality among intensive care unit patients coinfected with tuberculosis and HIV

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Submitted: 2 September 2017.
Accepted: 14 January 2018.

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ABSTRACT

Objective: To identify factors predictive of mortality in patients admitted to the ICU with tuberculosis (TB)/HIV coinfection in the Manaus, Amazon Region. **Methods:** This was a retrospective cohort study of TB/HIV coinfected patients over 18 years of age who were admitted to an ICU in the city of Manaus, Brazil, between January of 2011 and December of 2014. Sociodemographic, clinical, and laboratory variables were assessed. To identify factors predictive of mortality, we employed a Cox proportional hazards model. **Results:** During the study period, 120 patients with TB/HIV coinfection were admitted to the ICU. The mean age was 37.0 ± 11.7 years. Of the 120 patients evaluated, 94 (78.3%) died and 62 (66.0%) of those deaths having occurred within the first week after admission. Data on invasive mechanical ventilation (IMV) and ARDS were available for 86 and 67 patients, respectively Of those 86, 75 (87.2%) underwent IMV, and, of those 67, 48 (71.6%) presented with ARDS. The factors found to be independently associated with mortality were IMV (p = 0.002), hypoalbuminemia (p = 0.013), and CD4 count < 200 cells/mm^3 (p = 0.002). **Conclusions:** A high early mortality rate was observed among TB/HIV coinfected ICU patients. The factors predictive of mortality in this population were IMV, hypoalbuminemia, and severe immunosuppression.

Keywords: Mycobacterium tuberculosis; Critical care; Respiration, artificial; Acquired immunodeficiency syndrome.

INTRODUCTION

Among communicable diseases, tuberculosis (TB) is the leading cause of death worldwide. In 2015, there were an estimated 10.4 million new TB cases and 1.8 million deaths worldwide, 400,000 of which occurred among HIV-infected individuals.[1] The reported incidence of TB in Brazil was 32.4 cases per 100,000 population in 2016, with 2.2 TB-related deaths per 100,000 population in 2015. Of the 66,796 new TB cases in Brazil in 2015, 6.8% were cases of TB/HIV coinfection. In 2016, the incidence of TB in Brazil was highest in the state of Amazonas, with 67.2 cases per 100,000 population and a mortality rate of 3.2 per 100,000 population. In the city of Manaus, which is the capital of the state of Amazonas and where 50% of the state population is concentrated, there were 93.2 cases per 100,000 population and 3.5 deaths per 100,000 population in 2016.[2]

Previous studies have shown that people living with HIV are 30 times more likely to develop infection with TB and progress to active disease than are individuals who do not have HIV, which increases the risk of latent TB reactivation up to 20-fold.[3] In TB/HIV coinfected individuals, the virus weakens the host immune response to *Mycobacterium tuberculosis* (*Mtb*), resulting in a more dramatic progression.[4]

Because of immunosuppression, TB is frequently paucibacillary in HIV-infected individuals, meaning that diagnosis and treatment are often delayed.[5] Admission to the ICU is required in 1-3% of cases, invasive mechanical ventilation (IMV) being required in 1.5%.[6] Patients coinfected with TB and HIV usually develop pulmonary lesions accompanied by intrapulmonary shunt and hypoxemic respiratory failure.[7]

Case-fatality rates are notoriously high in TB/HIV coinfected patients, ranging from 22.4% to 67%.[6,8-21] In patients coinfected with TB and HIV, death has been associated with the following: IMV; miliary (i.e., disseminated) TB; renal replacement therapy; use of vasoactive drugs; low Glasgow Coma Scale scores; high Simplified Acute Physiology Score II; high Acute

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado do Amazonas* (FAPEAM, Foundation for the Support of Research in the State of Amazonas).

ISSN 1806-3713

Physiology And Chronic Health Evaluation II (APACHE II) scores; high Sequential Organ Failure Assessment scores; lymphopenia; concomitant nontuberculous mycobacterial infection; organ failure; sepsis; and hypoalbuminemia.[8,11-13,16,18-21]

Only a few studies have assessed case-fatality rates in patients with severe TB,[6,10,12,15,17-21] and most had a small sample (of < 100 patients) and were retrospective in design. Prospective studies have focused on investigating ICU patients with TB (n = 83, 44 of whom were coinfected with HIV)[12] or predicting survival among HIV-infected patients (n = 125, 58 of whom were coinfected with TB).[19] There is a lack of studies investigating ICU patients with severe TB/HIV coinfection. In a retrospective study involving a small sample (of 12 patients), the reported mortality was 58.3%.[15]

Since 2004, strategies to minimize the impact of TB/HIV coinfection and improve the treatment of TB/HIV coinfected patients have been adopted, including improved integration between TB and HIV programs and early antiretroviral therapy (ART) to reduce the viral load in patients with a presumptive diagnosis of TB.[22] In the present study, we sought to describe the clinical features of a large cohort of severe TB/HIV coinfected patients admitted to the ICU of a referral hospital in the city of Manaus, Brazil, as well as to identify factors predictive of mortality in that population.

METHODS

This was a retrospective cohort study of TB/HIV coinfected patients admitted to the ICU of a referral hospital for infectious diseases in the city of Manaus, Brazil, between January of 2011 and December of 2014. The study was approved by the local research ethics committee in August of 2014 (Protocol no. CAAE 34073314.3.0000.0005).

HIV-infected patients who were 18 years of age or more and who were diagnosed with TB were included in the study. For a diagnosis of active TB, at least two of the following criteria had to be met[11]: a) two AFB-positive sputum smears; b) one positive *Mtb* culture; c) chest X-ray findings suggestive of TB; and d) postmortem histopathological findings of TB granuloma, caseous necrosis, or AFB. ARDS was defined as low PaO_2/FiO_2, recent appearance of bilateral pulmonary infiltrates, and no clinical evidence of left atrial hypertension.[23]

All of the HIV-infected patients who were included in the present study had serologically confirmed HIV infection, in accordance with the criteria established by the Brazilian National Ministry of Health.[24] The microbiology laboratory in which the tests were performed is quality-controlled within the World Health Organization (WHO) scheme for external quality assurance.

Patients who habitually smoked cigarettes were classified as smokers regardless of the number of cigarettes smoked per day. Alcoholism was defined as consumption of ≥ 60 g of pure alcohol on at least one single occasion at least monthly, in accordance with the WHO criteria.[25] Drug use was defined as use of ecstasy, cocaine, heroin, cannabis, or any combination of the four in the last 12 months.

Sociodemographic and clinical data were collected from the electronic medical records of the participating patients. Laboratory data regarding Xpert MTB/RIF test results, smear microscopy results, *Mtb* culture results, and autopsy findings were collected from the laboratory database. All chest X-rays were assessed with IMPAX digital imaging software, version 1.0 build 1.0389 (Agfa HealthCare, Mortsel, Belgium) and reviewed by the same radiologist, who was unaware of the clinical outcomes.

Age, gender, smoking status, alcohol use, illicit drug use, fever, cough, weight loss, diarrhea, dyspnea, opportunistic infections, and comorbidities were analyzed. Time to anti-TB treatment initiation, therapeutic regimen, ART, time to ICU discharge, and ICU clinical outcome (discharge to the ward or death) were also analyzed.

Glasgow Coma Scale and APACHE II scores were used in order to assess the level of consciousness and prognosis in the ICU. Laboratory parameters included hemoglobin levels, leukocyte count, lymphocyte count, platelet count, albumin levels, and CD4 count.

Patients were treated in accordance with the WHO guidelines recommending at least 6 months of rifampin/isoniazid/pyrazinamide/ethambutol for all clinical forms of TB if the patient has never undergone treatment or has undergone up to 30 days of treatment. In people living with HIV/AIDS with active TB, ART should be started 2-8 weeks after initiation of anti-TB treatment.[26,27]

Data on the study variables were imported into a spreadsheet and analyzed with the Stata statistical software package, version 9.0 (StataCorp LP, College Station, TX, USA) and the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Data were expressed as mean ± standard deviation or median (interquartile range). Normality was assessed by the Kolmogorov-Smirnov test. Patient survival was analyzed by the Kaplan-Meier method and the log-rank test. Variables with values of $p \leq 0.20$ in the univariate analysis were included in a Cox proportional hazards model adjusted for age and gender for survival analysis. The confidence interval was 95%, and values of $p < 0.05$ were considered significant.

RESULTS

Between January of 2011 and December of 2014, 858 patients were admitted to the ICU. Of those, 141 (16.4%) were diagnosed with TB, 131 (92.9%) being coinfected with HIV. A total of 120 patients were included in the study and underwent further analysis.

The mean age of the patients was 37.0 ± 11.7 years, and 70.0% were male. Alcohol consumption, smoking, and illicit drug use were identified in 48.9%, 36.7%, and 25.4%, respectively. As can be seen in Table 1,

the most commonly reported signs and symptoms were weight loss (94.1%), dyspnea (86.4%), and cough (82.9%).

Pulmonary TB was found in 47.0%, and disseminated TB was found in 39.0%. The primary reason for ICU admission was acute respiratory failure (in 80.0%). Data on IMV and ARDS were available for 86 and 67 patients respectively. Of those 86, 75 (87.2%) underwent IMV, and, of those 67, 48 (71.6%) presented with ARDS. The median APACHE II score was 18 (interquartile range, 5-35). Comorbidities were found in 83 (69.2%) of the 120 patients evaluated: neurotoxoplasmosis, in 21.7%; pneumocystis pneumonia, in 15.8%; acute kidney injury, in 13.3%; pneumonia, in 10.8%; and histoplasmosis, in 7.5%.

A total of 80 patients underwent bacteriological screening for TB. Of those, 16 (13.3%) had positive smear results/positive culture results and 8 (6.6%) had negative smear results/positive culture results. Of the 99 patients who underwent chest X-rays or CT scans, 26 had findings suggestive of TB. Autopsy findings were consistent with TB in 5 of the 10 patients in whom an autopsy was performed.

The median length of ICU stay was 5 days (interquartile range, 3-10.5 days). Information on TB treatment initiation was available for 107 patients. Of those, 90 (84.1%) had been receiving anti-TB treatment before ICU admission (for at least 1 month in 33.6%). Of the 120 patients evaluated, 94 (78.3%) died. Of those 94 deaths, 62 (66.0%) occurred within the first week after admission.

In the univariate analysis, mortality was found to be associated with illicit drug use, diarrhea, low CD4 count, hypoalbuminemia, and IMV (Table 1). As can be seen in Figure 1, the Kaplan-Meier method and the log-rank test showed that mortality was associated with low CD4 count ($p = 0.008$), hypoalbuminemia ($p = 0.001$), and IMV ($p < 0.001$).

All of the variables showing $p \leq 0.20$ in the univariate analysis were included in a Cox proportional hazards model adjusted for age and gender. The factors found to be independently associated with mortality were IMV (hazard ratio [HR] = 0.10; 95% CI: 0.02-0.45; $p = 0.002$), hypoalbuminemia (HR = 0.47; 95% CI: 0.26-0.85; $p = 0.013$), and low CD4 count (< 200 cells/mm^3; HR = 0.26; 95% CI: 0.08-0.87; $p = 0.02$; Table 1).

DISCUSSION

The objective of the present study was to describe the clinical features of a large cohort of severe TB/HIV coinfected individuals admitted to the ICU of a referral hospital in the Brazilian Amazon, as well as to identify factors predictive of mortality in that population. We found a mortality rate of 78.3% in the study population, most of the deaths having occurred within the first week after admission. The factors found to be independently associated with mortality were IMV, hypoalbuminemia, and low CD4 count.

The case-fatality rate observed in our cohort was higher than those reported by Balkema et al. (57%)[12] and Silva et al. (65%)[6] in South Africa and Brazil, respectively, as well as being higher than those reported by Zahar et al. (26.7%),[18] Lanoix et al. (28%),[17] and Valade et al. (42%)[10] in France. However, none of these cohorts were designed for studying TB/HIV coinfected patients in the ICU; such patients were primarily evaluated in a subanalysis of larger studies. In addition, as previously mentioned, TB is usually paucibacillary in HIV-infected individuals, and diagnosis remains a challenge. Of the 120 patients in our sample, only 24 (20.0%) had a microbiological diagnosis of TB. Therefore, the case-fatality rate found in the present study can be attributed, at least in part, to histoplasmosis and other fungal diseases (which are generally underdiagnosed), as well as to noninfectious diseases that mimic TB. It is also of note that 89.0% of those patients had been receiving treatment. It is possible that some patients were diagnosed late, meaning that treatment was also delayed. Given the severity of the clinical conditions, it is possible that the doses of the anti-TB drugs used were lower than required, that adherence was suboptimal, or both. Therefore, the directly observed treatment strategy should be revised.

In Brazil, 25% of patients have a low CD4 count at diagnosis of HIV infection.[28] In the state of Amazonas, as many as 30% have a mean count of 282 cells/mm^3 at diagnosis.[28] Most (79.0%) of the deaths among the patients included in the present study occurred in those with a CD4 count of < 200 cells/mm^3 at ICU admission, a finding that is consistent with those of other studies.[12,29] This is probably due to delayed HIV diagnosis and advanced AIDS. In highly immunosuppressed individuals requiring critical care, it is best to "hit hard and hit early" with active bactericidal agents in order to stop TB progression and save time in the ICU. Another issue that merits further investigation is whether there is a need to wait 2 weeks before initiating ART or whether ART should be initiated earlier. In HIV-infected patients, a low CD4 count is known to be associated with early ICU admission and increased case-fatality rates.[30,31]

Belperio & Rhew reported the prevalence and outcomes of anemia in HIV-infected individuals,[32] in whom anemia is commonly caused by disseminated TB.[33] Although low hemoglobin levels are common among HIV-infected patients and have previously been described as constituting an important predictor of mortality in such patients,[32] we found no association between anemia and mortality in our cohort. However, anemia is a common sign of TB and HIV infection, being present not only in critically ill patients in the ICU but also in recently diagnosed patients in an outpatient setting. Therefore, it might have no impact on ICU prognosis.[33]

In the present study, acute respiratory failure was the main reason for ICU admission (in 80.0% of the patients) and a variable that was associated with high mortality rates among our patients. These results

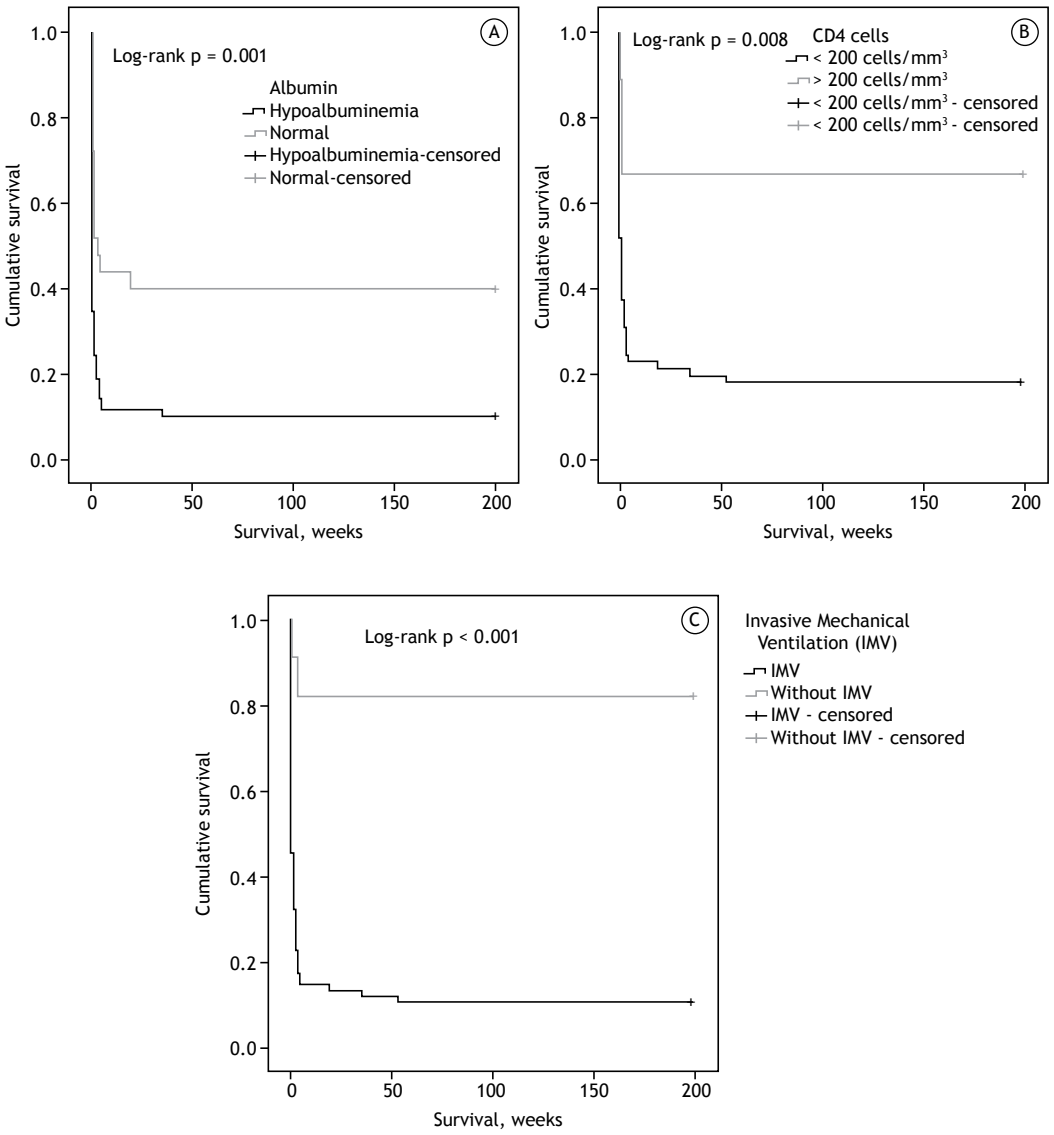

Figure 1. Kaplan-Meier curves for survival among TB/HIV coinfected patients in the ICU. In A, albumin levels; in B, CD4 cell count; and in C, invasive mechanical ventilation.

are similar to those of studies analyzing patients undergoing IMV.[6,12,13]

Potential factors responsible for low rates of bacteriological confirmation include the lack of quality assurance schemes[34] and the empirical approach to TB treatment in the ICU. Suboptimal diagnostic quality can hinder differential diagnosis as well. In the present study, the rate of bacteriological confirmation among patients facing high case-fatality rates was found to be low (i.e., 27.5%). Despite evidence of increased mortality among patients without microbiological confirmation because of HIV-related immunosuppression,[35] we found no significant differences in mortality rates between TB cases with and without microbiological confirmation.

Few studies have examined treatment adequacy and patient adherence.[5] It is of note that although 75.0% of our patients were started on TB treatment before ICU admission, the mean time from admission to treatment in most studies is 1.6-5 days.[9,10,12] The high prevalence of TB/HIV coinfection in Brazil pushes health professionals to the edge. There are currently few ART regimens that can be prescribed in combination with anti-TB drugs; new regimens based on different drugs might make it easier to combine the two in the future.

ICU patients with severe TB pose a major challenge in TB diagnosis (microbiological confirmation of TB) and treatment (poor absorption of anti-TB drugs; organ dysfunction; and apparent deterioration of TB during appropriate treatment, i.e., paradoxical reactions).[7] The potential role of malabsorption of anti-TB drugs in severe cases and the potential utility of therapeutic drug monitoring have been poorly studied and deserve more attention.[36,37] To our knowledge, this is the first

Table 1. Demographic, clinical, and laboratory characteristics of TB/HIV coinfected ICU patients who either survived or died in the 2011-2014 period.[a]

Characteristic	Total sample (N = 120)	Patients who survived (n = 26)	Patients who died (n = 94)	OR (95% CI)	p	HR (95% CI)	p
Age, years		34.3 ± 12.0	37.7 ± 11.54	-	0.393	-	-
Male gender	84 (70.0)	18 (21.4)	66 (78.6)	1.04 (0.40-2.68)	0.884	-	-
Alcoholism	44/90 (48.9)	13 (29.6)	31 (70.5)	0.42 (0.15-1.20)	0.167	1.32 (0.81-2.16)	0.264
Smoking	33/90 (36.7)	10 (30.6)	23 (69.7)	0.48 (0.17-1.34)	0.254	-	-
Drug use	17/67 (25.4)	8 (47.1)	9 (52.9)	0.18 (0.05-0.63)	0.012	0.50 (0.23-1.06)	0.074
Comorbidities	83 (69.2)	19 (22.9)	64 (77.1)	0.78 (0.29-2.07)	0.804	-	-
Cough	73/88 (82.9)	16 (21.9)	57 (78.1)	0.25 (0.03-2.08)	0.284	-	-
Fever	31/109 (28.4)	6 (19.4)	25 (80.1)	1.07 (0.37-3.06)	0.897	-	-
Weight loss	80/85 (94.1)	13 (16.3)	67 (83.8)	1.28 (0.13-12.4)	1.000	-	-
Diarrhea	37/84 (44.0)	2 (5.4)	35 (94.6)	5.34 (1.10-25.8)	0.034	1.34 (0.83-2.17)	0.220
Dyspnea	89/103 (86.4)	15 (16.9)	74 (83.3)	2.74 (0.80-9.33)	0.140	1.57 (0.78-3.16)	0.199
Clinical form of TB	120			-	0.938	-	-
Pulmonary	57 (47.5)	13 (22.8)	44 (77.2)	0.88 (0.36-2.09)	0.946	-	-
Disseminated	47 (39.2)	10 (21.3)	37 (78.7)	1.03 (0.42-2.53)	0.885	-	-
Extrapulmonary	16 (13.3)	3 (18.8)	13 (81.3)	1.23 (0.32-4.69)	1.000	-	-
TB treatment initiation[b]	107			-	0.232	-	-
< 30 days before ICU admission	54 (50.5)	11 (20.3)	43 (79.6)	-	-	-	-
≥ 30 days before ICU admission	36 (33.6)	10 (27.8)	26 (72.2)	-	-	-	-
After ICU admission	17 (15.9)	4 (23.5)	13 (76.5)	-	-	-	-
CD4 count	71			7.53 (1.65-34.28)	< 0.009	0.29 (0.09-0.94)	0.04
< 200 cells/mm^3	62 (87.3)	13 (21)	49 (79)	-	-	-	-
≥ 200 cells/mm^3	9 (12.7)	6 (66.7)	3 (33.3)	-	-	-	-
Hemoglobin level	83	18 (21.6)	65 (78)	0.70 (0.22-2.21)	0.747	-	-
Males (8-13 g/dL)	55 (66.3)	13 (23.6)	42 (76.4)	-	-	-	-
Females (7-12 g/dL)	28 (33.7)	5 (17.9)	23 (82.1)	-	-	-	-
Lymphocyte count	114			-	0.081	0.73 (0.46-1.14)	0.175
Lymphocytosis	4 (3.5)	0 (0.0)	4 (100.0)	-	-	-	-
Lymphocytopenia	84 (73.7)	14 (16.7)	70 (83.3)	-	-	-	-
Normal	26 (22.8)	9 (34.6)	17 (65.4)	-	-	-	-
Albumin level	94			5.99 (2.03-17.64)	0.001	0.48 (0.26-0.88)	0.018
Hypoalbuminemia	69 (73.4)	8 (11.6)	61 (88.4)	-	-	-	-
Normal	25 (26.6)	11 (44.0)	14 (56.0)	-	-	-	-
APACHE II score	96			-	0.362	-	-
1-15	37 (38.4)	6 (16.2)	31 (83.8)	-	-	-	-
16-30	51 (53.1)	14 (27.5)	37 (72.5)	-	-	-	-
31-45	8 (8.3)	1 (12.5)	7 (87.5)	-	-	-	-
IMV	75/86 (87.2)	10 (13.3)	65 (86.7)	29.25 (5.50-155.4)	0.000	0.12 (0.03-0.51)	0.004
ARDS	67			0.80 (0.22-2.88)	1.00	-	-
Yes	48 (71.6)	12 (25.0)	36 (75.0)	-	-		
No	19 (28.4)	4 (21.1)	15 (79.0)	-	-		

TB: tuberculosis; HR: hazard ratio; APACHE II: Acute Physiology and Chronic Health Evaluation II; and IMV: invasive mechanical ventilation. [a]Values expressed as n, n (%), or mean ± SD, except where otherwise indicated. [b]Information on TB treatment initiation was unavailable for 13 patients.

study to evaluate TB/HIV coinfected ICU patients in the Amazon region, being the largest of its kind. Information on how to improve TB/HIV coinfection management in the ICU is still anecdotal, and important issues (such as uncertainty regarding severity classification, mortality scores, vulnerable populations, and effective treatment) have yet to be resolved.

Our study has several limitations. First, all data were obtained retrospectively by reviewing patient medical records and were probably not as complete or accurate as are data that are collected prospectively. Second, although our cohort is the largest available sample of TB/HIV coinfected patients in the ICU, its power was too low to allow subanalyses to be undertaken. Despite these limitations, our results provide important implications for similar demographic areas and clinical settings. In addition, our study poses questions on how to approach TB/HIV coinfected patients and how to predict their prognosis while providing timely interventions.

The high mortality rate found in the present study underlines how difficult it is to manage TB in the ICU. Pre-ICU interventions (including early diagnosis and effective treatment) can have a major impact on TB/HIV mortality in the ICU, as well as improving the quality of TB control.

REFERENCES

1. World Health Organization. Global tuberculosis report 2016. Geneva: World Health Organization; 2016.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância à Saúde. Indicadores prioritários para o monitoramento do Plano Nacional pelo Fim da Tuberculose como Problema de Saúde Pública no Brasil. Boletim Epidemiológico. 2017;48(8):1-11.
3. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLOS Pathog. 2012;8(2):e1002464. https://doi.org/10.1371/journal.ppat.1002464
4. Collins KR, Qui-ones-Mateu ME, Toossi Z, Arts EJ. Impact of tuberculosis on HIV-1 replication, diversity, and disease progression. AIDS Rev. 2002;4(3):165-76.
5. Klautau GB, Kuschnaroff TM. Clinical forms and outcome of tuberculosis in HIV-infected patients in a tertiary hospital in São Paulo - Brazil. Braz J Infect Dis. 2005;9(6):464-78. https://doi.org/10.1590/S1413-86702005000600004
6. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT. Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC Infect Dis. 2010;10:54. https://doi.org/10.1186/1471-2334-10-54
7. Hagan G, Nathani N. Clinical review: tuberculosis on the intensive care unit. Crit Care. 2013;17(5):240. https://doi.org/10.1186/cc12760
8. Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur Respir J. 2006;27(6):1223-8. https://doi.org/10.1183/09031936.06.00088105
9. Levy H, Kallenbach JM, Feldman C, Thorburn JR, Abramowitz JA. Acute respiratory failure in active tuberculosis. Crit Care Med. 1987;15(3):221-5. https://doi.org/10.1097/00003246-198703000-00008
10. Valade S, Raskine L, Aout M, Malissin I, Brun P, Deye N, et al. Tuberculosis in the intensive care unit: A retrospective descriptive cohort study with determination of a predictive fatality score. Can J Infect Dis Med Microbiol. 2012;23(4):173-8. https://doi.org/10.1155/2012/361292
11. Calligaro GL, Theron G, Khalfey H, Peter J, Meldau R, Matinyenya B, et al. Burden of tuberculosis in intensive care units in Cape Town, South Africa, and assessment of the accuracy and effect on patient outcomes of the Xpert MTB/RIF test on tracheal aspirate samples for diagnosis of pulmonary tuberculosis: a prospective burden of disease study with a nested randomised controlled trial. Lancet Respir Med. 2015;3(8):621-30. https://doi.org/10.1016/S2213-2600(15)00198-8
12. Balkema CA, Irusen EM, Taljaard JJ, Koegelenberg CF. Tuberculosis in the intensive care unit: a prospective observational study. Int J Tuberc Lung Dis. 2014;18(7):824-30. https://doi.org/10.5588/ijtld.13.0044
13. Madkour A, Fouda M, Mansour M. Outcome of active pulmonary tuberculosis patients requiring respiratory intensive care admission. Egypt J Bronchol. 2014;8(2):79-86. https://doi.org/10.4103/1687-8426.145692
14. Lee PL, Jerng JS, Chang YL, Chen CF, Hsueh PR, Yu CJ, et al. Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation. Eur Respir J. 2003;22(1):141-7. https://doi.org/10.1183/09031936.03.00038703
15. Gachot B, Wolff M, Clair B, Régnier B. Severe tuberculosis in patients with human immunodeficiency virus infection. Intensive Care Med. 1990;16(8):491-3. https://doi.org/10.1007/BF01709398
16. De Palo VA, Millstein BH, Mayo PH, Salzman SH, Rosen MJ. Outcome of intensive care in patients with HIV infection. Chest. 1995;107(2):506-10. https://doi.org/10.1378/chest.107.2.506
17. Lanoix JP, Gaudry S, Flicoteaux R, Ruimy R, Wolff M. Tuberculosis in the intensive care unit: a descriptive analysis in a low-burden country. Int J Tuberc Lung Dis. 2014;18(5):581-7. https://doi.org/10.5588/ijtld.13.0901
18. Zahar JR, Azoulay E, Klement E, De Lassence A, Lucet JC, Regnier B, et al. Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. Intensive Care Med. 2001;27(3):513-20. https://doi.org/10.1007/s001340000849
19. Amâncio FF, Lambertucci JR, Cota GF, Antunes CM. Predictors of the short- and long-term survival of HIV-infected patients admitted to a Brazilian intensive care unit. Int J STD AIDS. 2012;23(10):692-7. https://doi.org/10.1258/ijsa.2012.011389
20. Loh WJ, Yu Y, Loo CM, Low SY. Factors associated with mortality among patients with active pulmonary tuberculosis requiring intensive care. Singapore Med J. 2017;58(11):656-659. https://doi.org/10.11622/smedj.2016160
21. Duro RP, Figueiredo Dias P, Ferreira AA, Xerinda SM, Lima Alves C, Sarmento AC, et al. Severe Tuberculosis Requiring Intensive Care: A Descriptive Analysis. Crit Care Res Pract. 2017;2017:9535463. https://doi.org/10.1155/2017/9535463
22. World Health Organization. A guide to monitoring and evaluation for collaborative TB/HIV activities–2015 revision. Geneva: World Health Organization; 2015.
23. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-33.
24. Brasil. Ministério da Saúde. Secretaria de Vigilância à Saúde. Manual técnico para o diagnósico da infecção pelo HIV. 2nd ed. Brasília: o Ministério; 2014.
25. World Health Organization. Dept. of Mental Health and Substance Dependence. International guide for monitoring alcohol consumption and related harm. Geneva: World Health Organization; 2000.
26. Brasil. Ministério da Saúde. Manual de recomendações para o controle da tuberculose no Brasil. 1st ed. Brasília: o Ministério; 2011.
27. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos. Brasília: o Ministério; 2013.
28. Brasil. Ministério da Saúde. Secr Vigilância Em Saúde. Departamento de DST, Aids e Hepatites Virais. Boletim Epidemiológico HIV/AIDS. Brasília: o Ministério; 2015.
29. Koegelenberg CF, Balkema CA, Jooste Y, Taljaard JJ, Irusen EM. Validation of a severity-of-illness score in patients with tuberculosis requiring intensive care unit admission. South Afr Med J. 2015;105(5):389-92. https://doi.org/10.7196/SAMJ.9148
30. Croda J, Croda MG, Neves A, De Sousa dos Santos S. Benefit of antiretroviral therapy on survival of human immunodeficiency virus-infected patients admitted to an intensive care unit. Crit Care Med. 2009;37(5):1605-11. https://doi.org/10.1097/CCM.0b013e31819da8c7

31. Khouli H, Afrasiabi A, Shibli M, Hajal R, Barrett CR, Homel P. Outcome of critically ill human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. J Intensive Care Med. 2005;20(6):327-33. https://doi.org/10.1177/0885066605281087
32. Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A:27S-43S. https://doi.org/10.1016/j.amjmed.2003.12.010
33. Kerkhoff AD, Meintjes G, Opie J, Vogt M, Jhilmeet N, Wood R, et al. Anaemia in patients with HIV-associated TB: relative contributions of anaemia of chronic disease and iron deficiency. Int J Tuberc Lung Dis. 2016;20(2):193-201. https://doi.org/10.5588/ijtld.15.0558
34. Khan MS, Dar O, Sismanidis C, Shah K, Godfrey-Faussett P. Improvement of tuberculosis case detection and reduction of discrepancies between men and women by simple sputum-submission instructions: a pragmatic randomised controlled trial. Lancet. 2007;369(9577):1955-60. https://doi.org/10.1016/S0140-6736(07)60916-7
35. Campos LC, Rocha MV, Willers DM, Silva DR. Characteristics of Patients with Smear-Negative Pulmonary Tuberculosis (TB) in a Region with High TB and HIV Prevalence. PLoS ONE. 2016;11(1):e0147933. https://doi.org/10.1371/journal.pone.0147933
36. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):853-67. https://doi.org/10.1093/cid/ciw566
37. Sotgiu G, Nahid P, Loddenkemper R, Abubakar I, Miravitlles M, Migliori GB. The ERS-endorsed official ATS/CDC/IDSA clinical practice guidelines on treatment of drug-susceptible tuberculosis. Eur Respir J. 2016;48(4):963-971. https://doi.org/10.1183/13993003.01356-2016

J Bras Pneumol. 2018;44(2):125-133
http://dx.doi.org/10.1590/S1806-37562017000000384

ORIGINAL ARTICLE

Who are the patients with tuberculosis who are diagnosed in emergency facilities? An analysis of treatment outcomes in the state of São Paulo, Brazil

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Submitted: 31 October 2017.
Accepted: 11 February 2018.

Study carried out in the Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Early tuberculosis diagnosis and treatment are determinants of better outcomes and effective disease control. Although tuberculosis should ideally be managed in a primary care setting, a proportion of patients are diagnosed in emergency facilities (EFs). We sought to describe patient characteristics by place of tuberculosis diagnosis and determine whether the place of diagnosis is associated with treatment outcomes. A secondary objective was to determine whether municipal indicators are associated with the probability of tuberculosis diagnosis in EFs. **Methods:** We analyzed data from the São Paulo State Tuberculosis Control Program database for the period between January of 2010 and December of 2013. Newly diagnosed patients over 15 years of age with pulmonary, extrapulmonary, or disseminated tuberculosis were included in the study. Multiple logistic regression models adjusted for potential confounders were used in order to evaluate the association between place of diagnosis and treatment outcomes. **Results:** Of a total of 50,295 patients, 12,696 (25%) were found to have been diagnosed in EFs. In comparison with the patients who had been diagnosed in an outpatient setting, those who had been diagnosed in EFs were younger and more socially vulnerable. Patients diagnosed in EFs were more likely to have unsuccessful treatment outcomes (adjusted OR: 1.54; 95% CI: 1.42-1.66), including loss to follow-up and death. At the municipal level, the probability of tuberculosis diagnosis in EFs was associated with low primary care coverage, inequality, and social vulnerability. In some municipalities, more than 50% of the tuberculosis cases were diagnosed in EFs. **Conclusions:** In the state of São Paulo, one in every four tuberculosis patients is diagnosed in EFs, a diagnosis of tuberculosis in EFs being associated with poor treatment outcomes. At the municipal level, an EF diagnosis of tuberculosis is associated with structural and socioeconomic indicators, indicating areas for improvement.

Keywords: Tuberculosis/diagnosis; Emergency treatment; Treatment outcome; Delivery of health care.

INTRODUCTION

Tuberculosis remains a common disease and a complex public health problem, particularly in low- and middle-income countries, as well as in the poorest sections of high-income countries.[1,2] Early diagnosis and treatment are the main determinants of favorable patient outcomes and effective control, reducing the period of transmissibility.[1-6]

There are barriers to early tuberculosis diagnosis and treatment, including delays in seeking medical attention after symptom onset, in establishing a definitive diagnosis, and in initiating appropriate treatment.[3,5,6] Several studies have examined factors associated with delayed diagnosis and treatment, including patient-related factors (e.g., age, female sex, other reasons for chronic cough, and self-perception), socioeconomic factors (e.g., social cohesion, poverty, and education), and health care system-related factors (e.g., access to primary care and tuberculosis caseload).[4-7]

The Brazilian public health care system provides universal coverage, being organized in a hierarchical and decentralized manner and providing full tuberculosis treatment free of charge.[8,9] Tuberculosis control in Brazil has improved in recent years, the overall incidence and associated mortality rate having decreased.[2] However, Brazil remains on the list of high-burden countries and has yet to achieve all of the World Health Organization (WHO) goals for tuberculosis control, particularly those related to treatment outcomes (i.e., a treatment success rate > 85%).[2,9,10] The state of São Paulo has a population of 44 million inhabitants distributed among 645 municipalities and accounts for nearly 20% of all tuberculosis cases in Brazil. Although the state of São Paulo is one of the

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Financial support: Otavio T. Ranzani is the recipient of a Master's Fellowship in Public Health and Tropical Medicine from the Wellcome Trust (Grant no. 104006/Z/14/Z).

wealthiest in the country, it has yet to achieve the goals related to treatment success.[9-13]

Previous studies have shown that the proportions of tuberculosis cases diagnosed in a hospital setting or in emergency facilities (EFs) are high in Brazil, which might indicate lack of access to health care and delayed diagnosis.[3,14-19] However, those studies were either single-center studies or studies conducted at the municipal level.[20,21] To overcome these limitations, we conducted the present population-based study, the objective of which was to describe patient characteristics by place of diagnosis and determine whether the place of diagnosis is associated with treatment outcomes. A secondary objective was to determine whether structural and socioeconomic indicators are associated with the likelihood of being diagnosed in EFs at the aggregate level, in order to inform targeted public health strategies.

METHODS

Population and setting

The present study was a retrospective analysis of data from the São Paulo State Tuberculosis Control Program database for the period between January of 2010 and December of 2013. Newly diagnosed patients over 15 years of age with pulmonary, extrapulmonary, or disseminated tuberculosis were included in the study. Only new patients were included because patients with recurrent tuberculosis (relapse or reinfection) are highly expected to go through a different diagnostic process. In addition, prison inmates were excluded, as were patients diagnosed through active case finding, including those who had been diagnosed after contact tracing investigation, because of the specific circumstances associated with place of diagnosis.

All of the tuberculosis cases included in the present study were either bacteriologically confirmed or clinically diagnosed cases, in accordance with the WHO definitions.[22]

Data sources

Patient-related data were collected from an electronic health system (the TBweb database).[9,23] Because tuberculosis notification (including reporting of treatment initiation) is compulsory, the TBweb database includes data for all municipalities in the state of São Paulo. In addition, the São Paulo State Tuberculosis Control Program has been investing human and financial resources in the TBweb database, data accuracy and quality therefore being guaranteed.[9,23]

Data on the municipalities were collected from the following databases: the Brazilian Institute of Geography and Statistics database[24]; the São Paulo *Sistema Estadual de Análise de Dados* (SEADE, State System of Data Analysis) Foundation database[13]; and the Brazilian National Ministry of Health Department of Primary Care database.[25] The São Paulo SEADE Foundation is an independent public agency, being a national referral center for analysis of socioeconomic and demographic data.[13]

Indicators at the municipal level

The following indicators were used: population size, population density, gross domestic product, per capita gross domestic product, and level of urbanization. Composite indicators were also used, including the *Índice de Desenvolvimento Humano* (IDH, Human Development Index)—which assesses education, life expectancy, and economic development and ranges from 0 to 1 (IDH values closer to 1 translating to greater human development)—and the Gini coefficient, which assesses inequality and ranges from 0 to 1 (a Gini coefficient of 0 indicating perfect equality and a Gini coefficient of 1 indicating maximal inequality), on the basis of data from the 2010 Census.[24] The 2010 version of the *Índice Paulista de Vulnerabilidade Social* (IPVS, São Paulo State Social Vulnerability Index), developed by the São Paulo SEADE Foundation, was also used.[26] The IPVS encompasses several demographic and socioeconomic variables, such as level of education, per capita household income, age, and sex distribution. The population of each municipality was divided into the seven categories of vulnerability defined by the IPVS. In the present study, the indicator selected was the proportion of the municipal population classified as highly vulnerable (i.e., individuals in category 5, 6, or 7). Data from the Brazilian National Ministry of Health were used in order to assess primary care coverage (i.e., family health strategy program or equivalent) in each municipality.[25] Other São Paulo SEADE Foundation indicators used in the present study included proportion of pregnancies with at least seven antenatal visits and infant mortality rate per 1,000 live births.[13] All primary care indicators were obtained from mid-year values.

Outcomes

The 2013 WHO treatment outcome definitions were used, being adapted to the TBweb database definitions.[9,22] The outcomes are divided into desirable outcomes (i.e., treatment success) and undesirable outcomes, the latter including treatment failure, death, loss to follow-up, and not evaluated.[9,22]

Data analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on their distribution. Categorical variables were expressed as absolute numbers and proportions, being compared by Fisher's exact test or the chi-square test, as appropriate.

A multiple logistic regression model was used in order to evaluate the association between place of diagnosis and unsuccessful treatment outcome. Adjusted ORs were calculated, allowing for potential confounding factors defined a priori. Patient-related factors, as well as disease- and treatment-related factors, were selected on the basis of the literature. Patient-related factors included age, sex, country of birth, self-reported ethnicity, homelessness, level of education, alcohol use, drug use, diabetes mellitus,

mental disorder, HIV status, and immunosuppression from etiologies other than HIV infection. Disease- and treatment-related factors included place of diagnosis, chest X-ray findings at diagnosis, microbiological status at diagnosis, initial drug regimen, and directly observed treatment. Given its importance among unsuccessful treatment outcomes, death was used as the dependent variable in a second multiple logistic regression model.

An additional analysis was performed at the municipal level. Initially, the number of cases and place of diagnosis were grouped by municipality. Subsequently, each indicator was tested in a univariate analysis as a predictor of diagnosis in EFs, the most important variables being retained in order to explain the variance in the outcome. When the same dimension was assessed by two different indicators, composite indicators were preferred over single indicators, multicollinearity being dealt with in the final model. In order to include the IPVS, which was available for all of the municipalities in the state of São Paulo, two final models were selected. All analyses were performed with the Stata statistical software package, version 13.1 (StataCorp LP, College Station, TX, USA), and the blogit command was used in order to run logistic models for grouped data at the municipal level.

RESULTS

Of a total of 62,178 patients who were diagnosed with tuberculosis between January of 2010 and January of 2013, 7,027 (11.3%) were excluded because they were prison inmates, 3,374 (5.4%) were excluded because they had been diagnosed through active case finding or contact tracing investigation, 696 (1.1%) were excluded because they had been diagnosed at autopsy, and 786 (1.3%) were excluded because there was no information regarding place of diagnosis. Therefore, the final sample consisted of 50,295 patients spontaneously seeking medical attention at health care units in the state of São Paulo.

The general characteristics of the patients analyzed in the present study are shown in Table 1. Most of the patients were young males. Of the sample as a whole, 55% had been diagnosed in an outpatient setting, 25% had been diagnosed in EFs, and 20% had been diagnosed in a hospital setting. In comparison with the patients who had been diagnosed in an outpatient or hospital setting, those who had been diagnosed in EFs were notably younger, the following being more common in the latter than in the former: being male, self-reporting mixed ethnicity, being homeless, using alcohol, using drugs, and having a low level of education. A diagnosis of tuberculosis during hospitalization was more common in patients with chronic disease (e.g., diabetes mellitus, HIV infection, and immunosuppression from etiologies other than HIV infection) than in those without it.

Table 2 shows the characteristics of tuberculosis and tuberculosis treatment, by place of diagnosis, among the patients analyzed in the present study. Of the patients who had been diagnosed in EFs, approximately 80% had pulmonary tuberculosis, the prevalence of positive sputum smears and cultures being higher in those patients than in those who were diagnosed in an outpatient or hospital setting. Other forms of tuberculosis, including extrapulmonary tuberculosis and disseminated/miliary tuberculosis, were more frequently diagnosed in a hospital setting than in an outpatient setting or in EFs.

As can be seen in Table 3 and Figure 1, the place of diagnosis was associated with tuberculosis treatment outcomes ($p < 0.001$), which were worse in the patients who had been diagnosed in EFs or in a hospital setting than in those who had been diagnosed in an outpatient setting. In addition, the proportion of loss to follow-up was higher among the patients who had been diagnosed in EFs. After adjustment for potential confounders, the likelihood of treatment failure and death was higher in the patients who had been diagnosed in EFs or in a hospital setting than in those who had been diagnosed in an outpatient setting, results that were consistent with those of a sensitivity analysis in the subgroups of HIV-positive and HIV-negative patients.

During the study period, 591 (92%) of the municipalities in the state of São Paulo reported cases of tuberculosis. In 96 (16%) of all municipalities in the state of São Paulo, more than 30% of all tuberculosis cases were diagnosed in the EFs; in 15 (2.5%), more than 50% of all cases were diagnosed in EFs.

Table 4 shows the variables that remained in the models at the municipal level. Municipalities in which primary care coverage was higher were less likely to have tuberculosis cases diagnosed in EFs, whereas municipalities in which inequality and vulnerability were high were more likely to have tuberculosis cases diagnosed in EFs. Figure 2 shows the relationship of the IDH, the Gini coefficient, and primary care coverage with the probability of being diagnosed in EFs, as estimated from adjusted model 1.

For illustrative purposes, we selected four municipalities. Municipality A notified 1,138 cases, being the third leading contributor to the burden of tuberculosis in the state (in absolute numbers). Of those cases, 53% had been diagnosed in EFs. Municipality A has a high IDH (i.e., 0.768), and 21% of its population are highly vulnerable; however, primary care coverage is only 34%. In municipality B, the proportion of cases diagnosed in EFs was 41%. Although the IDH is very high (i.e., 0.814) and primary care coverage is 48% in that municipality, inequality is very high (Gini coefficient, 0.6858) and 36% of its population are highly vulnerable. In municipality C, inequality is high (Gini coefficient, 0.5971) and 33% of the population are highly vulnerable; however, primary care coverage is 99%, and the proportion of cases diagnosed in EFs was 21%. Finally, in municipality D, the proportion of cases diagnosed in EFs was 7%, primary care coverage is 89%, the IDH is high (i.e., 0.798), and only 8% of the population are highly vulnerable.

Table 1. General characteristics of patients newly diagnosed with tuberculosis, by place of diagnosis, in the state of São Paulo, Brazil, in the period between January of 2010 and December of 2013.[a]

Variable	Primary care/ outpatient setting (n = 27,415)	EFs (n = 12,696)	During hospitalization (n = 10,184)	p
Age, years[b]				
15.0-25.0	5,009 (18.3)	2,676 (21.1)	1,500 (14.7)	
25.1-35.0	6,458 (23.6)	3,285 (25.9)	2,284 (22.4)	
35.1-45.0	5,565 (20.3)	2,614 (20.6)	2,264 (22.2)	
45.1-55.0	5,047 (18.4)	2,123 (16.7)	1,906 (18.7)	< 0.001
55.1-65.0	3,122 (11.4)	1,239 (9.8)	1,200 (11.8)	
65.1-75.0	1,470 (5.4)	499 (3.9)	614 (6.0)	
75.1-85.0	605 (2.2)	207 (1.6)	333 (3.3)	
85.1-105	125 (0.5)	41 (0.3)	78 (0.8)	
Sex				
Female	9,615 (35.1)	3,785 (29.8)	3,236 (31.8)	< 0.001
Male	17,800 (64.9)	8,911 (70.2)	6,948 (68.2)	
Country of birth[c]				
Brazil	22,802 (96.6)	10,285 (96.8)	8,500 (98.5)	< 0.001
Other	805 (3.4)	334 (3.2)	129 (1.5)	
Self-reported ethnicity[d]				
White	13,157 (55.1)	5,296 (47.9)	5,087 (56.6)	
Black	2,645 (11.1)	1,392 (12.6)	1,012 (11.3)	< 0.001
Mixed	7,441 (31.2)	4,208 (38.1)	2,756 (30.7)	
Asian	356 (1.5)	102 (0.9)	107 (1.2)	
Indigenous	270 (1.1)	55 (0.5)	23 (0.3)	
Level of education, number of years of schooling[e]				
0 (illiterate)	838 (3.7)	360 (3.6)	339 (4.3)	
1-3	2,639 (11.5)	1,119 (11.3)	817 (10.5)	< 0.001
4-7	7,949 (34.6)	3,519 (35.5)	2,673 (34.2)	
8-11	8,668 (37.7)	4,041 (40.8)	3,077 (39.4)	
12-14	1,923 (8.4)	602 (6.1)	572 (7.3)	
≥ 15	951 (4.1)	275 (2.8)	342 (4.4)	
Homelessness	524 (1.9)	514 (4.1)	220 (2.2)	< 0.001
Alcohol use	3,720 (13.6)	2,375 (18.7)	1,771 (17.4)	< 0.001
Diabetes mellitus	1,708 (6.2)	863 (6.8)	755 (7.4)	< 0.001
Drug use	2,136 (7.8)	1,535 (12.1)	1,042 (10.2)	< 0.001
Mental disorder	407 (1.5)	252 (2.0)	290 (2.9)	< 0.001
HIV status				
Negative	21,353 (77.9)	9,591 (75.5)	6,682 (65.6)	< 0·001
Positive	2,417 (8.8)	1,281 (10.1)	2,187 (21.5)	
Unknown	3,645 (13.3)	1,824 (14.4)	1,315 (12.9)	
Immunosuppression from etiologies other than HIV infection	169 (0.6)	113 (0.9)	284 (2.8)	< 0.001

EFs: emergency facilities. [a]Values expressed as n (%). [b]Missing data: n = 31 (0.1%). [c]Missing data: n = 7,440 (14.8%). [d]Missing data: n = 6,388 (12.7%). [e]Missing data: n = 9,591 (19.1%).

DISCUSSION

In the present population-based study of data regarding the state of São Paulo, one in every four tuberculosis patients was found to have been diagnosed in EFs. The likelihood of poor outcomes, including death and loss to follow-up, was found to be higher in the patients diagnosed in EFs than in those diagnosed in an outpatient setting. At the municipal level, structural and socioeconomic factors were found to be associated with a higher probability of being diagnosed in EFs.

Our study shows that tuberculosis remains a public health challenge and that there is a need for improving the process of diagnosing tuberculosis in the public health system.[1,14] The proportion of patients diagnosed with tuberculosis in EFs was found to be high, despite the fact that the state of São Paulo is one of the wealthiest in the country and the fact that tuberculosis treatment is provided free of charge in Brazil. This might be due to difficult access to health care, which results in delayed diagnosis and affects

Table 2. Characteristics of tuberculosis and tuberculosis treatment, by place of diagnosis, among patients newly diagnosed with tuberculosis in the state of São Paulo, Brazil, in the period between January of 2010 and December of 2013.[a]

Variable	Primary care/ outpatient setting (n = 27,415)	EFs (n = 12,696)	During hospitalization (n = 10,184)	p
Anatomical classification				
PTB	22,758 (83.0)	10,314 (81.2)	5,895 (57.9)	
PTB + EPTB	524 (1.9)	371 (2.9)	653 (6.4)	< 0.001
EPTB	3,754 (13.7)	1,684 (13.3)	3,015 (29.6)	
Miliary/disseminated TB	379 (1.4)	327 (2.6)	621 (6.1)	
Microbiological status				
A positive microbiological test result	19,018 (69.4)	9,578 (75.4)	5,674 (55.7)	< 0.001
A positive microbiological test result for a pulmonary form (PTB/PTB + EPTB)	18,289 (78.6)	9,103 (85.2)	4,873 (74.4)	< 0.001
Positive sputum smear at diagnosis[b]	16,162 (74.2)	8,548 (84.4)	4,097 (70.5)	< 0.001
Positive sputum culture at diagnosis[c]	6,017 (63.5)	2,411 (65.7)	1,525 (61.1)	< 0.001
Chest X-ray[d]				
Not performed	2,998 (11.4)	848 (6.9)	957 (9.9)	
Normal	2,134 (8.1)	602 (4.9)	1,066 (11.0)	< 0.001
Additional pathology	177 (0.7)	118 (1.0)	192 (2.0)	
Suspected TB	15,829 (60.4)	8,344 (68.1)	6,211 (64.1)	
Suspected TB + cavitation	5,087 (19.4)	2,336 (19.1)	1,263 (13.0)	
Initial drug regimen				
Other	848 (3.1)	373 (2.9)	406 (4.0)	< 0.001
RHZE	26,567 (96.9)	12,323 (97.1)	9,778 (96.0)	
Directly observed treatment[e]	18,872 (69.1)	9,120 (72.4)	6,466 (64.0)	< 0.001

EFs: emergency facilities; TB: tuberculosis; PTB: pulmonary TB; EPTB: extrapulmonary TB; and RHZE: rifampin, isoniazid, pyrazinamide, and ethambutol. [a]Values expressed as n (%).[b]Proportions calculated among patients undergoing sputum collection (n = 37,717/40,515; 93%). [c]Proportions calculated among patients undergoing sputum collection and culture (n = 15,638/40,515; 39%). [d]Missing data: n = 2,133 (4.2%). [e]Missing data: n = 290; (0.6%).

treatment outcomes, as well as increasing the risk of transmission in the population and costs to the health care system.[14,19,21,27]

A diagnosis of tuberculosis in EFs is associated with a variety of problems.[3,4,27-30] First, there is a risk of transmission to other patients, given the high prevalence of patients with pulmonary tuberculosis and positive sputum smears in contact with ill patients in a crowded area.[30] Second, given the intrinsic characteristics of the care delivered in EFs, the possibility of tuberculosis is unlikely to be raised, thus increasing the delay in initiating appropriate treatment.[4] Third, tuberculosis patients who are diagnosed in EFs are at a high risk of loss to follow-up because EF patients must be referred to primary care clinics. In addition, the underlying reasons for an EF diagnosis of tuberculosis—including patient vulnerability, lack of access to health care, and lack of self-awareness—potentiate the risk of loss to follow-up.[21] Health care systems should develop strategies to facilitate the retention of tuberculosis patients diagnosed in the EFs, including internet-based scheduling of visits, mobile reminders, and direct communication between hospitals and primary care clinics.

Given that tuberculosis is a chronic disease, early diagnosis and treatment (in an outpatient setting) are preferred over a diagnosis in EFs. This reinforces the importance of improving the screening of individuals with respiratory symptoms, as well as reinforcing the importance of active case finding and contact tracing.[1,14,31-33] In addition, the level of population awareness of tuberculosis should be raised. A Brazilian soccer player has recently participated in a Brazilian national campaign against tuberculosis, the campaign being an example of how to increase population awareness and knowledge of tuberculosis and, consequently, reduce the stigma associated with the disease.[34] However, at the municipal level, low primary care coverage was found to be associated with a higher likelihood of being diagnosed in EFs. Therefore, it is imperative to improve primary care coverage.[19] In addition, primary care clinics must have adequate infrastructure and trained staff for tuberculosis diagnosis and treatment, the lack of adequate infrastructure and trained staff having been reported as problems in studies investigating the pathway to tuberculosis diagnosis in Brazil.[27,29,35] Although we have no data as to whether EFs are equipped to diagnose tuberculosis, we speculate that a large proportion of EFs in the country have a laboratory and an X-ray machine, either on site or elsewhere (i.e., at a referral site).

In the present study, treatment outcomes were found to be worse in the patients who had been diagnosed in EFs or in a hospital setting than in those who had been diagnosed in an outpatient setting.[20] We found that it was possible to divide the patients who had been diagnosed in EFs into three groups: socially vulnerable patients, patients with known

Table 3. Logistic regression models for the association between place of diagnosis and tuberculosis treatment outcomes.

	Unsuccessful treatment		Death	
Sample as a whole				
	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Primary care/outpatient setting	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
EFs	1.87 (1.77-1.97) p < 0.001	1.54 (1.42-1.66) p < 0.001	2.88 (2.65-3.14) p < 0.001	2.75 (2.40-3.16) p < 0.001
During hospitalization	2.26 (2.14-2.39) p < 0.001	1.78 (1.63-1.94) p < 0.001	5.12 (4.72-5.56) p < 0.001	3.88 (3.40-4.43) p < 0.001
HIV-negative patients				
	Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Primary care/outpatient setting	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
EFs	1.60 (1.49-1.72) p < 0.001	1.33 (1.20-1.46) p < 0.001	2.44 (2.15-2.78) p < 0.001	2.36 (1.95-2.85) p < 0.001
During hospitalization	1.75 (1.61-1.89) p < 0.001	1.60 (1.43-1.79) p < 0.001	4.27 (3.77-4.84) p < 0.001	3.34 (2.86-4.16) p < 0.001
HIV-positive patients				
	Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Primary care/outpatient setting	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
EFs	2.43 (2.11-2.80) p < 0.001	1.97 (1.59-2.44) p < 0.001	3.52 (2.94-4.20) p < 0.001	3.45 (2.58-4.61) p < 0.001
During hospitalization	2.05 (1.83-2.34) p<0.001	1.78 (1.48-2.15) p<0.001	3.48 (2.97-4.09) p<0.001	3.63 (2.80-4.71) p<0.001

EFs: emergency facilities. [a]Adjusted for age, sex, country of birth, self-reported ethnicity, level of education, homelessness, alcohol use, drug use, diabetes mellitus, mental disorder, HIV status, immunosuppression from etiologies other than HIV infection, anatomical classification, microbiological diagnosis, chest X-ray findings at diagnosis, initial drug treatment, and directly observed treatment. [b]Adjusted for age, sex, country of birth, self-reported skin color/ethnicity, level of education, homelessness, alcohol use, drug use, diabetes mellitus, mental disorder, immunosuppression from etiologies other than HIV infection, anatomical classification, microbiological diagnosis, chest X-ray findings at diagnosis, initial drug treatment, and directly observed treatment.

Table 4. Structural and socioeconomic indicators aggregated at the municipal level and associated with tuberculosis diagnosis in emergency facilities.

Indicator	Model 1		Indicator	Model 2	
	OR (95% CI)	p		OR (95% CI)	p
Primary care coverage (1% increase)	0.997 (0.995-0.998)	< 0.001	Primary care coverage (1% increase)	0.998 (0.997-0.999)	0.002
IDH (1% increase)	0.936 (0.926-0.947)	< 0.001			
Gini coefficient (1% increase)	1.036 (1.030-1.041)	< 0.001	Highly vulnerable population[a] (1% increase)	1.018 (1.016-1.020)	< 0.001
Urbanization (1% increase)	1.032 (1.026-1.037)	< 0.001			
Population density (100/km^2 increase)	1.001 (1.000-1.002)	0.036	Population density (100/km^2 increase)	1.005 (1.005-1.006)	< 0.001

IDH: *Índice de Desenvolvimento Humano* (Human Development Index). [a]As determined by the 2010 version of the *Índice Paulista de Vulnerabilidade Social* (IPVS, São Paulo State Social Vulnerability Index), developed by the São Paulo *Sistema Estadual de Análise de Dados* (SEADE, State System of Data Analysis) Foundation.[26]

chronic diseases, and patients who are young and "healthy". For each group of patients, a different set of interventions is required in order to improve their outcomes. Socially vulnerable patients usually have limited access to primary care because of their marginalization and weak social capital.[9,36] Recent studies have shown that homeless individuals commonly seek EF treatment for diseases at an advanced stage.[37] To tackle this group of patients, the health community should focus on specific goals, including mobile health care clinics,[33,38] active case finding in shelters,[33] and, fundamentally, a multidisciplinary political and societal approach.[9,36] There is a need for improving socioeconomic indicators and advocating government actions that have been shown to be effective, such as conditional cash transfers.[39]

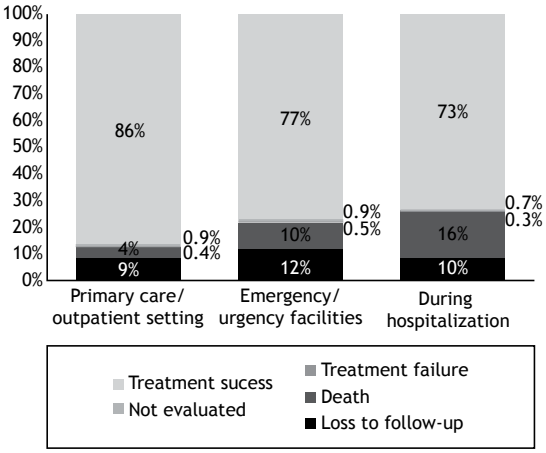

Figure 1. Tuberculosis treatment outcomes stratified by place of diagnosis.

Patients with known chronic diseases have a close relationship with the health care system. Our hypothesis is that such patients commonly have severe clinical presentations of tuberculosis or present with chronic disease exacerbations caused by tuberculosis, posing additional challenges for the diagnosis of tuberculosis and requiring a different approach (e.g., invasive procedures).[20] One expected limitation of studies such as ours (i.e., studies of secondary data) is the lack of detailed information on the degree of disease severity and the diagnostic process in such patients to determine whether they could have been diagnosed outside the hospital setting. Further studies are needed in order to gain a better understanding of this group of patients and provide data to inform potential interventions. Nevertheless, it is clear that we should focus on continuing tuberculosis education for health care workers at all levels of care and act to bridge the "knowledge-do gap", thus facilitating the implementation of tuberculosis guidelines in real practice.[40]

Of particular interest is the third group, which comprises young and "healthy" patients. The likely reason why such patients are diagnosed in EFs is that they live in areas where access to primary care is limited or where primary care clinics lack adequate infrastructure.[14,19,21] The stigma surrounding tuberculosis management at a health care clinic in the community likely leads such patients to seek medical assistance only when the disease is at an advanced stage or to expect a rapid solution in EFs.[3-5,21]

In the present study, traditional structural and socioeconomic indicators were found to be associated with a high probability of being diagnosed in EFs. We selected four municipalities to illustrate how the aforementioned indicators can influence the place of diagnosis. The most important message is that it is not enough to assess only one indicator. Many of the municipalities in the state of São Paulo are wealthy (as evidenced by a high IDH) but have a high proportion of socially vulnerable individuals (as evidenced by a high IPVS), as well as inadequate primary care coverage. In these municipalities, we can assume that

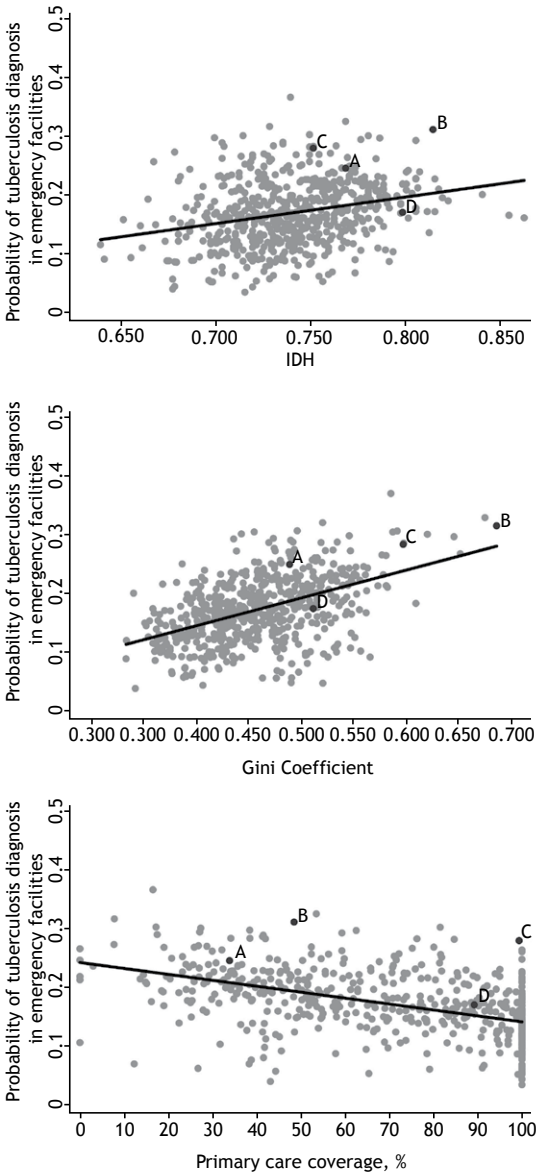

Figure 2. Relationship between municipal indicators and the probability of tuberculosis diagnosis in emergency facilities.* *The probability of tuberculosis diagnosis in emergency facilities was estimated from adjusted model 1, on the basis of the Índice de Desenvolvimento Humano (IDH, Human Development Index), the Gini coefficient, primary care coverage, population density, and urbanization. A, B, C, and D represent the four municipalities discussed in the manuscript, the proportions of patients diagnosed in emergency facilities being 53% for A, 41% for B, 21% for C, and 7% for D.

the richest are treated at private hospitals whereas the poorest have limited access to primary care, a factor that plays a major role in delaying the diagnosis of tuberculosis. Therefore, in order to improve tuberculosis care, it is essential to perform further analysis of each metropolitan area, municipality, and region for a tailored multifaceted intervention.

Our study has limitations that should be acknowledged. First, we analyzed data regarding one Brazilian state

rather than the entire country. However, we do not expect to observe a different pattern at the country level regarding place of tuberculosis diagnosis.[19,28] Second, we have no data regarding the number of health care visits before tuberculosis diagnosis or the time elapsed from symptom onset to diagnosis and treatment initiation. Third, data regarding large cities and smaller municipalities in the state were not analyzed separately, because our objective was to characterize the state of São Paulo as a whole. However, we speculate that our findings are also applicable to the large cities of the state. Finally, tuberculosis was microbiologically confirmed in 68% of all cases and in 85% of the patients who had pulmonary tuberculosis and valid sputum samples, proportions that are higher than the global average.[2] The TBweb database has a dedicated team of professionals who continuously check for consistency, and cases of patients whose initial diagnosis was changed or who were diagnosed with nontuberculous mycobacterial infection were excluded. However, we cannot exclude the possibility of misclassification. Nevertheless, this would have introduced only a minimal bias toward the null rather than a differential bias across places of diagnosis.

Although there has been a major improvement in tuberculosis control, there is a need for further improvement. In the state of São Paulo, 25% of all tuberculosis patients are diagnosed in EFs, a factor that is associated with poor treatment outcomes. At the municipal level, an EF diagnosis of tuberculosis is associated with inequality, social vulnerability, and inadequate primary care coverage, indicating areas for improvement.

ACKNOWLEDGMENTS

We are grateful to the dedicated staff of the Tuberculosis Control Department of the Prof. Alexandre Vranjac Center for Epidemiological Surveillance of the São Paulo State Department of Health for supervising the São Paulo State Tuberculosis Control Program and managing the TBweb database.

REFERENCES

1. Lönnroth K, Raviglione M. The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. Trans R Soc Trop Med Hyg. 2016;110(3):148-50. https://doi.org/10.1093/trstmh/trv108
2. World Health Organization. Global tuberculosis report 2015. Geneva: World Health Organization; 2015.
3. Almeida CP, Skupien EC, Silva DR. Health care seeking behavior and patient delay in tuberculosis diagnosis. Cad Saude Publica. 2015;31(2):321-30. https://doi.org/10.1590/0102-311X00195413
4. Miller AC, Polgreen LA, Cavanaugh JE, Hornick DB, Polgreen PM. Missed Opportunities to Diagnose Tuberculosis Are Common Among Hospitalized Patients and Patients Seen in Emergency Departments. Open Forum Infect Dis. 2015;2(4):ofv171. https://doi.org/10.1093/ofid/ofv171
5. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis. 2009;9:91. https://doi.org/10.1186/1471-2334-9-91
6. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008;8:15. https://doi.org/10.1186/1471-2458-8-15
7. Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. Int J Tuberc Lung Dis. 2014;18(3):255-266. https://doi.org/10.5588/ijtld.13.0585
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
9. Ranzani OT, Carvalho CR, Waldman EA, Rodrigues LC. The impact of being homeless on the unsuccessful outcome of treatment of pulmonary TB in Sao Paulo State, Brazil. BMC Med. 2016;14:41. https://doi.org/10.1186/s12916-016-0584-8
10. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Boletim Epidemiológico da Secretaria de Vigilância em Saúde; 2013.
11. Lindoso AA, Waldman EA, Komatsu NK, Figueiredo SM, Taniguchi M, Rodrigues LC. Profile of tuberculosis patients progressing to death, city of São Paulo, Brazil, 2002. Rev Saude Publica. 2008;42(5):805-12. https://doi.org/10.1590/S0034-89102008000500004
12. Governo do Estado de São Paulo. Secretaria de Estado da Saúde [homepage on the Internet]. São Paulo: a Secretaria; c2015 [cited 2015 Nov 15]. Center for Disease Control (CCD). CVE - Centro de Vigilância Epidemiológica "Prof. Alexandre Vranjac". Sistemas de Informação. Available from: http://www.saude.sp.gov.br/cve-centro-de-vigilancia-epidemiologica-prof.-alexandre-vranjac/areas-de-vigilancia/tuberculose/sistemas-de-informacao/
13. Portal de Estatísticas do Estado de São Paulo. Fundação Sistema Estadual de Análise de Dados [homepage on the Internet]. São Paulo: SEADE; [cited 2017 Sep 20]. Available from: http://www.seade.gov.br/
14. Popolin MP, Touso MM, Yamamura M, Rodrigues LB, da Cunha Garcia MC, Arroyo LH, et al. Integrated health service delivery networks and tuberculosis avoidable hospitalizations: is there a relation between them in Brazil? BMC Health Serv Res. 2016;16:78.
15. Coimbra I, Maruza M, Militao-Albuquerque Mde F, Moura LV, Diniz GT, Miranda-Filho Dde B, et al. Associated factors for treatment delay in pulmonary tuberculosis in HIV-infected individuals: a nested case-control study. BMC Infect Dis. 2012;12:208. https://doi.org/10.1186/1471-2334-12-208
16. dos Santos MA, Albuquerque MF, Ximenes RA, Lucena-Silva NL, Braga C, Campelo AR, et al. Risk factors for treatment delay in pulmonary tuberculosis in Recife, Brazil. BMC Public Health. 2005;5:25. https://doi.org/10.1186/1471-2458-5-25
17. Maior Mde L, Guerra RL, Cailleaux-Cezar M, Golub JE, Conde MB. Time from symptom onset to the initiation of treatment of pulmonary tuberculosis in a city with a high incidence of the disease. J Bras Pneumol. 2012;38(2):202-9.
18. Machado AC, Steffen RE, Oxlade O, Menzies D, Kritski A, Trajman A. Factors associated with delayed diagnosis of pulmonary tuberculosis in the state of Rio de Janeiro, Brazil. J Bras Pneumol. 2011;37(4):512-20. https://doi.org/10.1590/S1806-37132011000400014
19. Bartholomay P, Pelissari DM, de Araujo WN, Yadon ZE, Heldal E. Quality of tuberculosis care at different levels of health care in Brazil in 2013. Rev Panam Salud Publica. 2016;39(1):3-11.
20. Perrechi MC, Ribeiro SA. Outcomes of tuberculosis treatment among inpatients and outpatients in the city of Sao Paulo, Brazil. J Bras Pneumol. 2011;37(6):783-90. https://doi.org/10.1590/S1806-37132011000600012
21. Deponti GN, Silva DR, Coelho AC, Muller AM, Dalcin Pde T. Delayed diagnosis and associated factors among new pulmonary tuberculosis patients diagnosed at the emergency department of a tertiary care hospital in Porto Alegre, South Brazil: a prospective patient recruitment study. BMC Infect Dis. 2013;13:538. https://doi.org/10.1186/1471-2334-13-538
22. World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision. Geneva: World Health Organization; 2013.
23. Galesi VM. Data on tuberculosis in the state of São Paulo, Brazil [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:121.

https://doi.org/10.1590/S0034-89102007000800017

24. Instituto Brasileiro de Geografia e Estatística [homepage on the Internet]. São Paulo: IBGE; c2016 [cited 2016 Nov 15]. Censo Demográfico 2010; [about 3 screens]. Available from: https://www.ibge.gov.br/estatisticas-novoportal/sociais/populacao/9662-censo-demografico-2010.html?&t=o-que-e
25. Brasil. Ministério da Saúde. Departamento de Atenção Básica. Secretaria de Atenção à Saúde [homepage on the Internet]. Brasília: o Ministério; [cited 2017 Oct 3]. e-Gestor–Cobertura da Atenção Básica; [about 2 screens]. Available from: https://egestorab.saude.gov.br/paginas/acessoPublico/relatorios/relHistoricoCoberturaAB.xhtml
26. Portal de Estatísticas do Estado de São Paulo. Fundação Sistema Estadual de Análise de Dados [homepage on the Internet]. São Paulo: SEADE; [cited 2017 Oct 3]. Índice Paulista de Vulnerabilidade Social, versão 2010. [Adobe Acrobat document, 18p.]. Available from: http://indices-ilp.al.sp.gov.br/view/pdf/ipvs/metodologia.pdf
27. de Oliveira MF, Arcencio RA, Ruffino-Netto A, Scatena LM, Palha PF, Villa TC. The front door of the Ribeirao Preto health system for diagnosing tuberculosis [Article in Portuguese]. Rev Esc Enferm USP. 2011;45(4):898-904.
28. Loureiro RB, Villa TC, Ruffino-Netto A, Peres RL, Braga JU, Zandonade E, et al. Access to the diagnosis of tuberculosis in health services in the municipality of Vitoria, state of Espírito Santo, Brazil [Article in Portuguese]. Cien Saude Colet. 2014;19(4):1233-44. https://doi.org/10.1590/1413-81232014194.01002013
29. Ponce MA, Wysocki AD, Scatolin BE, Andrade RL, Arakawa T, Ruffino Netto A, et al. Tuberculosis diagnosis and performance assessment of the first health service used by patients in São José do Rio Preto, São Paulo State, Brazil [Article in Portuguese]. Cad Saude Publica. 2013;29(5):945-54. https://doi.org/10.1590/S0102-311X2013000500012
30. Escombe AR, Huaroto L, Ticona E, Burgos M, Sanchez I, Carrasco L, et al. Tuberculosis transmission risk and infection control in a hospital emergency department in Lima, Peru. Int J Tuberc Lung Dis. 2010;14(9):1120-6.
31. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2:16076. https://doi.org/10.1038/nrdp.2016.76
32. Jiménez-Fuentes MA, Augé CM, Gómez MN, Peiró JS, de Souza Galvão ML, Maldonado J, et al. Screening for active tuberculosis in high-risk groups. Int J Tuberc Lung Dis. 2014;18(12):1459-65. https://doi.org/10.5588/ijtld.14.0271
33. Story A, Aldridge RW, Abubakar I, Stagg HR, Lipman M, Watson JM, et al. Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. Int J Tuberc Lung Dis. 2012;16(11):1461-7. https://doi.org/10.5588/ijtld.11.0773
34. YouTubeBR [homepage on the Internet]. San Bruno (CA): YouTube; [cited 2017 Oct 3]. Ministry of Health - Brazil. Campanha Contra a Tuberculose | Filme Oficial 2015. Available from: https://www.youtube.com/watch?v=LCLfSQ_BDoI
35. Paula Rd, Lefevre F, Lefevre AM, Galesi VM, Schoeps D. Why do tuberculosis patients look for urgency and emergency unities for diagnosis: a study on social representation. Rev Bras Epidemiol. 2014;17(3):600-14. https://doi.org/10.1590/1809-4503201400030003
36. Hwang SW, Tolomiczenko G, Kouyoumdjian FG, Garner RE. Interventions to improve the health of the homeless: a systematic review. Am J Prev Med. 2005;29(4):311-9. https://doi.org/10.1016/j.amepre.2005.06.017
37. D'Amore J, Hung O, Chiang W, Goldfrank L. The epidemiology of the homeless population and its impact on an urban emergency department. Acad Emerg Med. 2001;8(11):1051-5. https://doi.org/10.1111/j.1553-2712.2001.tb01114.x
38. Hallais JA, Barros NF. Street Outreach Offices: Visibility, invisibility, and enhanced visibility [Article in Portuguese]. Cad Saude Publica. 2015;31(7):1497-504. https://doi.org/10.1590/0102-311X00143114
39. Torrens AW, Rasella D, Boccia D, Maciel EL, Nery JS, Olson ZD, et al. Effectiveness of a conditional cash transfer programme on TB cure rate: a retrospective cohort study in Brazil. Trans R Soc Trop Med Hyg. 2016;110(3):199-206. https://doi.org/10.1093/trstmh/trw011
40. Datta S, Saunders MJ, Tovar MA, Evans CA. Improving tuberculosis diagnosis: Better tests or better healthcare? PLoS Med. 2017;14(10):e1002406. https://doi.org/10.1371/journal.pmed.1002406

J Bras Pneumol. 2018;44(2):134-144
http://dx.doi.org/10.1590/S1806-37562017000000461

REVIEW ARTICLE

Epidemiological aspects, clinical manifestations, and prevention of pediatric tuberculosis from the perspective of the End TB Strategy

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Submitted: 14 December 2017.
Accepted: 11 February 2018.

Study carried out under the auspices of European Respiratory Society/Latin-American Thoracic Association and European Respiratory Society/Brazilian Thoracic Association collaborative projects.

ABSTRACT

Tuberculosis continues to be a public health priority in many countries. In 2015, tuberculosis killed 1.4 million people, including 210,000 children. Despite the recent progress made in the control of tuberculosis in Brazil, it is still one of the countries with the highest tuberculosis burdens. In 2015, there were 69,000 reported cases of tuberculosis in Brazil and tuberculosis was the cause of 4,500 deaths in the country. In 2014, the World Health Organization approved the End TB Strategy, which set a target date of 2035 for meeting its goals of reducing the tuberculosis incidence by 90% and reducing the number of tuberculosis deaths by 95%. However, to achieve those goals in Brazil, there is a need for collaboration among the various sectors involved in tuberculosis control and for the prioritization of activities, including control measures targeting the most vulnerable populations. Children are highly vulnerable to tuberculosis, and there are particularities specific to pediatric patients regarding tuberculosis development (rapid progression from infection to active disease), prevention (low effectiveness of vaccination against the pulmonary forms and limited availability of preventive treatment of latent tuberculosis infection), diagnosis (a low rate of bacteriologically confirmed diagnosis), and treatment (poor availability of child-friendly anti-tuberculosis drugs). In this review, we discuss the epidemiology, clinical manifestations, and prevention of tuberculosis in childhood and adolescence, highlighting the peculiarities of active and latent tuberculosis in those age groups, in order to prompt reflection on new approaches to the management of pediatric tuberculosis within the framework of the End TB Strategy.

Keywords: Tuberculosis, pulmonary/prevention & control; *Mycobacterium tuberculosis*; Lung diseases/etiology; Child; Adolescent.

INTRODUCTION

Tuberculosis is still one of the main causes of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that, in 2016, there were 10.4 million new cases of tuberculosis, as well as that, in that same year, tuberculosis caused the deaths of 1.3 million non-HIV-infected individuals and 374,000 HIV-infected individuals. Also in 2016, tuberculosis was one of the ten leading causes of death worldwide, ranking above HIV/AIDS as the leading cause of death from a single infectious agent.[1]

Children are particularly vulnerable to tuberculosis. Pediatric cases of tuberculosis account for 10% of all cases of the disease. In 2015, there were an estimated 1 million new cases of childhood tuberculosis and an estimated 210,000 deaths from tuberculosis in children.[2]

Despite the advances in tuberculosis control achieved in the last decade, our country still ranks among those with the highest tuberculosis burdens. In the new WHO classification of priority countries for tuberculosis control worldwide (comprising three lists of 30 countries each), Brazil ranked 20th regarding the burden of disease and 19th regarding the tuberculosis/HIV coinfection.[2,3] In 2015, 69,000 tuberculosis cases were reported in Brazil (4,500 of those cases resulting in death), 6,800 HIV-infected individuals were diagnosed with tuberculosis, and more than 1,000 individuals developed multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB).[3]

In 2014, the WHO approved The End TB Strategy, which is in alignment with the United Nations Sustainable Development Goals. The new strategy adopts the vision of "A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis" and has the goal of ending

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ISSN 1806-3713

the global epidemic and eliminating tuberculosis in low-incidence countries. The goals, to be met by 2035, are a 90% reduction in the incidence rate and a 95% reduction in the number of deaths due to tuberculosis—both in comparison with the rates reported for 2015. The first translates to a reduction in the tuberculosis incidence rate to fewer than 10 cases/100,000 population, which would represent the end of tuberculosis as a public health problem and a major step forward in disease control worldwide. However, the complete elimination of tuberculosis, defined as below 1 case/100,000,000 population, is an even more ambitious goal. In order for these objectives of the End TB Strategy to be achieved, there must be effective control measures that are based on three pillars[3-6]: integrated, patient-centered tuberculosis care and prevention; bold policies and supportive systems; and intensified research and innovation related to tuberculosis.

Given the considerations listed above, the relevance of tuberculosis at the global, regional, and national levels becomes evident. However, the importance of tuberculosis as a cause of morbidity and mortality in individuals under 15 years of age and the peculiarities of its prevention, diagnosis, and treatment in that age group have only recently gained prominence in the international scientific community.[7] In this review, we present the main clinical and epidemiological aspects of tuberculosis in children, together with aspects related to its prevention, aiming to contribute to the discussion of interventions to be implemented in pediatric tuberculosis patients within the framework of the End TB Strategy.

EPIDEMIOLOGY

The occurrence of tuberculosis in children is closely related to the prevalence of tuberculosis among adults. The risk of developing infection with *Mycobacterium tuberculosis* is higher for children living in regions where there is a high prevalence of active tuberculosis, in dwellings with high population density (many people sleeping in the same room), and in buildings with poor ventilation.[8-10]

In 2016, new cases of tuberculosis notified among children accounted for 6.9% of all tuberculosis cases worldwide. In that same year, there were over a million estimated new cases of pediatric tuberculosis—550,000 (range, 340,000-760,000) among males and 490,000 (range, 300,000-680,000) among females—corresponding to 10% of all new tuberculosis cases worldwide. According to the WHO, the three regions where most pediatric tuberculosis cases are concentrated are Southeast Asia, Africa, and the Western Pacific, which respectively accounted for 35%, 30%, and 20% of the new cases reported in 2015.[1]

It is estimated that tuberculosis caused the death of 210,000 children worldwide in 2015,[2] although mathematical models indicate that the number could have reached 239,000, 80% (191,000) of those deaths having occurred in children under 5 years of age in Africa and Southeast Asia.[11] Based on those estimates, Dodd et al.[11] stated that tuberculosis might be the sixth leading cause of death in the 1- to 5-year age group, causing more deaths than do diseases such as meningitis, AIDS, measles, and whooping cough.

The mortality associated with tuberculosis among children who go untreated has been estimated to be 21.9% overall and 43.6% among those under 5 years of age. However, it has been reported that such mortality can be reduced to 0.9% when tuberculosis treatment is carried out properly.[12] Mortality due to tuberculosis in children is underestimated, because, for many children who die from tuberculosis, the cause of death is listed as pneumonia, HIV/AIDS, meningitis, or malnutrition.[13,14]

There are no official estimates of the prevalence of latent tuberculosis infection (LTBI) among children, because there are no accurate diagnostic tests. However, in a study using mathematical modeling,[11] it was estimated that the number of children with LTBI worldwide in 2010 was 53,000,000 (95% CI: 41,000,000-69,000,000).

NATURAL HISTORY OF TUBERCULOSIS IN CHILDREN

Approximately 90% of people do not become ill after primary infection with *M. tuberculosis*, subsequently developing LTBI.[15-17] However, children are at a higher risk of rapid progression from tuberculosis infection to active tuberculosis and more often develop the extrapulmonary or disseminated forms of the disease. The risk of active tuberculosis is highest in children under 5 years of age, and recent evidence suggests that children can become infected after only 15-20 min of exposure to *M. tuberculosis*.[17-20] After *M. tuberculosis* infection, the disease can manifest at any time in life, depending on the balance between the pathogen and the host immunity, especially cellular immunity, although most children will develop active tuberculosis within a year after becoming infected. That is why determining the history of contact with cases of pulmonary tuberculosis (PTB) is so important and reveals the maintenance of tuberculosis transmission within the community.[17]

The differences between the pediatric and adult populations in terms of the pathophysiology and clinical features of tuberculosis make the diagnosis of the disease more challenging in the former.[18,21] Various factors seem to influence the balance between the risk of LTBI and the progression to active tuberculosis, such factors including age, nutritional status, BCG vaccination, and immune status.[18,22]

Data regarding active surveillance in the era before tuberculosis treatment suggest that most children develop radiological signs after *M. tuberculosis* infection, including 60-80% of children under 2 years of age. However, less than 10% of those cases were reported,

suggesting that *M. tuberculosis* infection was controlled by the host immune response in most cases.[22,23]

Pulmonary infection with *M. tuberculosis* occurs when bacilli successfully reach a terminal airway, resulting in a localized pulmonary inflammatory process called a parenchymal focus (Ghon focus). From this focus, the bacilli disseminate through the local lymphatic system to regional lymph nodes. A Ghon focus is characterized by local tuberculous lymphangitis and the involvement of regional lymph nodes. This combination is known as the primary complex. From the regional lymph nodes, the bacilli enter the systemic circulation directly or via the lymph duct. This occult hematogenous dissemination occurs before an appropriate immune response is able to prevent the development of active tuberculosis. After dissemination, the bacilli can survive within the target organs for long periods. The future course of active tuberculosis depends on the dynamic balance between the host immunity and the pathogen.[24]

In children under 2 years of age, primary tuberculosis infection frequently progresses to severe disease, without significant prior symptoms, usually in the first 12 months after contact with active tuberculosis cases. In children 2-10 years of age, primary infection rarely progresses to severe disease; when that does occur, it is accompanied by significant clinical symptoms. In children over 10 years of age, primary infection usually evolves to adult-type active tuberculosis. Effective early intervention in this age group will reduce the possibility of cavitary disease and transmission of the disease to the community. The disease has been observed to behave the same way in immunocompromised children as in children with immature immunity (those under 2 years of age).[18,24]

The evolution of tuberculosis after pulmonary infection in childhood includes a number of phases[24]:

- Phase 1 begins 3 to 8 weeks after the primary infection. At the end of the initial asymptomatic period, the patient may present hypersensitivity reactions, such as fever, erythema nodosum, a positive response to the tuberculin skin test (TST), and development of the primary complex, which can be seen on a chest X-ray.
- Phase 2 begins 1-3 months after the primary infection, following the occult hematogenous dissemination that occurs during the incubation. This is the period of greatest risk for the development of tuberculous meningitis and miliary tuberculosis in small children, although these manifestations of tuberculosis may occur at any time after hematogenous dissemination.
- Phase 3 begins 3-7 months after the primary infection. During this phase, there can be pleural effusion in children over 5 years of age and bronchial disease in children under 5 years of age.
- Phase 4 lasts from the end of phase 3 until the calcification of the primary complex, which occurs 1-3 years after the primary infection. In phase 4, osteoarticular tuberculosis can occur in children under 5 years of age and adult-type active tuberculosis can develop in adolescents. In general, the risk of disease progression is minimal when calcification occurs. However, adult-type active tuberculosis, a delayed manifestation following the primary infection, develops after the calcification is present.
- Phase 5 begins after the calcification is concluded, more than 3 years after the primary infection. This phase represents the period of late tuberculosis manifestations, including reactivation of pulmonary tuberculosis.

CLINICAL MANIFESTATIONS OF TUBERCULOSIS IN CHILDHOOD

From the clinical perspective, childhood tuberculosis presents nonspecific signs and symptoms that worsen with time, and some children with active PTB can be asymptomatic, in which case active PTB can be clinically mistaken for LTBI.[25] The main symptoms of pediatric tuberculosis include fatigue, loss of appetite, night sweats, weakness, weight loss, and evening fever. When the disease reaches the lungs, the child can present chest pain and cough (productive or nonproductive), which can, in rare cases, be accompanied by hemoptysis. Other signs and symptoms include fever (moderate, persistent for 15 days or more, and often arising in the evening), weight loss, anorexia, hemoptysis, pallor, lymphadenopathy, and hepatosplenomegaly. Persistent cough (productive or not) is the main symptom of the pulmonary form of the disease, which is the most common form of pediatric tuberculosis.[16,26] Erythema nodosum, keratoconjunctivitis, and joint pain can also occur. It is noteworthy that hemoptysis can occur in adolescence but is rare in childhood.[27]

Tuberculosis can affect organs other than the lungs; approximately 20% of tuberculosis cases in children have extrapulmonary manifestations.[26] In such cases, the symptoms vary according to the organs affected and can occur in the lymph nodes, kidneys, bones, and meninges, among other sites. One of the most serious forms of the disease is miliary tuberculosis, resulting from the hematogenous dissemination of *M. tuberculosis*, which increases the risk of meningitis.[16]

In HIV-infected patients, the clinical presentation of tuberculosis is influenced by the degree of immunosuppression and, in general, the diagnostic investigation in patients with tuberculosis/HIV coinfection is similar to that employed for the general population.[28,29] In addition, because of the greater frequency of extrapulmonary and disseminated forms in HIV-infected children, an appropriate diagnostic investigation includes invasive procedures to obtain clinical specimens (such as those of pleural fluid and cerebrospinal fluid) or biopsy samples from solid organs (such as lymph nodes and the pleura).[29]

DIAGNOSING TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

The diagnosis of tuberculosis in childhood continues to be a challenge. The main international consensus statement on childhood tuberculosis, published by the WHO, emphasizes this notion and states that the

clinical, radiological, and epidemiological features are the most indicative of active tuberculosis in childhood. Therefore, the approach to diagnosing tuberculosis in children is based on the following[17]: careful clinical history taking (including the history of contact with tuberculosis cases and of symptoms consistent with the disease); a thorough clinical examination, with special attention to aspects of childhood development; the TST result; chest X-ray findings (when available); bacteriological confirmation whenever possible; specific investigation of the organ involved in suspected cases of pulmonary and extrapulmonary tuberculosis; and HIV testing. The WHO consensus statement also highlights the importance of seeking bacteriological or molecular confirmation with the molecular test for *M. tuberculosis* and for resistance to rifampin (Xpert MTB/RIF) and does not recommend the so-called "therapeutic test"; that is, the attempt to establish a diagnosis by applying the treatment for tuberculosis and awaiting an improvement in the clinical status of the patient.[17]

In children living with HIV/AIDS, tuberculosis should be investigated at all routine clinical visits by inquiring about the existence of the four main symptoms: fever, cough, night sweats, and weight loss. The presence of any of those symptoms is suggestive of active tuberculosis and indicates the need for a more detailed investigation.[30]

Radiological aspects of tuberculosis in children and adolescents

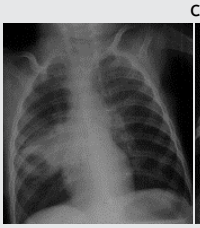
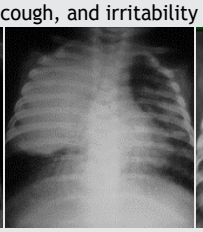
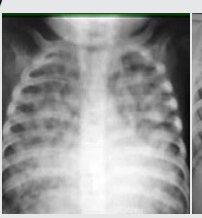
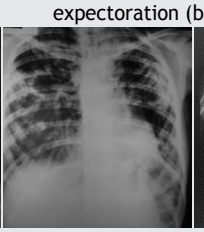
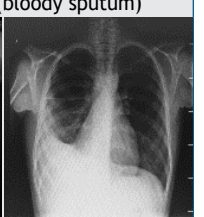
Some of the radiological aspects of tuberculosis in childhood are shown in Chart 1. The radiological aspects most commonly associated with PTB fall into two categories: those observed in patients < 10 years of age; and those observed in patients 10-18 years of age. In children under 10 years of age, there is a predominance of images consistent with primary tuberculosis or the primary complex. In such patients, the primary complex is evolving and the manifestations usually occur within the first 5 years after primary infection. Such manifestations include hilar lymphadenopathy, miliary images (diffuse micronodular or nodular infiltrates, usually bilateral), and characteristics of chronic or slowly evolving pneumonia—also known as expansive pneumonia.[31] In patients 10-18 years of age, the radiological aspect is one of post-primary tuberculosis (i.e., adult type tuberculosis).[31] In such patients, the images are predominantly in the upper third or in the superior segment of the lower lobe of both lungs, often showing cavitations.[31]

Microbiological diagnosis

The confirmation of a diagnosis of tuberculosis by means of bacteriological testing is, in general, difficult to achieve in younger children but viable in those ≥ 10 years of age, who typically develop bacteriological PTB. Most children who develop primary tuberculosis are sputum smear-negative or produce paucibacillary specimens. Children under 8 years of age rarely produce sputum, and the diagnosis of tuberculosis in such children is made without bacteriological confirmation in 80% of cases. For children who cannot expectorate, it is recommended that samples be collected through gastric lavage if possible.[17] However, the use (direct examination and culture) of induced sputum samples in children has proven to be more sensitive than is gastric lavage and is usually well accepted.[32,33]

In practice, the conventional Ziehl-Neelsen method is still used for direct staining for AFB. However, the method has low (10-15%) sensitivity for specimens with a concentration below 5×10^3 bacilli/mL, which explains the negative results in children who produce paucibacillary specimens.[17] The alternative method would be fluorescent light-emitting diode microscopy, which, in most studies, has higher sensitivity and specificity than does Ziehl-Neelsen staining. Likewise, the culture can be carried out on conventional Löwenstein-Jensen medium or, more recently, in Middlebrook 7H9 liquid medium, the latter having the advantages of more rapid *M. tuberculosis* growth and higher sensitivity for paucibacillary specimens (including blood samples). Middlebrook 7H9 has become the culture medium of choice for use in automated methods (Chart 2). Among such methods, the most well-known is the use of the BACTEC Mycobacteria Growth Indicator Tube 960 system, which is a fully automated, nonradiometric method with an average detection time of 7 days.[28]

Chart 1. Most common clinical and radiological aspects of pulmonary tuberculosis in children and adolescents.

Aspect	Pediatric patients				
	< 10 years of age			10-18 years of age	
Signs and symptoms	Persistent fever, weight loss, cough, and irritability			Persistent fever, adynamia, and expectoration (bloody sputum)	
Chest X-ray					
Finding	Right hilar lymphadenopathy	Chronic pneumonia	Miliary pattern	Pulmonary cavitations	Pleural effusion

Molecular diagnosis

The molecular diagnosis of tuberculosis involves genotypic tests based on the amplification of nucleic acids (nucleic acid amplification tests). Such tests include line probe assays and the Xpert MTB/RIF assay. All of these methods offer the great advantage of faster laboratory results and identification of resistance to drugs such as rifampin and isoniazid, as well as high sensitivity and specificity (Chart 2).

The Xpert MTB/RIF assay has been available in several cities in Brazil since 2014. It is a nucleic acid amplification test that employs the technique of real-time polymerase chain reaction on the GeneXpert platform. In Brazil, it is known as the rapid molecular tuberculosis test. The Xpert MTB/RIF assay facilitates the identification of mycobacterial DNA and reduces the risk of cross-reactivity during the amplification of the DNA. Its result can be obtained in the laboratory in approximately 2 h, allowing the identification of *M. tuberculosis* and the detection of rifampin-resistant strains.[34] The incorporation of the molecular diagnosis of tuberculosis has also been recommended for use in children since 2013.[35] The use of the Xpert MTB/RIF assay in pediatric tuberculosis is still limited, because its performance is best in bacteriologically confirmed tuberculosis, which accounts for only a minority of cases in children.[36]

In a retrospective study on the use of the Xpert MTB/RIF assay at primary health care clinics in the city of Rio de Janeiro, the Xpert MTB/RIF assay result was positive (detectable levels of *M. tuberculosis*) in 131 (16%) of 852 cases of suspected tuberculosis in adolescents, rifampin-resistant strains being identified in 3 (2%).[37] A part of the samples obtained from cases detected by the Xpert MTB/RIF assay were submitted to drug susceptibility testing and 17% were found to be resistant to drugs other than rifampin.[37]

Scoring system for tuberculosis diagnosis in childhood

In 2002, the Brazilian National Ministry of Health (NMH) proposed a new scoring system for the diagnosis of intrathoracic tuberculosis (PTB),[15] which has already been validated, in HIV-infected and non-HIV-infected children,[38,39] and tested in other countries,[40,41] showing high accuracy. Recently, a group of authors[42] employed a variety of diagnostic systems, including that proposed by the NMH, to study a cohort of 121 HIV-infected children and adolescents. The NMH system has been found to produce few false-positive results and to be useful as a screening test in such patients (Chart 3). However, the bacteriological diagnosis of active tuberculosis should be carried out whenever possible, because, among other advantages, it allows the identification of *M. tuberculosis* and of the profile of susceptibility to anti-tuberculosis drugs, which is particularly relevant given the increasing number of cases of MDR-TB and XDR-TB.[35]

New diagnostic methods

The recent introduction of a new version of the Xpert MTB/RIF assay, known as the Xpert MTB/RIF Ultra assay, could improve the accuracy of the diagnosis childhood tuberculosis, because its sensitivity is superior to that of the conventional Xpert MTB/RIF assay for paucibacillary samples. The frequency of positive results in respiratory and cerebrospinal fluid samples obtained from children has been found to be greater with the use of the Xpert MTB/RIF Ultra assay than with that of the Xpert MTB/RIF assay.[1]

The string test is a new diagnostic method that has been used for the diagnosis of tuberculosis in children. The patient swallows a capsule containing a thin string, which unravels in the stomach and is coated with gastrointestinal secretion. After some time, the string is removed and the material is sent to the laboratory so it can be processed by bacteriological or molecular methods. The string test resembles conventional gastric lavage but is less invasive. However, there have been few studies of the use of the string test in diagnosing tuberculosis in children. In a study conducted by Nansumba et al.,[43] the results were similar to those obtained from induced sputum.

Chart 2. Bacteriological and molecular methods for the diagnosis of childhood tuberculosis.

Method	Time to results	Sensitivity	Specificity
Microscopy			
Ziehl-Neelsen staining	Same day	32-94%	50-99%
Fluorescent LED	Same day	52-97%	94-100%
Culture			
Liquid media with susceptibility testing	10-21 days	89% (AFB+) 73% (AFB− and culture+)	> 99%
Molecular technique (NAATs)			
Xpert MTB/RIF assay	Same day	98% (AFB+); 67% (AFB−) 95%, RIF-resistant	99% (AFB−) 98%, RIF-resistant
LPA (1 line) [INH and RIF]	1-2 days	98%, RIF; 84%, INH	99%
LPA (2 lines) [Fluo; Injet]	1-2 days	86-87%	99%
LAMP	Same day	76-80%	97-99%

LED: light-emitting diode; NAATs: nucleic acid amplification tests; Xpert MTB/RIF assay: molecular test for *M. tuberculosis* and for resistance to rifampin; RIF: rifampin; INH: isoniazid; LPA: line probe assay; Fluo: fluoroquinolones; Injet: second-line injectable drugs; and LAMP: loop-mediated isothermal amplification. Source: Pai et al.[45]

Chart 3. Diagnosis of pulmonary tuberculosis using the Brazilian National Ministry of Health scoring system in children and adolescents who have tested negative on sputum smear microscopy.[a]

Clinical findings	Chest X-ray findings	History of contact with an adult pulmonary tuberculosis case	TST	Nutritional status
Fever or fatigue, productive cough, weight loss, night sweats for > 2 weeks despite nonspecific antibiotic use	Adenomegaly or miliary pattern; infiltration (with or without cavitations) unaltered for > 2 weeks or worsening despite nonspecific antibiotic use	Close contact for < 2 years	BCG > 2 years prior or no BCG (induration ≥ 5 mm) or BCG < 2 years prior (induration ≥ 10 mm)	Severe malnutrition
Score = 15	Score = 15	Score = 10	Score = 15	Score = 5
Asymptomatic or symptomatic for < 2 weeks	Infiltration (with or without cavitations) for< 2 weeks	No contact or occasional contact	Induration 0-4 mm	Normal
Score = 0	Score = 5			
Respiratory symptoms improved spontaneously or with nonspecific antibiotic use	Normal findings	Score = 0	Score = 0	Score = 0
Score = −10	Score = −5			

TST: tuberculin skin test. [a]Diagnostic interpretation of the chart: ≥ 40 points: highly likely; ≥ 30 and ≤ 39 points: possible; and ≤ 29 points: unlikely. Source: Brasil. Ministério da Saúde.[28]

TREATMENT OF ACTIVE TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

The treatment strategy in Brazil follows what has been proposed by the WHO, separating children under 10 years of age from adolescents and adults. The doses of isoniazid and rifampin have been adjusted according to the WHO standards.[17] The basic treatment regimens for childhood tuberculosis and tuberculous meningitis are detailed in Chart 4 and Chart 5, respectively.

The treatment of MDR-TB (infection with an *M. tuberculosis* strain resistant to at least rifampin and isoniazid) in childhood is still based on the regimens recommended for adults. There has been recent progress toward reducing treatment time in special situations that are relevant to children, mainly due to the recent introduction of the diarylquinoline bedaquiline in such treatment regimens. Therefore, regimens of only 9-12 months can be prescribed in patients who have not previously been treated for MDR-TB.[44] The long-duration regimens in patients with MDR-TB can involve treatment for 20 months or more, according to the particularities of each case. The factors to be considered in choosing between a short and a long treatment regimen for MDR-TB in childhood can be seen in Chart 6.

In special situations, isoniazid and ethambutol can strengthen the treatment regimen for MDR-TB.[35,45] Another drug that is in the process of being incorporated into treatment regimens for children with MDR-TB is delamanid, which has been shown to be effective in studies of tolerance and pharmacokinetics, although such studies have not included patients with HIV infection, heart disease, severe malnutrition, or other comorbidities. The WHO recommends the use of delamanid in the treatment regimen for MDR-TB in children who are not eligible for the previously mentioned short regimen, especially taking into account that there is no safe position regarding the interaction of bedaquiline and delamanid in the same patient.[46] It has been proposed that the administration of delamanid in childhood constitutes compassionate use.[47,48] However, systematic reviews of bedaquiline and delamanid use in children recommend caution and accurate monitoring of the Q_T interval corrected with Fridericia's formula.[49-51] Studies of those drugs are scarce, which limits their current usage.[52]

In the evaluation of tuberculosis/HIV coinfection in children, it is recommended that all individuals diagnosed with HIV/AIDS and active tuberculosis should start combined antiretroviral therapy (ART), regardless of the clinical form of the tuberculosis and the CD4+ T lymphocyte count.[28,29] It should be borne in mind that the atypical forms of the disease occur in patients with a higher degree of immunodeficiency caused by HIV infection.[28,53]

During the treatment of tuberculosis/HIV coinfection, when the ART regimen is chosen, it should be taken into consideration that rifampin is a potent inducer of cytochrome P450 and glycoprotein P, which significantly reduces the plasma concentrations of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, because those drugs use the same metabolic pathway.[28]

Since 2015, formulations of anti-tuberculosis drugs in fixed-dose combinations, presented as dissolvable tablets with a pleasant taste, have been available in the following doses: rifampin (75 mg), isoniazid (50

Chart 4. Basic regimen for the treatment of tuberculosis in children under 10 years of age.

Treatment phase	Drugs	Daily dosage, by patient weight						
		≤ 20 kg	21-25 kg	26-30 kg	31-35 kg	36-40 kg	41-45 kg	≥ 45 kg
		mg/kg	mg	mg	mg	mg	mg	mg
2RHZ	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300
	Pyrazinamide	35 (30-40)	750	1000	1000	1500	1500	2000
4RH	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300

Source: World Health Organization.[17]

Chart 5. Basic regimen for the treatment of tuberculous meningitis in children.

Treatment phase	Drugs[a]	Daily dosage, by patient weight						
		≤ 20 kg	21-25 kg	26-30 kg	31-35 kg	36-40 kg	41-45 kg	≥ 45 kg
		mg/kg	mg	mg	mg	mg	mg	mg
2RHZ	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300
	Pyrazinamide	35 (30-40)	750	1000	1000	1500	1500	2000
10RH	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300

Source: World Health Organization.[17] [a]During the treatment of tuberculous meningitis, a corticosteroid can be added to the anti-tuberculosis regimen: oral prednisone (1-2 mg/kg daily) for four weeks or, in severe cases, intravenous dexamethasone (0.3-0.4 mg/kg daily) for 4-8 weeks, with gradual dose reductions over the subsequent 4 weeks.

Chart 6. Factors to consider when choosing the treatment regimen for children with multidrug-resistant tuberculosis.

- Confirmed susceptibility to or presumed efficacy of all drugs of the short MDR-TB regimen (isoniazid resistance excepted)
- No exposure to the second-line MDR-TB regimen for > 1 month
- No intolerance to any drug in the short non-toxic MDR-TB regimen (i.e., drug interactions)
- Pregnancy excluded
- Pulmonary disease only
- All drugs in the short MDR-TB regimen are available for the program

↓ YES ↓ → Short MDR-TB regimen

Regimen failure, drug intolerance, return after interruption for > 2 months, emergence of an exclusion criterion →

↓ NO ↓ → Longer (individualized) MDR-TB regimen

MDR-TB: multidrug-resistant tuberculosis. Source: Grzemska M.[9]

mg), and pyrazinamide (150 mg) for the intensive phase; and rifampin (75 mg) and isoniazid (75 mg) for the maintenance phase. Although those formulations are not yet available in Brazil, there are ongoing negotiations to acquire them. There are as yet no second-line drugs available in formulations suitable for children. Therefore, the treatment of MDR-TB still presents obstacles related to the administration of many drugs that need to be adapted to administration in pediatric patients, which clearly has a negative impact on adherence.[54,55]

TUBERCULOSIS PREVENTION IN CHILDREN

The health interventions currently available for tuberculosis prevention which relate specifically to children are LTBI treatment and BCG vaccination. LTBI is defined as a state of persistent immune response to exposure to *M. tuberculosis* without clinical or radiological evidence of active tuberculosis.[56] Adults and children who are in contact with smear-positive PTB patients are at a higher risk of LTBI and of progression from LTBI to active disease, as well as a higher incidence of active tuberculosis.[57-60] The pharmacological treatment of LTBI is the main intervention capable of preventing the progression to active tuberculosis in such individuals.[2]

Children, in particular those under 5 years of age, represent a group for which there is clear evidence of the benefits of testing for and treating LTBI.[58-60] The WHO,[59] the International Union against Tuberculosis and Lung Disease,[19] and the International Standards for Tuberculosis Care,[61] as well as the main North-American and European guidelines,[62-65] are unanimous in recommending that, after active tuberculosis has been excluded, LTBI be treated in two high-risk groups: children under 5 years of age and people living with HIV who have been exposed to cases of bacteriologically

confirmed PTB. Screening children under 5 years of age for active tuberculosis and LTBI is a strategy recommended by the WHO, even in countries with limited resources.[57,59]

The Brazilian National Tuberculosis Program guidelines recommend that the investigation and, if necessary, the treatment of LTBI in children under 5 years of age who have been in contact with smear-positive PTB cases be prioritized.[28] However, only 44.9% of such contacts were screened in 2015 in the country as a whole; in the states of Amapá and Rio de Janeiro, that proportion was only 22.3% and 22.1%, respectively, in that same year.[3]

In 2016, there were, worldwide, approximately 1.3 million children under 5 years of age who were close contacts of bacteriologically confirmed PTB cases and were therefore eligible for preventive tuberculosis treatment. Although the number of children in this age group who reportedly started the treatment for LTBI increased by 85% between 2015 and 2016, it still represents only 13% of the children who are eligible to receive treatment.[1]

Administration of the treatment for LTBI in children under 5 years of age who are contacts of smear-positive PTB cases (some guidelines use the term "cases of contagious tuberculosis", also including cases of laryngeal tuberculosis) is recommended whether or not there has been confirmation of LTBI.[56,57,61] As in adults, the diagnosis of LTBI in children is based on the results of a TST performed by the Mantoux method. The interpretation of those results (skin induration measured in millimeters) varies according to the degree of exposure to the index case and to the BCG immunization status. In Brazil, children and adolescents who are household contacts of PTB cases and have not been vaccinated with BCG or were vaccinated more than 2 years prior are considered positive if their response to a TST is a skin induration of at least 5 mm. In the case of those vaccinated with BCG less than 2 years prior, the cut-off induration for positivity is 10 mm. Contacts initially showing negative TST results should repeat the test after 8 weeks.[28]

Interferon-gamma release assays (IGRAs) have lower sensitivity in children under 2 years of age and in those who are immunosuppressed; IGRAs are not typically recommended for use in this age group.[17,65,66] The frequency of indeterminate test results among such children is apparently higher with the QuantiFERON-TB Gold In-Tube test than with the T-SPOT.TB test. For older children, the sensitivity and specificity of the QuantiFERON-TB Gold In-Tube test and the T-SPOT.TB test are comparable to those reported for their use in adults. However, in comparison with TSTs, IGRAs are more expensive and require laboratory support that is more sophisticated, therefore not being indicated as a substitute for TST in regions where resources are limited.[17,56]

The recommended treatment regimens for LTBI are as follows[56,62]: isoniazid daily for 6 months or 9 months (the 9-month regimen is the only one that the U.S. Centers for Disease Control and Prevention recommend for use in children); isoniazid plus rifampin daily for 3-4 months; rifampin daily for 3-4 months; and isoniazid plus rifapentine weekly for 3 months (not recommended for children under 2 years of age or for HIV-infected patients on ART).

The effectiveness of treating LTBI with isoniazid for 6-12 months (ideally, for 9 months) is estimated to be 60-90%, with no significant differences in the level of protection among treatments of different durations.[67] A recent review showed that prophylaxis with isoniazid given to HIV-infected children in Africa reduces the risk of active tuberculosis and death among those who are not on ART, although there was no clearly observed benefit for the children who are on ART.[68] The use of the 6-month regimen of isoniazid (5-10 mg/kg daily, up to a maximum of 300 mg/day) is the strategy recommended by the Brazilian National Tuberculosis Program, and the regimen is generally well tolerated by children and adolescents.[28] For adults and children who are contacts of MDR-TB cases, there are as yet no regimens for preventive treatment based on efficacy studies, although the execution of such studies is considered a priority by the scientific community. The combination of at least two drugs (at least one of which should be a bactericide) is the regimen recommended by experts.[35,69]

One of the priority indicators of the End TB Strategy is the preventive treatment of ≥ 90% of HIV-infected individuals and children who are contacts of PTB cases.[4] However, to achieve that objective, it will be necessary to increase the capacity of programs to investigate contacts and to offer preventive therapy. Several barriers to the preventive treatment in children have been identified, such as the inability to exclude active tuberculosis, the fear of creating resistance to tuberculosis drugs, the poor adherence to long-duration treatment regimens, the low socioeconomic level of some families, and poor adherence to active tuberculosis treatment by index cases.[14,70] Unless those barriers can be overcome, the indicators concerning the investigation of contacts and the completion of preventive tuberculosis treatment with isoniazid in children will be far from what is expected.

For more than 100 years, the BCG vaccine has been available for the primary prevention of tuberculosis in children. Although the vaccine prevents 60-90% of cases of the severe forms of active tuberculosis in children (disseminated forms and tuberculosis meningitis), it is not efficacious in the prevention of the disease in adults.[17] In Brazil, there is a high level of BCG immunization coverage.[3,28] However, that has not had a significant impact on the number of cases of PTB or the less severe forms of extrapulmonary tuberculosis among children infected by *M. tuberculosis* after vaccination. The slow decline in the incidence of tuberculosis observed worldwide in recent decades underscores the need for a more effective vaccine against tuberculosis, one that would provide protection

against all forms of tuberculosis in different age groups. In 2017, there were 12 new tuberculosis vaccines being tested in phase I, II, or III trials.[1]

FINAL COMMENTS

Children represent the most fragile link among the complex mechanisms currently involved in the control of tuberculosis. In order to achieve the ambitious goals outlined in the End TB Strategy, concerted efforts are required from the various sectors of society. Priority should be given to measures that address the peculiarities of tuberculosis in childhood: ensuring the early identification (through contact screening) and treatment of active tuberculosis and LTBI in children; using methods that are more sensitive and less invasive for the diagnosis of extrapulmonary tuberculosis and of tuberculosis in patients who produce paucibacillary samples; making child-friendly anti-tuberculosis drugs more widely available; developing tuberculosis vaccines that are more effective; and formulating new drugs for resistant forms of tuberculosis that have low toxicity in children. Adequate financial resources and political will are essential if these goals are to be met and tuberculosis is finally to be removed from the list of the leading causes of death among children worldwide.

ACKNOWLEDGMENTS

The paper is part of the European Respiratory Society/Latin-American Thoracic Association and European Respiratory Society/Brazilian Thoracic Association collaborative projects.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Nov 27]. Global tuberculosis report 2017. [Adobe Acrobat document, 262p.]. Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1
2. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Nov 27]. Global tuberculosis report 2016. [Adobe Acrobat document, 214p.]. Available from: http://apps.who.int/medicinedocs/documents/s23098en/s23098en.pdf
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis [homepage on the Internet]. Brasília: Ministério da Saúde; [cited 2017 Feb 24]. Brasil Livre da Tuberculose. Plano nacional pelo fim da tuberculose como problema de saúde pública; 1st ed; 2017. [Adobe Acrobat document, 40p.]. Available from http://portalarquivos.saude.gov.br/images/pdf/2017/fevereiro/24/Plano-Nacional-Tuberculose.pdf
4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Mar 24]. The End TB Strategy. [Adobe Acrobat document, 20p.]. Available from: http://www.who.int/tb/End_TB_brochure.pdf?ua=1
5. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015;45(4):928-52. https://doi.org/10.1183/09031936.00214014
6. Rendon A, Fuentes Z, Torres-Duque CA, Granado MD, Victoria J, Duarte R, et al. Roadmap for tuberculosis elimination in Latin American and Caribbean countries: a strategic alliance. Eur Respir J. 2016;48(5):1282-1287. https://doi.org/10.1183/13993003.01549-2016
7. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Feb 24]. Roadmap for childhood tuberculosis: towards zero deaths. [Adobe Acrobat document, 44p.]. Available from: http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf
8. Carvalho AC, DeRiemer K, Nunes ZB, Martins M, Comelli M, Marinoni A, et al. Transmission of Mycobacterium tuberculosis to contacts of HIV-infected tuberculosis patients. Am J Respir Crit Care Med. 2001;164(12):2166-71. https://doi.org/10.1164/ajrccm.164.12.2103078
9. Grzemska M. Updated WHO treatment guidelines and the use of new drugs in children. Resid Pediatr. 2017;7(Suppl 1):7-10. https://doi.org/10.25060/residpediatr-2017.v7s1-03
10. Seddon JA, Shingadia D. Epidemiology and disease burden of tuberculosis in children: a global perspective. Infect Drug Resist. 2014;7:153-65.
11. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health. 2014;2(8):e453-9. https://doi.org/10.1016/S2214-109X(14)70245-1
12. Jenkins HE, Yuen CM, Rodriguez CA, Nathavitharana RR, McLaughlin MM, Donald P, et al. Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17(3):285-295. https://doi.org/10.1016/S1473-3099(16)30474-1
13. Graham SM, Sismanidis C, Menzies HJ, Mariais BJ, Detjen AK, Black RE. Importance of tuberculosis control to address child survival. Lancet. 2014;383(9928):1605-7. https://doi.org/10.1016/S0140-6736(14)60420-7
14. Marais BJ. Improving access to tuberculosis preventive therapy and treatment for children. Int J Infect Dis. 2017;56:122-125. https://doi.org/10.1016/j.ijid.2016.12.015
15. Brasil. Ministério da Saúde. Secretaria de Políticas de Saúde. Departamento de Atenção Básica. Manual técnico para o controle da tuberculose. Brasília: Ministério da Saúde; 2002.
16. Sant'Anna CC. Diagnóstico da tuberculose na infância e na adolescência. Pulmão RJ. 2012; 21(1):60-64.
17. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Dec 2]. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. [Adobe Acrobat document, 146p.]. Available from: http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf
18. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis. 2008;8(8):498-510. https://doi.org/10.1016/S1473-3099(08)70182-8
19. The Union -- International Union against Tuberculosis and Lung Diseases [homepage on the Internet]. Paris: The Union; [cited 2017 Nov 29]. The Union's desk guide for diagnosis and management of TB in children. 3rd ed; 2016. [Adobe Acrobat document, 40p.]. Available from: https://www.theunion.org/what-we-do/publications/english/2016_Desk-guide_Africa_Web.pdf
20. Luzzati R, Migliori GB, Zignol M, Cirillo DM, Maschio M, Tominz R. Children under 5 years are at risk for tuberculosis after occasional contact with highly contagious patients: outbreak from a smear-positive healthcare worker. Eur Respir J. 2017;50(5). pii: 1701414. https://doi.org/10.1183/13993003.01414-2017
21. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis. 2003;3(10):624-32. https://doi.org/10.1016/S1473-3099(03)00771-0
22. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Nelson LJ, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(3):278-85.
23. Donald PR. The North American contribution to our knowledge of childhood tuberculosis and its epidemiology. Int J Tuberc Lung Dis. 2014;18(8):890-8. https://doi.org/10.5588/ijtld.13.0915
24. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(4):392-402.
25. Marais BJ, Gie RP, Obihara CC, Hesseling AC, Schaaf HS, Beyers N. Well defined symptoms are of value in the diagnosis of childhood

pulmonary tuberculosis. Arch Dis Child. 2005;90(11):1162-5. https://doi.org/10.1136/adc.2004.070797

26. Sant'Anna C, March MF, Barreto M, Pereira S, Schmidt C. Pulmonary tuberculosis in adolescents: radiographic features. Int J Tuberc Lung Dis. 2009;13(12):1566-8.
27. Marques HHS, Sant'Anna C. Tuberculose. In: Rodrigues JC, Adde FV, Silva LVRF. Doenças Respiratórias. São Paulo: Manole; 2008.
28. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
29. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de DST e Aids. Protocolo clínico e diretrizes terapêuticas para manejo da infecção pelo HIV em crianças e adolescentes. Guia de Tratamento. Brasília: Ministério da Saúde; 2017.
30. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Dec 12]. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. [Adobe Acrobat document, 52p.]. Available from: http http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf
31. Gie R. Diagnostic Atlas of Intrathoracic Tuberculosis in Children. Paris: International Union Against Tuberculosis and Lung Disease; 2003.
32. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet. 2005;365(9454):130-4. https://doi.org/10.1016/S0140-6736(05)17702-2
33. Planting NS, Visser GL, Nicol MP, Workman L, Isaacs W, Zar HJ. Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis. Int J Tuberc Lung Dis. 2014;18(1):8-12. https://doi.org/10.5588/ijtld.13.0132
34. Nicol MP, Whitelaw A, Stevens W. Using Xpert MTB/RIF. Curr Resp Med Rev. 2013;9:187-192. https://doi.org/10.2174/1573398X113099990015
35. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [updated 2016 Oct; cited 2017 Dec 14]. WHO treatment guidelines for drug-resistant tuberculosis–2016 update. [Adobe Acrobat document, 64p.]. Available from: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1
36. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [updated 2016 Oct; cited 2017 Dec 14]. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update 2013. [Adobe Acrobat document, 97p.]. Available from http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1
37. Sieiro TLA, Aurílio RB, Soares ECC, Chiang SS, Sant'Anna CC. The role of the Xpert MTB/RIF assay among adolescents suspected of pulmonary tuberculosis in Rio de Janeiro, Brazil. Rev Soc Bras Med Trop. In press 2018.
38. Sant'Anna C, Orfaliais CT, March Mde F, Conde MB. Evaluation of a proposed diagnostic scoring system for pulmonary tuberculosis in Brazilian children. Int J Tuberc Lung Dis. 2006;10(4):463-5.
39. Pedrozo C, Sant'Anna C, de Fatima March M, Lucena S. Clinical scoring system for paediatric tuberculosis in HIV-infected and non-infected children in Rio de Janeiro. Int J Tuberc Lung Dis. 2009;13(3):413-5.
40. Edwards DJ, Kitetele F, Van Rie A. Agreement between clinical scoring systems used for the diagnosis of pediatric tuberculosis in the HIV era. Int J Tuberc Lung Dis. 2007;11(3):263-9.
41. Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC, Ayaya SO. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Res Trat 2012;2012:401896. https://doi.org/10.1155/2012/401896
42. David SG, Lovero KL, Pombo March MFB, Abreu TG, Ruffino Netto A, Kritski AL. A comparison of tuberculosis diagnostic systems in a retrospective cohort of HIV-infected children in Rio de Janeiro, Brazil. Int J Infect Dis. 2017;59:150-155. https://doi.org/10.1016/j.ijid.2017.01.038
43. Nansumba M, Kumbakumba E, Orikiriza P, Muller Y, Nackers F, Debeaudrap P, et al. Detection Yield and Tolerability of String Test for Diagnosis of Childhood Intrathoracic Tuberculosis. Pediatr Infect Dis J. 2016;35(2):146-51. https://doi.org/10.1097/INF.0000000000000956
44. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3). pii: 1602308. https://doi.org/10.1183/13993003.02308-2016
45. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2:16076. https://doi.org/10.1038/nrdp.2016.76
46. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016.
47. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Resp J. 2016;48(3):938-943. https://doi.org/10.1183/13993003.00705-2016
48. Esposito S, Bosis S, Tadolini M, Bianchini S, Migliori GB, Principi N. Efficacy, safety, and tolerability of a 24-month treatment regimen including delamanid in a child with extensively drug-resistant tuberculosis: A case report and review of the literature. Medicine (Baltimore). 2016;95(46):e5347. https://doi.org/10.1097/MD.0000000000005347
49. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2016;47(2):394-402. https://doi.org/10.1183/13993003.01891-2015
50. Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J. 2017;49(3). pii: 1700146. https://doi.org/10.1183/13993003.00146-2017
51. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J. 2017;50(5). pii: 1701462. https://doi.org/10.1183/13993003.01462-2017
52. D'Ambrosio L, Centis R, Tiberi S, Tadolini M, Dalcolmo M, Rendon A, et al. Delamanid and bedaquiline to treat multidrug-extensively drug-resistant tuberculosis in children: a systematic review. J. Thorac Dis. 2017;9(7):2093-2101. https://doi.org/10.21037/jtd.2017.06.16
53. Brasil. Ministério da Saúde. Secretaria-Executiva. Recomendações para o manejo da coinfecção TB-HIV em serviços de atenção especializada a pessoas vivendo com HIV/AIDS. Brasília: Ministério da Saúde; 2013.
54. Brands A, Volz A. Childhood tuberculosis in Americas: challenges, opportunities and steps to be taken. Resid Pediat. 2016;6(1):11-15. https://doi.org/10.25060/residpediatr-2016.v6n1-02
55. TB ALLIANCE [homepage on the Internet]. New York City: TB ALLIANCE; [cited 2017 Nov 30]. Child-friendly medicines; [about 11 screens]. Available from: https://www.tballiance.org/child-friendly-medicines
56. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Feb 24]. Guidelines on the management of latent tuberculosis infection. [Adobe Acrobat document, 38p.]. Available from: http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1
57. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Dec 10]. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. [Adobe Acrobat document, 70p.]. Available from: http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf
58. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013;41(1):140-56. https://doi.org/10.1183/09031936.00070812
59. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46(6):1563-76. https://doi.org/10.1183/13993003.01245-2015
60. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974;99(2):131-8. https://doi.org/10.1093/oxfordjournals.aje.a121593
61. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Nov 29]. TB CARE I. International Standards for Tuberculosis Care, 3rd ed; 2014. [Adobe

Acrobat document, 92p.]. Available from: http://www.who.int/tb/publications/ISTC_3rdEd.pdf?ua=1

62. Centers for Disease Control and Prevention – CDC [homepage in the internet]. Atlanta (GA): CDC; [cited 2017 Nov 29]. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. [Adobe Acrobat document, 40p.]. Available from: https://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf
63. Public Health Agency of Canada. Centre for Communicable Diseases and Infection Control [homepage on the Internet]. Ottawa: Public Health Agency of Canada; [cited 2017 Nov 29]. Canadian Tuberculosis Standards. 7th ed. 2014. [Adobe Acrobat document, 468p.]. Available from: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-18-2014-eng.pdf
64. Migliori GB, Zellweger JP, Abubakar I, Ibraim E, Caminero JA, De Vries G, et al. European union standards for tuberculosis care. Eur Respir J. 2012;39(4):807-19. https://doi.org/10.1183/09031936.00203811
65. Bergamini BM, Losi M, Vaienti F, D'Amico R, Meccugni B, Meacci M, et al. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. Pediatrics. 2009;123(3):e419-24. https://doi.org/10.1542/peds.2008-1722
66. Carvalho AC, Schumacher RF, Bigoni S, Soncini E, Notarangelo L, Apostoli A, et al. Contact investigation based on serial interferon-gamma release assays (IGRA) in children from the hematology-oncology ward after exposure to a patient with pulmonary tuberculosis. Infection. 2013;41(4):827-31. https://doi.org/10.1007/s15010-013-0450-y
67. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 2000;(2):CD001363.
68. Zunza M, Gray DM, Young T, Cotton M, Zar HJ. Isoniazid for preventing tuberculosis in HIV-infected children. Cochrane Database Syst Rev. 2017;8:CD006418. https://doi.org/10.1002/14651858.CD006418.pub3
69. Lange C, Abubakar I, Alffenaar JW, Bothamley G, Caminero JA, Carvalho AC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J. 2014;44(1):23-63. https://doi.org/10.1183/09031936.00188313
70. Mendonça AM, Kritski AL, Land MG, Sant'Anna CC. Abandonment of Treatment for Latent Tuberculosis Infection and Socioeconomic Factors in Children and Adolescents: Rio De Janeiro, Brazil. PLoS One. 2016;11(5):e0154843. https://doi.org/10.1371/journal.pone.0154843

J Bras Pneumol. 2018;44(2):145-152
http://dx.doi.org/10.1590/S1806-37562017000000443

REVIEW ARTICLE

Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs

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Submitted: 16 December 2017.
Accepted: 9 March 2018.

Study carried out in the Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre (RS) Brasil.

ABSTRACT

Tuberculosis continues to be a major public health problem. Although efforts to control the epidemic have reduced mortality and incidence, there are several predisposing factors that should be modified in order to reduce the burden of the disease. This review article will address some of the risk factors associated with tuberculosis infection and active tuberculosis, including diabetes, smoking, alcohol use, and the use of other drugs, all of which can also contribute to poor tuberculosis treatment results. Tuberculosis can also lead to complications in the course and management of other diseases, such as diabetes. It is therefore important to identify these comorbidities in tuberculosis patients in order to ensure adequate management of both conditions.

Keywords: Tuberculosis/epidemiology; Tuberculosis/prevention & control; Diabetes mellitus/prevention & control; Smoking/adverse effects; Alcohol drinking/adverse effects; Street drugs/adverse effects.

RISK FACTORS FOR TUBERCULOSIS

Diabetes mellitus

Patients with diabetes mellitus (DM) are at a higher risk of transitioning from latent to active tuberculosis. A diagnosis of DM also increases the risk of progressing from the initial infection to active tuberculosis.[1] Case-control studies have demonstrated that the odds ratio of developing tuberculosis is 2.44 to 8.33 times higher in patients with DM than in those without.[2-5] A systematic review of 13 observational studies found that a diagnosis of DM triples the risk of developing tuberculosis (relative risk = 3.11; 95% CI: 2.27-4.26).[6] Some studies have shown that patients with DM are more likely to develop multidrug-resistant tuberculosis (MDR-TB), although there is as yet no explanation for that association.[7-9] In fact, other studies have shown no increased risk of MDR-TB in patients with DM.[10-123]

Approximately 15% of tuberculosis cases worldwide might be linked to DM.[1] The reported prevalence of DM among tuberculosis patients ranges from 1.9% to 45.0% worldwide. The reported prevalence of tuberculosis among DM patients ranges from 0.38% to 14.0%, and the overall median prevalence is reported to be 4.1%, with an interquartile range (IQR) of 1.8%-6.2%.[14] The World Health Organization (WHO) collaborative framework for tuberculosis and DM currently recommends bidirectional screening—screening for DM in all patients with tuberculosis and vice versa.[15]

Active tuberculosis develops most frequently in patients with poor glycemic control. One study of patients with DM showed that the risk of active tuberculosis was three times greater among those who with a hemoglobin A1c (HbA1c) level ≥ 7% than among those with an HbA1c level < 7% (hazard ratio = 3.11; 95%

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Financial support: None.

CI: 1.63-5.92). In addition, insulin dependence is purported to be a risk factor for tuberculosis. In the Philadelphia Diabetic Survey, the likelihood of developing tuberculosis was found to be twice as high among patients with DM using more than 40 units of insulin per day than among those using lower doses.[16]

Poorly controlled DM can lead to multiple complications, including increased susceptibility to infection. Diabetes causes increased susceptibility to tuberculosis through several mechanisms, including hyperglycemia and cellular insulinopenia, which have indirect effects on macrophage and lymphocyte function.[14] However, tuberculosis can temporarily cause impaired glucose tolerance, which is a risk factor for developing DM.[1] Transient hyperglycemia can occur due to the inflammation induced during tuberculosis.[9] Therefore, to establish a new diagnosis of DM, glucose levels should be measured again after 4 weeks of treatment for tuberculosis, especially after the patient is no longer febrile.[9,17]

Tuberculosis patients with DM have a worse clinical presentation and more symptoms, especially weight loss, fever, dyspnea, and night sweats.[16] Patients with tuberculosis and previously-diagnosed DM are usually female, older, and obese. In contrast, patients with tuberculosis and newly-diagnosed DM are more likely to be male and younger, as well as to have lower levels of HbA1c.[9]

Radiologically, patients with tuberculosis and DM have more extensive lesions, more often have multilobar disease, and more frequently present cavitation.[13] Lower-lung involvement is typically as common in DM patients as it is in controls, except in patients > 40 years, among whom it is more common in the presence of DM.[16]

In comparison with patients without DM, the bacillary burden at presentation is higher in patients with DM, who also take longer to transition to culture negativity. However, the rates of sputum-culture conversion after 2 months of treatment are similar between the two patient populations.[16]

Rifampin is a powerful inducer of the hepatic microsomal enzyme system and can lower the serum levels of sulfonylureas and biguanides,[17] leading to hyperglycemia, either directly, or indirectly via interactions with oral hypoglycemic drugs.[16] Therefore, in patients with DM who take rifampin, the doses of oral antidiabetic drugs should be adjusted upwards according to plasma glucose levels. In patients with severe DM, insulin should be used initially.[17] In addition, if isoniazid is prescribed, pyridoxine should also be given, in order to avoid the peripheral neuropathy associated with the use of the former.[16]

The likelihood that a person with tuberculosis will die or relapse is significantly higher if the person also has DM.[1] Two retrospective cohort studies have shown that, in patients with pulmonary tuberculosis, the risk of death is 6.5–6.7 times higher for those who have DM than for those who do not.[18,19] In a systematic review and meta-analysis, Baker et al. concluded that patients with tuberculosis and DM have a nearly 4-fold higher risk of relapse than do those with tuberculosis alone.[9] In addition, one study showed that patients with DM are at a 3.9 times higher risk of treatment failure.[16] Tuberculosis patients with DM are also more likely to be lost to follow-up than are those without.[15]

Smoking

It is estimated that, worldwide, 1.3 billion people consume tobacco and that most of them live in underdeveloped or developing countries, where the tuberculosis rates are also higher.[20] Therefore, the greatest impact of smoking in terms of public health issues related to infection is probably the increase in the risk of tuberculosis. Some systematic reviews and meta-analyses of observational studies have shown an unfavorable association between the global epidemics of tuberculosis and smoking, exposure to tobacco smoke having been associated with tuberculosis infection, active tuberculosis, and tuberculosis-related mortality.[21,22]

The role that cigarette smoke plays in the pathogenesis of tuberculosis is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count, increasing susceptibility to infection with *Mycobacterium tuberculosis*.[20] The alveolar macrophage binds to the bacillus through complement receptors 1, 3, and 4. Activated lymphocytes release cytokines while recruiting macrophages, fibroblasts, and other lymphocytes. The major cytokine involved in granuloma formation is TNF-α, which is released by macrophages immediately after exposure to *M. tuberculosis* antigens. The TNF-α activates macrophages and dendritic cells. In smokers, nicotine, acting through the α7 nicotinic receptor, reduces the production of TNF-α by macrophages, thereby preventing its protective action and favoring the development of tuberculosis.[23,24]

Secretion of IL-12 by macrophages induces the production of IFN-γ in natural killer cells. This immune response aspect, known as the Th1 response, aims to destroy *M. tuberculosis* by forming a fibrous granuloma. Cigarette smoke selectively promotes low production of interleukin-12 and TNF-α, impeding granuloma formation, which would contain the infection at this stage in immunocompetent individuals, smoking therefore creating conditions that allow the development of active tuberculosis.[23,24]

Tuberculosis-related mortality rates are significantly higher in smokers than in never-smokers.[25] Among individuals without a history of tuberculosis, the risk of death due to tuberculosis is nine times higher for smokers than for never-smokers.[25] One recent study showed that smoking and HIV infection were significant risk factors for mortality in patients with MDR-TB.[26] When smokers quit smoking, the risk of

death due to tuberculosis drops significantly (by 65% compared with that observed for those who continue smoking), which indicates that smoking cessation is an important factor in reducing tuberculosis-related mortality.[25]

A prospective study, conducted in rural China in 2017, underscored the supposition that smoking is an independent risk factor for tuberculosis infection, especially in elderly smokers, as well as demonstrating a direct correlation between smoking history (pack-years) and the risk of latent tuberculosis.[27] Recent investigations suggest that, in the detection of latent tuberculosis with IFN-γ methods, the proportion of false-negative results is higher among smokers than among nonsmokers, and that smoking has a negative impact on the results of tuberculosis treatment, delaying conversion of the sputum culture during the treatment and extending the time of treatment.[28] Likewise, nicotine withdrawal has been shown to be strongly associated with successful completion of the treatment for latent tuberculosis.[29]

A study conducted in Brazil showed that men with a history of tuberculosis are 4.1 times more likely to present airway obstruction than are those with no such history, and those results remained unchanged after having been adjusted for age, gender, level of education, ethnicity, smoking, exposure to dust or smoke, respiratory morbidity in childhood, and current morbidity. In conclusion, a history of tuberculosis is associated with airway obstruction in middle-aged and older adults.[30]

Passive and active exposure to cigarette smoke are both associated with an increased risk of infection with *M. tuberculosis* and of the development of active tuberculosis. A qualitative systematic review, published in 2007, highlighted the strong correlation between smoking and active tuberculosis, as well as showing that passive smoking correlated moderately with active tuberculosis and with the need for retreatment.[31] A history of parental smoking is already part of the investigation of episodes of respiratory infection in children. A recent study also showed that the risk of infection with *M. tuberculosis* was increased in children living in a region endemic for tuberculosis, and that parental smoking was significantly associated with the risk of active tuberculosis, even after having been adjusted for associated factors.[32] Therefore, the effects of passive smoking are also a concern regarding active tuberculosis, and every smoker with tuberculosis should be educated about the harm that their addiction can cause to other individuals, especially their contacts, who are at greater risk of contracting active tuberculosis. A study of children who were household contacts of tuberculosis patients showed that exposure to passive smoking, as confirmed by the measurement of urinary nicotine levels, is a major risk factor for active tuberculosis (OR = 5.39; 95% CI: 2.44-11.91).[33]

Another crucial point in the control of tuberculosis is the abandonment of treatment. Smoking has been associated with the abandonment of tuberculosis treatment, and that association has been found to be independent of alcohol or illicit drug use.[34] Therefore, abandonment of tuberculosis treatment might be related to the psychosocial aspects of smoking, the predominance of males, and the lower socioeconomic status of the affected populations, all of which are factors associated with lower rates of adherence to treatment.[34] The recognition of that association is of paramount importance in combating exposure to tobacco smoke in order to reduce the risk of tuberculosis, as is simultaneous treatment for smoking and tuberculosis, both of which mainly affect the respiratory system. Because the smoking epidemic is increasing in some parts of the world and tuberculosis control is still far from being achieved, the prospects are quite worrisome. In one study, a mathematical model was applied in order to evaluate the impact of smoking on the incidence of tuberculosis, that impact being calculated on the basis of the trend in smoking, as well as on the projections for tuberculosis incidence, prevalence, and mortality from 2010 to 2050.[35] The authors estimated that smoking will produce in excess of 18 million tuberculosis cases and 40 million deaths if the number of smokers around the world continues to increase at the current rate. They also estimated that, between 2010 and 2050, smoking will be responsible for a 7% increase in the number of new cases of tuberculosis (from 256 million to 274 million) and a 66% increase in the number of tuberculosis-related deaths (from 61 million to 101 million), making it even more problematic to reach the tuberculosis control targets set by the WHO.[35] For a tuberculosis control program to be effective in daily clinical practice, patients with tuberculosis should be encouraged to undergo smoking cessation treatment, which can also improve the quality of life of such patients.

Alcohol use

Although the consumption of alcohol is considered socially acceptable worldwide, it can lead to dependence. Alcohol consumption problems vary widely. The harmful use of alcohol ranks among the top five risk factors for disease, disability, and death, as well as being a causal factor in more than 200 disease and injury conditions, including tuberculosis, worldwide.[36] It has been estimated that approximately 10% of all tuberculosis cases are attributable to alcohol use.[37]

One major obstacle to making a diagnosis of alcohol abuse is the difficulty in quantifying alcohol intake. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association, alcohol use disorder (AUD) is a chronic, relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. The presentation of AUD can range from mild to severe, and recovery is possible

regardless of the level of severity.[38] The prevalence of AUD among tuberculosis patients varies depending on the population studied. Russia and countries of the former Soviet Union are among the regions most critically impacted by alcohol use. In a cohort of individuals starting tuberculosis treatment in Tomsk, Siberia, 60.2% had a lifetime history of AUD and, most importantly, approximately 28% were female.[39] In a prospective study conducted in New York City, a cohort of individuals with AUD were followed for 8 years and the incidence of tuberculosis was found to be 464 cases/100,000 person-years, which was 9 times the incidence found for the age-matched general population.[40]

The association between alcohol use and tuberculosis has long been known, although there have been inconclusive findings related to various confounding factors, because it is still not known whether the increased risk of tuberculosis is due to the use of alcohol per se or because of the sequelae of AUD, such as liver damage and nutritional deficiency, or social factors, such as crowding, malnutrition, homelessness, and imprisonment, independently of the alcohol consumption. However, in vivo and in vitro studies have demonstrated that alcohol use significantly disrupts the immune response, increasing susceptibility to respiratory diseases such as tuberculosis.[41]

Various population-based studies have shown that there is a strong association between AUD and tuberculosis.[42,43] In a meta-analysis that included 3 cohort studies and 18 case-control studies,[44] heavy alcohol use (defined as ≥ 40 g alcohol per day) or a clinical diagnosis of AUD was found to have a pooled relative risk for the development of active tuberculosis of 3.50 (95% CI: 2.01-5.93). Neither exclusion of the smaller studies (because of suspected publication bias) nor adjustment for various sets of confounders altered the results significantly. In a prospective study conducted in China, a cohort of adults were followed for a mean of 16.8 ± 5.2 years.[45] The authors found that alcohol consumption (≥ 2 drinks per day) were associated with an increased risk of tuberculosis when accompanied by smoking (hazard ratio = 1.51; 95% CI: 1.11-2.05), which is another risk factor for the development of active tuberculosis.[46]

Alcohol abuse influences not only the incidence of tuberculosis but also its clinical evolution and outcome. Individuals with AUD are considered more infectious because AUD has been associated with the finding of cavitary disease on chest X-rays and therefore with smear positivity.[46,47] In addition, AUD has been associated with higher rates of treatment default (OR = 1.99; 95% CI: 1.04-3.81) and relapse (OR = 3.9; 95% CI: 2.5-6.1).[48,49] There are several reasons for that, including precarious living conditions and the increased risk of hepatotoxicity due to tuberculosis treatment in this group of patients.[50]

Whether alcohol abuse increases the risk of MDR-TB is not well established. In a case-control study conducted in Botswana, the prevalence of alcohol use was found to be higher among the individuals with MDR-TB than among those in three different control groups, even after adjustment for several confounders.[51]

Ensuring healthy lives and promoting well-being for individuals of all ages are among the United Nations Sustainable Development Goals for 2030, calling for the prevention and treatment of substance abuse, including the harmful use of alcohol.[52] It is clear that AUD has an negative impact on tuberculosis risk and treatment outcomes. Therefore, in populations at high risk for AUD, it is important to evaluate this condition, integrating the management of AUD and the treatment for tuberculosis, as well as to monitor treatment adherence in order to avoid default and to follow patients closely to identify adverse events.

Illicit drug use

It is estimated that 1 in 20 adults, or a quarter of a billion people between 15 and 64 years of age, used at least one illicit drug in 2015. That is the equivalent of the combined populations of France, Germany, Italy, and the United Kingdom. Over 29 million people who use drugs are estimated to suffer from drug use disorders, 12 million of those are injection drug users, and 14% of injection drug users are living with HIV. Therefore, the impact of drug use, in terms of its consequences on health, continues to be devastating, with an estimated 207,400 drug-related deaths in 2014. Among all forms of illicit drug use, the most common is the use of the cocaine. In 2015, cocaine (either in powder form or as crack cocaine) was used by 18.3 million people, corresponding to 0.3-0.4% of the global population. The magnitude of the harm caused by illicit drug use is evidenced by the estimated 7.4 million illicit drug users seeking treatment via health care systems and the 1 million disability-adjusted life years lost in 2014 because of drug-related premature death and disability.[53,54] According to the WHO, approximately 10% of people living in large urban centers consume psychoactive substances, regardless of gender, age, level of education, or social status. That has been confirmed in a study of large urban centers in Brazil.[55]

Cocaine can be administered by inhalation (smoking or snorting) or by intravenous injection. Currently, the most widely used route of administration is inhalation, especially in the form of crack, or freebase, cocaine smoking. The shift in preference from intravenous injection to inhalation in recent decades is mainly due to the increase in HIV transmission via injection drug use, to the intense euphoric effect (occurring within the first few minutes) of crack, and to the lower cost of the latter.[56]

Epidemiological data suggest that the relationship between tuberculosis and illicit drug use is increasing, leading to a public health problem because it involves political, human, social, and economic aspects.[57,58] The presence of illicit drug users infected with tuberculosis in families and communities is a crucial

factor in maintaining the chain of tuberculosis transmission. Among illicit drug users, infection with *M. tuberculosis* and the progression to active disease are both promoted by a number of factors[55]: the risky lifestyle of such users; the crowded housing conditions; the accumulation and isolation of people indoors for the consumption of illicit drugs; the sharing of materials such as pipes; the malnutrition and severe cough presented by many users; the spread of HIV infection among illicit drug users; and the high number of imprisonments. The proportion of individuals who present risk factors for infection with *M. tuberculosis* and progression to active tuberculosis is 8.0% among injection drug users, compared with only 0.2% in the general population.[54]

Marked and repeated exposure to smoked cocaine has been associated with a broad spectrum of pulmonary complications, including pulmonary edema, diffuse alveolar hemorrhage, acute asthma exacerbations, barotrauma, pulmonary eosinophilic infiltrates, nonspecific interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia, as well as acute pulmonary infiltration, together with a variety of clinical and pathological findings, collectively referred to as "crack lung".[59] Hard drugs such as cocaine can be injected intravenously or ingested through other routes such as inhalation. However, the respiratory damage caused by habitual cocaine smoking makes the users more vulnerable to pulmonary tuberculosis. That might be attributable to the fact that cocaine consumption has been shown to impede the production of alveolar macrophages and immunoregulatory cytokines, both of which are of vital importance in conferring resistance against active tuberculosis. Cocaine use causes a significant reduction in inducible nitric oxide synthase activity, which in turn reduces the antibacterial activity of alveolar macrophages. In addition, cocaine decreases proinflammatory responses, including those involving IFN-γ, chemokine CCL2, TNF-α, and GM-CSF, which are required in the immune response to tuberculosis. Overall, cocaine use attenuates the capacity of monocyte and alveolar macrophage protective mechanisms, resulting in failure to respond to a mycobacterial challenge, the ultimate consequence of which is a failure to prevent active tuberculosis.[60]

In two separate studies,[61,62] the use of powder or crack cocaine was found to correlate directly with the prevalence of active and latent tuberculosis; delays in the diagnosis of the disease; noncompliance with and abandonment of treatment; higher rates of retreatment; and the emergence of multidrug-resistant strains. A study conducted in the United States showed that the use of crack cocaine correlated with a positive PPD skin test result in 147 individuals with schizophrenia. The relative risk of a positive PPD result was 3.53 for the crack cocaine users when compared with the non-drug-using patients.[63] A study conducted in the Brazilian city of Porto Alegre evaluated diagnostic delays in 153 patients with tuberculosis. The authors reported that the median total time of the delay was 60 days (IQR: 30.0-90.5 days), the median patient delay and health care system delay being 30 days (IQR: 7.0-60.0 days) and 18 days (IQR: 9.0-39.5 days), respectively. The factors that were found to be independently associated with a patient delay > 30 days were crack cocaine use (OR = 4.88; p = 0.043) and powder cocaine use (OR = 6.68; p = 0.011).[64]

In a case-control study of patients with pulmonary tuberculosis, conducted in London, England, 19 (86%) of 22 crack cocaine users were smear positive at diagnosis, compared with 302 (36%) of 833 non-drug-using patients.[65] The authors found that smear positivity at the time of diagnosis of pulmonary tuberculosis was 2.4 times and 1.6 times more likely in patients who were crack cocaine users and in patients who were hard drug users not known to use crack cocaine, respectively, than in their non-drug-using counterparts. There was also a significant difference between the crack cocaine users and the users of other drugs, in terms of smear positivity at diagnosis.

A study carried out at a university hospital in the city of São Paulo, Brazil, studied the causes of abandonment of treatment in 100 patients with pulmonary tuberculosis followed as outpatients.[66] The authors showed that alcoholics, smokers, and illicit drug users abandoned tuberculosis treatment with greater frequency than did the patients who did not present any of those risk factors. Among the illicit drug users, marijuana use was reported in 33%, inhaled cocaine use was reported in 29%, intravenous cocaine use was reported in 17%, and crack cocaine use was reported in 11%; half of the illicit drug users reported using combinations of those drugs. The authors of a study conducted in Portugal used data from the Portuguese National Surveillance Center to evaluate the causes of failure to treat tuberculosis (bankruptcy, abandonment of treatment, and death) between 2000 and 2012.[67] The overall rate of such failure was found to be 11.9%, the rate being higher in patients with tuberculosis/HIV coinfection (OR = 4.93), patients over 64 years of age (OR = 4.37), patients who used illicit drugs (OR = 2.29), patients with other diseases, excluding DM/HIV (OR = 2.09), and patients undergoing retreatment (OR = 1.44).

Casal et al.[68] evaluated risk factors for multidrug resistance among patients with pulmonary tuberculosis in four European Union countries (France, Germany, Italy, and Spain) between 1997 and 2000.[68] The authors evaluated a total of 138 cases and 276 controls. In the four countries as a whole, the most statistically significant risk factors were as follows: intravenous drug use (OR = 4.68); asylum-seeker support as income (OR = 2.55); living in a nursing home (OR = 2.05); a history of pulmonary tuberculosis (OR = 2.03); imprisonment (OR = 2.02); known contact with an active tuberculosis case (OR = 2.01); immunosuppression other than that related to HIV infection (OR = 1.96); AIDS (OR = 1.96); current

pulmonary tuberculosis (OR = 1.77); and being a health care worker (OR = 1.69).

FINAL CONSIDERATIONS

In addition to having a direct effect on the health of individuals, tuberculosis is a public health problem. Given the complexity of the combination of illicit drug use and tuberculosis, together with the profile of the population affected and the scarcity of studies dealing with this issue, there is a need for authorities and health professionals to create new, better strategies for evaluating user behavior and to establish intervention policies to control this disease combination, the prevalence of which is increasing in Brazil.

ACKNOWLEDGMENTS

The paper is part of the European Respiratory Society/Latin-American Thoracic Association and European Respiratory Society/Brazilian Thoracic Association collaborative projects.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2016 [cited 2016 Dec 1]. Tuberculosis and diabetes. [Adobe Acrobat document, 2p.]. Available from: http://www.who.int/tb/publications/diabetes_tb.pdf
2. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis. 2006;10(1):80-6.
3. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ. 2006;332(7533):85-7. https://doi.org/10.1136/bmj.38684.687940.80
4. Mboussa J, Monabeka H, Kombo M, Yokolo D, Yoka-Mbio A, Yala F. Course of pulmonary tuberculosis in diabetics [Article in French]. Rev Pneumol Clin. 2003;59(1):39-44.
5. Jabbar A, Hussain SF, Khan AA. Clinical characteristics of pulmonary tuberculosis in adult Pakistani patients with co-existing diabetes mellitus. East Mediterr Health J. 2006;12(5):522-7.
6. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5:1091–1101.
7. Bashar M, Alcabes P, Rom WN, Condos R. Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service, 1987 to 1997. Chest. 2001;120(5):1514-9. https://doi.org/10.1378/chest.120.5.1514
8. Fisher-Hoch SP, Whitney E, McCormick JB, Crespo G, Smith B, Rahbar MH, et al. Type 2 diabetes and multidrug-resistant tuberculosis. Scand J Infect Dis. 2008;40(11-12):888-93. https://doi.org/10.1080/00365540802342372
9. Restrepo BI. Diabetes and tuberculosis. Microbiol Spectr. 2016;4(6):1-19.
10. Singla R, Khan N. Does diabetes predispose to the development of multidrug-resistant tuberculosis? Chest. 2003;123(1):308-9; author reply 309. https://doi.org/10.1016/S0012-3692(16)34416-6
11. Subhash HS, Ashwin I, Mukundan U, Danda D, John G, Cherian AM, et al. Drug resistant tuberculosis in diabetes mellitus: a retrospective study from south India. Trop Doct. 2003;33(3):154-6. https://doi.org/10.1177/004947550303300311
12. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is Associated with Severe Adverse Events in Multidrug-Resistant Tuberculosis. Arch Bronconeumol. 2017;53(5):245-250. https://doi.org/10.1016/j.arbr.2016.10.003
13. Muñoz-Torrico M, Caminero Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data. Rev Port Pneumol (2006). 2017;23(1):27-30.
14. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PLoS One 2017;12(4):e0175925. https://doi.org/10.1371/journal.pone.0175925
15. Pizzol D, Di Gennaro F, Chhaganlal KD, Fabrizio C, Monno L, Putoto G, et al. Tuberculosis and diabetes: current state and future perspectives. Trop Med Int Health. 2016;21(6):694-702. https://doi.org/10.1111/tmi.12704
16. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46. https://doi.org/10.1016/S1473-3099(09)70282-8
17. Deng C, Wang X, Liao Y. Current recommendations on managing tuberculosis patients with diabetes & its epidemiology. Microb Pathog. 2016;92:43-45. https://doi.org/10.1016/j.micpath.2015.12.005
18. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80(4):634-9.
19. Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS, Chaisson RE. Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. Clin Infect Dis. 2002;34(6):752-9. https://doi.org/10.1086/338784
20. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. 2010;35(1):27-33. https://doi.org/10.1183/09031936.00072909
21. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. The risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch Intern Med. 2007;167(4):335-42. https://doi.org/10.1001/archinte.167.4.335
22. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med. 2007;4(1):e20. https://doi.org/10.1371/journal.pmed.0040020
23. North RJ, Jung YJ. Immunity to tuberculosis. Ann Rev Immunol. 2004;22:599-623. https://doi.org/10.1146/annurev.immunol.22.012703.104635
24. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med. 2009;360(23):2445-54. https://doi.org/10.1056/NEJMra0804752
25. Wen CP, Chan TC, Chan HT, Tsai MK, Cheng TY, Tsai SP. The reduction of tuberculosis risks by smoking cessation. BMC Infect Dis. 2010;10:156. https://doi.org/10.1186/1471-2334-10-156
26. Mollel EW, Chilongola JO. Predictors for Mortality among Multidrug-Resistant Tuberculosis Patients in Tanzania. J Trop Med. 2017;2017:9241238.
27. Zhang H, Xin H, Li X, Li H, Li M, Lu W, et al. A dose-response relationship of smoking with tuberculosis infection: A cross-sectional study among 21008 rural residents in China. PLoS One. 2017;12(4):e0175183. https://doi.org/10.1371/journal.pone.0175183
28. Altet N, Latorre I, Jiménez-Fuentes MÁ, Maldonado J, Molina I, González-Díaz Y, et al. Assessment of the influence of direct tobacco smoke on infection and active TB management. PLoS One. 2017;12(8):e0182998. https://doi.org/10.1371/journal.pone.0182998
29. Eastment MC, McClintock AH, McKinney CM, Narita M, Molnar A. Factors That Influence Treatment Completion for Latent Tuberculosis Infection. J Am Board Fam Med. 2017;30(4):520-527. https://doi.org/10.3122/jabfm.2017.04.170070
30. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Mui-o A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the

PLATINO study in Latin America. Eur Respir J. 2007;30(6):1180-5. https://doi.org/10.1183/09031936.00083507

31. Slama K, Chiang CY, Enarson DA, Hassmiller K, Fanning A, Gupta P, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. Int J Tuberc Lung Dis. 2007;11(10):1049-61.
32. Du Preez K, Mandalakas AM, Kirchner HL, Grewal HM, Schaaf HS, van Wyk SS, Hesseling AC. Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children. Int J Tuberc Lung Dis. 2011;15(11):1490-6, i. https://doi.org/10.5588/ijtld.10.0759
33. Altet MN, Alcaide J, Plans P, Taberner JL, Saltó E, Folguera LI, et al. Passive smoking and risk of pulmonary tuberculosis in children immediately following infection. A case control study. Tuber Lung Dis. 1996;77(6):537-44. https://doi.org/10.1016/S0962-8479(96)90052-0
34. Cherkaoui I, Sabouni R, Ghali I, Kizub D, Billioux AC, Bennani K, et al. Treatment default amongst patients with tuberculosis in urban Morocco: predicting and explaining default and post-default sputum smear and drug susceptibility results. PLoS One. 2014;9(4):93574. https://doi.org/10.1371/journal.pone.0093574
35. Basu S, Stuckler D, Bitton A, Glantz SA. Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modeling analysis. BMJ. 2011;343:d5506. https://doi.org/10.1136/bmj.d5506
36. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2016 Dec 1]. Global Health Risks: Mortality and burden of disease attributable to selected major risks. [Adobe Acrobat document, 70p.]. Available from: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf
37. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, Patra J, Poznyak V, Popova S. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009;9:450. https://doi.org/10.1186/1471-2458-9-450
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Update. Washington (DC): American Psychiatric Association; 2016.
39. Shin SS, Mathew TA, Yanova GV, Fitzmaurice GM, Livchits V, Yanov SA, et al. Alcohol consumption among men and women with tuberculosis in Tomsk, Russia. Cent Eur J Public Health. 2010;18(3):132-8.
40. Friedman LN, Williams MT, Singh TP, Frieden TR. Tuberculosis, AIDS, and death among substance abusers on welfare in New York City. N Engl J Med. 1996;334(13):828-33. https://doi.org/10.1056/NEJM199603283341304
41. Molina PE, Happel KI, Zhang P, Kolls JK, Nelson S. Focus on: Alcohol and the immune system. Alcohol Res Health. 2010;33(1-2):97-108.
42. Francisco J, Oliveira O, Felgueiras Ó, Gaio AR, Duarte R. How much is too much alcohol in tuberculosis? Eur Respir J. 2017;49(1). pii:1601468. https://doi.org/10.1183/13993003.01468-2016
43. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J 2017;50(1). pii: 1700216. https://doi.org/10.1183/13993003.00216-2017
44. Lönnroth K, Williams B, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008;8:289. https://doi.org/10.1186/1471-2458-8-289
45. Soh AZ, Chee CBE, Wang YT, Yuan JM, Koh WP. Alcohol drinking and cigarette smoking in relation to risk of active tuberculosis: prospective cohort study. BMJ Open Respir Res. 2017;4(1):e000247. https://doi.org/10.1136/bmjresp-2017-000247
46. Hermosilla S, You P, Aifah A, Abildayev T, Akilzhanova A, Kozhamkulov U, et al. Identifying risk factors associated with smear positivity of pulmonary tuberculosis in Kazakhstan. PLoS One. 2017;12(3):e0172942. https://doi.org/10.1371/journal.pone.0172942
47. Fiske CT, Hamilton CD, Stout JE. Alcohol use and clinical manifestations of tuberculosis. J Infect. 2009;58(5):395-401. https://doi.org/10.1016/j.jinf.2009.02.015
48. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Kourbatova EV. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. Int J Tuberc Lung Dis. 2007;11(1):46-53.
49. Selassie AW, Pozsik C, Wilson D, Ferguson PL. Why pulmonary tuberculosis recurs: a population-based epidemiological study. Ann Epidemiol. 2005;15(7):519-25. https://doi.org/10.1016/j.annepidem.2005.03.002
50. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax. 1996;51(2):132-6. https://doi.org/10.1136/thx.51.2.132
51. Zetola NM, Modongo C, Kip EC, Gross R, Bisson GP, Collman RG. Alcohol use and abuse among patients with multidrug-resistant tuberculosis in Botswana. Int J Tuberc Lung Dis. 2012;16(11):1529-34. https://doi.org/10.5588/ijtld.12.0026
52. United Nations. [homepage on the Internet]. New York City: United Nations, c2017 [cited 2017 Dec 1].Transforming our world: the 2030 Agenda for Sustainable Development. [Adobe Acrobat document, 35p.]. Available from: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E
53. United Nations Office on Drugs and Crime [homepage on the Internet]. Vienna: United Nations Office on Drugs and Crime; c2017 [cited 2017 Dec 1]. World Drug Report 2016 [about 2 screens]. Available from: http://www.unodc.org/wdr2016/
54. United Nations Office on Drugs and Crime [homepage on the Internet]. Vienna: United Nations Office on Drugs and Crime; c2017 [cited 2017 Dec 1]. World Drug Report 2017 [about 2 screens]. Available from: https://www.unodc.org/wdr2017/index.html
55. Cruz VD, Harter J, Oliveira MM, Gonzales RI, Alves PF. Crack consumption and tuberculosis: an integrative review. Rev Eletronica Saude Mental Alcool Drog. 2013;9(1):48-55.
56. Almeida RR, Zanetti G, Souza AR Jr, Souza LS, Silva JL, Escuissato DL et al. Cocaine-induced pulmonary changes: HRCT findings. J Bras Pneumol. 2015;41(4):323-30. https://doi.org/10.1590/S1806-37132015000000025
57. Marques AC, Cruz MS. O adolescente e o uso de drogas. Rev Bras Psiquiatr. 2000;22(2):32-6. https://doi.org/10.1590/S1516-44462000000600009
58. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009;48(1):72-82. https://doi.org/10.1086/594126
59. Mançano A, Marchiori E, Zanetti G, Escuissato DL, Duarte BC, Apolinario Lde A. Pulmonary complications of crack cocaine use: high-resolution computed tomography of the chest. J Bras Pneumol. 2008;34(5):323-7. https://doi.org/10.1590/S1806-37132008000500012
60. Kiboi NG, Nebere SN, Karanja JK. Immunological Interactions of Tuberculosis with Drugs and Substance Use: A Systematic Review and Update. J Pulm Respir Med. 2016;6:2. https://doi.org/10.4172/2161-105X.1000326
61. Paixão LM, Gontijo ED. Profile of notified tuberculosis cases and factors associated with treatment dropout [Article in Portuguese]. Rev Saude Publica. 2007;41(2):205-13. https://doi.org/10.1590/S0034-89102007000200006
62. Rodrigues IL, Monteiro LL, Pacheco RH, da Silva SE. Abandonment of tuberculosis treatment among patients co-infected with TB/HIV [Article in Portuguese]. Rev Esc Enferm USP. 2010;44(2):383-7. https://doi.org/10.1590/S0080-62342010000200020
63. Taubes T, Galanter M, Dermatis H, Westreich L. Crack cocaine and schizophrenia as risk factors for PPD reactivity in the dually diagnosed. J Addict Dis. 1998;17(3):63-74. https://doi.org/10.1300/J069v17n03_06
64. Deponti GN, Silva DR, Coelho AC, Muller AM, Dalcin Pde T. Delayed diagnosis and associated factors among new pulmonary tuberculosis patients diagnosed at the emergency department of a tertiary care hospital in Porto Alegre, South Brazil: a prospective patient recruitment study. BMC Infect Dis. 2013;13:538. https://doi.org/10.1186/1471-2334-13-538
65. Story A, Bothamley G, Hayward A. Crack cocaine and infectious tuberculosis. Emerg Infect Dis. 2008;14(9):1466-9. https://doi.org/10.3201/eid1409.070654
66. Ribeiro SA, Amado VM, Camalier AA, Fernandes MA, Schenkman

S. Estudo caso-controle de indicadores de abandono em doentes com tuberculose. J Pneumol. 2000;26(6):291-6. https://doi.org/10.1590/S0102-35862000000600004

67. Costa-Veiga A, Briz T, Nunes C. Unsuccessful treatment in pulmonary tuberculosis: factors and a consequent predictive model. Eur J Public Health. 2017 Oct 3. [Epub ahead of print] https://doi.org/10.1093/eurpub/ckx136

68. Casal M, Vaquero M, Rinder H, Tortoli E, Grosset J, Rüsch-Gerdes S, et al. A case-control study for multidrug-resistant tuberculosis: risk factors in four European countries. Microb Drug Resist. 2005;11(1):62-7. https://doi.org/10.1089/mdr.2005.11.62

J Bras Pneumol. 2018;44(2):153-160
http://dx.doi.org/10.1590/S1806-37562017000000436

REVIEW ARTICLE

New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis

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Submitted: 1 December 2017.
Accepted: 18 January 2018.

Study carried out under the auspices of the WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italia.

ABSTRACT

Multidrug-resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB, respectively) continue to represent a challenge for clinicians and public health authorities. Unfortunately, although there have been encouraging reports of higher success rates, the overall rate of favorable outcomes of M/XDR-TB treatment is only 54%, or much lower when the spectrum of drug resistance is beyond that of XDR-TB. Treating M/XDR-TB continues to be a difficult task, because of the high incidence of adverse events, the long duration of treatment, the high cost of the regimens used, and the drain on health care resources. Various trials and studies have recently been undertaken (some already published and others ongoing), all aimed at improving outcomes of M/XDR-TB treatment by changing the overall approach, shortening treatment duration, and developing a universal regimen. The objective of this review was to summarize what has been achieved to date, as far as new and repurposed drugs are concerned, with a special focus on delamanid, bedaquiline, pretomanid, clofazimine, carbapenems, and linezolid. After more than 40 years of neglect, greater attention has recently been paid to the need for new drugs to fight the "white plague", and promising results are being reported.

Keywords: Tuberculosis/therapy; Tuberculosis, multidrug-resistant; Extensively drug-resistant tuberculosis; Antitubercular agents.

INTRODUCTION

In its 2017 Global Tuberculosis Report, the World Health Organization (WHO) estimated that there were 1.67 million deaths attributable to tuberculosis in 2016, indicating that the so-called "white plague" continues to be a public health priority.[1] Given that 490,000 cases of multidrug-resistant tuberculosis (MDR-TB, resistant to at least isoniazid and rifampin) were reported in 2016, and that 6.2% of those cases were attributed to infection with extensively drug-resistant tuberculosis (XDR-TB) strains (i.e., MDR-TB strains with additional resistance to fluoroquinolones and at least one of the second-line injectable drugs), there is grave concern that the global epidemic is becoming resistant to the existing treatments. Unfortunately, although there have been encouraging reports of higher success rates,[2] the overall rate of favorable outcomes of M/XDR-TB treatment is only 54%,[1] or much lower when the spectrum of drug resistance is beyond that of XDR-TB.[3]

Treating M/XDR-TB continues to be a difficult task for clinicians, because of the high incidence of adverse events, the long duration of treatment, the high cost of the regimens used, and the drain on health care resources.[4-9] Various trials and studies have recently been undertaken (some already published and others ongoing), all aimed at improving outcomes of M/XDR-TB treatment by changing the overall approach and perhaps even shortening treatment duration.[1,4,10-12] The objective of this review was to summarize what has been achieved to date, as far as new and repurposed drugs are concerned.

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METHODS

We performed a nonsystematic review of the literature, using Google, Google Scholar, PubMed, and ClinicalTrials.gov to identify reports in English, Spanish, or Portuguese published between November 1, 2014 and November 1, 2017. Numerous searches were performed using the following keywords: "TB", "MDR-TB", "XDR-TB", "drugs", "trials", and "drug development". Individual searches were also performed for the following new or repurposed tuberculosis drugs: bedaquiline, delamanid, clofazimine, levofloxacin, moxifloxacin, pretomanid (previously known as Pa-824), pyrazinamide, rifapentine, rifampin, linezolid, delpazolid, sutezolid, carbapenems, imipenem, meropenem, ertapenem, and faropenem. We also performed a search for information on new and repurposed drugs in the WHO Global Tuberculosis Report 2017, as well as from relevant websites: the Global Alliance for Tuberculosis Drug Development (TB Alliance); Unitaid; the Treatment Action Group; and the Stop TB Partnership Working Group on New Drugs. Oral presentations and posters presented at the 2017 conference of the International Union Against Tuberculosis and Lung Disease (IUATLD) were also reviewed.

We have employed WHO-accepted definitions.[13] The search results are divided into three main topics: repurposed drugs, new drugs, and trials.

REPURPOSED DRUGS

Clofazimine is a riminophenazine originally used to treat leprosy. It has not traditionally been used against tuberculosis, because it has little bactericidal activity. However, recent studies have shown that it has sterilizing and treatment-shortening potentials, although the mechanism of action has yet to be fully elucidated. Clofazimine darkens the skin (a side effect that is unacceptable to a significant proportion of patients). Clofazimine can also cause gastrointestinal distress and prolongs the QT interval (the time between the start of the Q wave and the end of the T wave on an electrocardiogram). In addition, cross-resistance between clofazimine and bedaquiline can occur. A phase 1 trial of a modified molecule, TBI-166, designed to reduce the occurrence of skin darkening, is currently underway.[14] The largest study of clofazimine conducted in Brazil achieved a 62% success rate, confirming previous results in smaller cohorts.[15] Clofazimine, which was in drug group 5 in the previous WHO classification, is presently classified as a WHO Group C drug (other core second-line agents), as shown in Chart 1.

Because of their potent beta lactamase, BlaC, carbapenems are not active against *Mycobacterium tuberculosis*; they become active in the presence of clavulanic acid, causing cell wall disruption via peptidoglycan modulation and thus becoming strongly bactericidal. They are presently in WHO Group D3 (non-core drugs), and the combination of a carbapenem with clavulanate has proven to be active against M/XDR-TB, with excellent tolerability.[16-18] The main drawbacks of carbapenems are their high cost, their possible contribution to greater antimicrobial resistance in commensal bacteria, and the need to administer them parenterally. Unfortunately, faropenem, an oral carbapenem, has not been found to be active against *M. tuberculosis*. However, ertapenem has recently been shown to be a suitable "switch therapy" option to be administered intramuscularly or intravenously once daily at home.[19]

Linezolid, an oxazolidinone, inhibits the 50S ribosomal subunit in protein synthesis, has demonstrated antimycobacterial efficacy, and is included in many drug trial regimens[20] However, its toxicity profile limits its use beyond drug-resistant tuberculosis. In the past, the WHO classified linezolid as a Group 5 drug, whereas it is now considered a core second-line agent, in the new WHO Group C (Chart 1). Sutezolid and delpazolid are two newer generation oxazolidinones used in early clinical trials; the hope is that they will be just as effective as linezolid and less toxic. Although not yet recommended by the WHO, efflux pump inhibitors such as verapamil and thioridazine might play a role in lowering resistance to and boosting the antimicrobial activity of drugs like bedaquiline.[21,22]

NEW DRUGS

Bedaquiline

Bedaquiline is a novel diarylquinoline with specific activity against mycobacteria, because it inhibits mitochondrial adenosine triphosphate synthase. Currently, the WHO recommends using bedaquiline to treat M/XDR-TB only in combination with three other effective drugs, excluding delamanid (Charts 1 and 2). A recent systematic review of bedaquiline use was published in the European Respiratory Journal in 2017, updating the results of a review carried out in 2016.[23,24]

By September of 2017, over 10,000 MDR-TB cases were estimated to have been treated with bedaquiline, the vast majority in South Africa.[25] Concerns about the safety of bedaquiline were based on the 10 (late) deaths occurring in the interventional arm of the phase 2b (C208) trial and on the risk of QT prolongation.[26]

Recently, a large, retrospective observational study reported the outcomes of 428 cases of MDR-TB treated with bedaquiline-containing regimens in 15 countries under specific conditions.[2] Sputum smear and culture conversion rates achieved at the end of treatment were 88.7% and 91.2%, respectively; the success rate in the cohort as a whole was 77%, 10% higher than that reported in the study conducted in South Africa.[25] The risk of QT prolongation appears to be lower than initially thought: bedaquiline was interrupted due to side effects in only 5.8% of cases. One patient died after having presented with electrocardiographic abnormalities, which were found not to be bedaquiline-related.[2]

Bedaquiline, which is currently being studied in the TB Alliance Nix-TB trial, is effective in the treatment

Chart 1. World Health Organization categorization of second-line antituberculosis drugs recommended for the treatment of rifampin-resistant and multidrug-resistant tuberculosis.[4]

Group A	Fluoroquinolones	Levofloxacin*
		Moxifloxacin*
		Gatifloxacin*,†
Group B	Aminoglycosides	Amikacin*
		Capreomycin
		Kanamycin
		(Streptomycin)‡
Group C	Other core second-line agents	Ethionamide/prothionamide
		Cycloserine/terizidone
		Linezolid*
		Clofazimine*
Group D	Add-on agents (non-core MDR-TB regimen)	D1
		Pyrazinamide
		Ethambutol
		High-dose isoniazid
		D2
		Bedaquiline§
		Delamanid§
		D3
		Para-aminosalicylic acid
		Imipenem plus cilastatin (requires clavulanate)*
		Meropenem (requires clavulanate)*
		Amoxicillin plus clavulanate*
		Thioacetazone*,‖

MDR-TB: Multidrug-resistant tuberculosis. *Repurposed antibiotics. †Not on the market. ‡Significant resistance, not recommended. §Approved but still under investigation. ‖Not for use in people living with HIV.

of cases of XDR-TB and pre-XDR-TB (resistance to fluoroquinolones or injectable drugs), as well as in the treatment of patients suffering drug intolerance or not responding to the treatment prescribed. The Nix-TB trial is a single-arm, open-label trial evaluating the regimen of 6 months of bedaquiline, pretomanid, and linezolid (600 mg twice daily); if patients are still sputum culture-positive at 4 months, the drugs are administered for an additional 3 months.[27] The most recent Nix-TB trial data (reported in 2017) show that 26 (86.7%) of the 30 patients who completed the treatment remained relapse-free during the subsequent 6 months of follow-up, although 4 patients died in the initial phase of treatment. It is of note that culture conversion was achieved in all patients by month 4, occurring in the first 8 weeks of treatment in 65%.[28] In November of 2017, the Nix-TB trial rolled over into the new ZeNix trial, which is aimed at evaluating different doses of linezolid.

Among the existing trials evaluating bedaquiline, the most relevant are the Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients With MDR-TB (STREAM) trial, which is ongoing (in stage II), results being expected by 2021[29]; the NEXT trial[30]; the Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen (TB-PRACTECAL) trial[31]; and the Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB) trial.[32] The NEXT (open-label) trial evaluates an injection-free regimen consisting of 6-9 months of treatment with bedaquiline, ethionamide (or high-dose isoniazid), linezolid, levofloxacin, and pyrazinamide, in comparison with the recently introduced shorter WHO regimen available for use in MDR-TB patients who meet specific criteria. The TB-PRACTECAL trial, which is a phase 2-3 trial with an adaptive design, is aimed at evaluating the safety and efficacy of a 6-month regimen of treatment with bedaquiline, pretomanid, and linezolid, with or without moxifloxacin or clofazimine, administered in adult patients with M/XDR-TB. The endTB trial, a phase 3 trial, is designed to evaluate different regimens (containing bedaquiline, delamanid, or both; moxifloxacin or levofloxacin; and pyrazinamide plus linezolid, clofazimine, or both), in various combinations, in comparison with the standard individualized regimen, in terms of their efficacy in treating M/XDR-TB.

The early findings of the ongoing NC-005 phase 2 trial, as reported in 2017, suggested that the combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (the BPaMZ regimen) has good bactericidal activity and appears to be well tolerated.[33] Another phase 3 trial,[34] conducted by the TB Alliance, is further evaluating this regimen by studying the effects of different doses of linezolid (ranging from 600 to 1,200 mg/day) to determine the optimal dose and treatment duration.

Through its A5343 study, the AIDS Clinical Trials Group (ACTG) aims to evaluate the combination of delamanid and bedaquiline within the WHO shorter regimen for MDR-TB. In its three arms, it evaluates the

use of bedaquiline, delamanid, and a combination of the two; clofazimine is removed to prevent increased QT prolongation.

A recent systematic review of published cases treated with bedaquiline provided, for the first time, details on QT prolongation.[26] The authors of that review found that information on QT prolongation ≥ 450 ms was available for only 35 (10.6%) of 329 cases, and that information on QT prolongation ≥ 500 ms was available for only 42 (3.2%) of 1,293 cases. Although bedaquiline was discontinued because of side effects in 44 (3.4%) of 1,293 cases, it was discontinued specifically because of QT prolongation in only 8 (0.9%) of 857 cases. It is of note that bedaquiline was restarted in 2 of those 8 cases.

Delamanid

Delamanid, which is in the same drug class as metronidazole (that of the nitroimidazoles), inhibits the biosynthesis of mycolic acid. For the treatment of M/XDR-TB, the WHO recommends delamanid only if it is used in combination with three other drugs of proven efficacy, excluding bedaquiline (Charts 1 and 2).

It has been estimated that approximately 700 patients underwent delamanid treatment by the end of 2017, either through the *Médecins sans Frontières* (Doctors without Borders) projects or the compassionate use program of the European Respiratory Society/WHO TB Consilium.[25,35,36] The Otsuka phase 3 delamanid trial appears as "completed" on ClinicalTrials.gov, and the final results are expected to be submitted for publication in the first or second quarter of 2018. Encouraging results were presented at the IUATLD Conference in Guadalajara, Mexico, in October of 2017.[37-40] The Otsuka delamanid studies provided consistent results with a high proportion of favorable outcomes: 74.5% (192 cases) in phase 2 trial 204[37]; 81.4% (339 cases) in phase 2 trial 213[38]; and 84.2% (19 cases) in a programmatic study conducted in Latvia.[39] The results of the compassionate use cases are encouraging, sputum culture conversion having been achieved in 53 (80.3%) of the 66 cases evaluated.[40]

There are data to support the efficacy and safety of delamanid in children over 6 years of age. Trial 232, which evaluates 18-day pharmacokinetic and safety profiles in a specific weight group, is expected to deliver results in 2018.[41,42] Otsuka Trial 233 is ongoing, evaluating 6-month pharmacokinetic and safety profiles in all pediatric weight groups, with results expected in 2020. Delamanid is also being tested in a number of new trials, most notably the endTB trial (Chart 2). The MDR-END trial is evaluating 9- and 12-month regimens comprising delamanid, linezolid, levofloxacin, and pyrazinamide. The H-35265 trial will evaluate the same regimens as those evaluated in the MDR-END trial, with arms for various shorter durations.

Combination treatment with bedaquiline and delamanid has recently been evaluated, although, in the absence of trial data, it is not yet recommended. However, recent evidence suggests that the bedaquiline-delamanid combination might be better tolerated than previously considered. In one study, QT prolongation was reported in only 1 of 5 cases,[43] and the condition was transient, being reduced after a short interruption of the drug and the inclusion of verapamil in the regimen, without clinical consequences, as reported in a second study of that same case.[44] There are two trials that are currently recruiting patients for a study of the bedaquiline-delamanid combination, although results are not expected until 2020 or 2021.[45] Although the WHO does not recommend the use of the bedaquiline-delamanid combination, it recognizes that physicians might require guidance and has provided recommendations, including active drug safety monitoring, that could provide for more rapid and robust phase 4 safety data collection.[46,47]

Pretomanid

Pretomanid is a nitroimidazole (in the same class as delamanid), developed by the TB Alliance to test three different regimens for the treatment of drug-susceptible tuberculosis as well as MDR-TB. Promising results from the NC-005 trial support the use of the BPaMZ regimen.[33] In the Shortening Treatments by Advancing Novel Drugs (STAND) trial, a phase 3 trial, pretomanid is being combined with moxifloxacin and pyrazinamide in treatment regimens of two different durations (4 and 6 months). In the Nix-TB trial, pretomanid is one of the core drugs. The TB Alliance has also planned to study the bedaquiline-moxifloxacin combination and pyrazinamide within the NC-008 trial. The NC-008 SimpliciTB trial is a phase 3 trial that tests a regimen including pretomanid and bedaquiline. Pretomanid is being studied in multiple arms of the phase 2-3 TB-PRACTECAL trial.

EXISTING TRIALS

A summary of the most important trials is presented in Chart 2. There are various ongoing trials aimed at identifying the best means of managing infection with isoniazid mono-resistant strains of tuberculosis.[48-50] The ACTG 5312 and NEXT trials are evaluating the effects of high-dose isoniazid when low-level drug resistance is identified. The RIFASHORT and STAND trials are focused on shortening the current pan-sensitive treatment regimen while looking at the role of rifapentine, high-dose rifampin, and a completely new regimen. A recent phase 2 trial demonstrated that a high dose of rifampin (20 mg/kg) did not increase the rate of adverse events, although efficacy remained the same.[51]

The PanACEA trial tested three different rifampin doses (35, 20, and 10 mg/kg) in comparison with the standard regimen. The authors found that the time to culture conversion was shorter in the 35 mg/kg arm and that inclusion of SQ109 and moxifloxacin did not increase the efficacy of the regimen.[52]

In the TBTC S31/ACTG A5349 trial, a phase 3 trial, rifapentine is being tested at the standard dose of 1,200

Chart 2. Tuberculosis drug development pipeline: class of drug, target, and phase of trial.

Class	Drug(s)	Target	Phase	Notes
Diarylquinoline	Bedaquiline	ATP synthase	3	Conditional marketing approval
Imidazopyridine amide	Q203	Targets the cytochrome b subunit of the cytochrome bc1 complex, essential for the respiratory electron chain, also depletes intracellular ATP	1	Phase 1b safety studies completed in the United States Phase 1 dose-escalation study underway (NCT02858973)
		Activity similar to that of bedaquiline		Early bactericidal activity study expected to have started before the end of 2017
Nitroimidazole	Delamanid	Inhibit cell wall synthesis and cell respiration	3	Conditional marketing approval
	Pretomanid		3	Awaiting regulatory approval
Oxazolidinone	Sutezolid	Protein synthesis 23s ribosome	2a	Significant reduction in counts of colony-forming units in an early bactericidal activity study Phase 1a completed only recently (NCT03199313), due to licensing problems
	Delpazolid (LCB01-0371)		2	A phase 2 safety and early bactericidal activity study of the drug expected to be completed in late 2017
1,2-ethylenediamine	SQ109	Inhibit cell wall synthesis (MmpL3)	2-3	May be synergic with bedaquiline Two SQ109-containing arms in a PanACEA trial testing high-dose rifampin stopped early because pre-specified efficacy thresholds were not met
Benzothiazinone	PBTZ169	DprE1 inhibitors (inhibit cell wall synthesis)	2	Synergies with bedaquiline and clofazimine
	OPC-167832		1	Co-developed as a companion drug for delamanid in view of a pan-tuberculosis regimen
	TBA-7371		1	Phase 1a trial has begun (NCT03199339)
Riminophenazine	TBI-166	Outer membrane, bacterial respiratory chain and ion transporters	1	Improved analogue of clofazimine Phase 1 to commence in China in October of 2017
Oxaborole	GSK 070, GSK 3036656	Protein synthesis (leucyl-tRNA synthetase)	1	Phase 1 completed (NCT03075410)

ATP: adenosine triphosphate.

mg/day.[53] The TRUNCATE-TB strategy phase 2c trial will test the possibility of shortening the treatment of drug-susceptible tuberculosis to 2 months by combining new and repurposed drugs, including rifamycins.[54] Recently, the use of rifabutin was shown to improve treatment outcomes.[55]

The Opti-Q phase 2 trial has been designed to identify the optimal daily dose of levofloxacin (11, 14, 17, or 20 mg/kg) for the treatment of MDR-TB.[56] Levofloxacin is also being studied in the H-35265 trial, the NEXT trial, the STREAM trial, and the MDR-END trial.[57]

Moxifloxacin is under evaluation in different trials as a replacement for isoniazid or ethambutol in mono-resistant cases or in patients with tolerability problems. The WHO has recently launched the so called "shorter regimen", also known as the "Bangladesh regimen", which is a 9- to 11-month standardized regimen—consisting of 4-6 months of treatment with gatifloxacin/moxifloxacin, kanamycin/amikacin, ethionamide/prothionamide, clofazimine, high-dose isoniazid (10 mg/kg, maximum 600 mg/day), ethambutol, and pyrazinamide, followed by 5 months of treatment with gatifloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[58,59] The shorter regimen is indicated for all patients with pulmonary MDR-TB or rifampin-resistant tuberculosis (excluding pregnant women and patients with extrapulmonary tuberculosis), not previously treated with second-line drugs, that is susceptible to fluoroquinolones and aminoglycosides.[4] It is important that adequate resistance testing be performed, to avoid selecting further resistance.[60-62] A recent meta-analysis reported that shorter regimens are effective, although failure and relapse were found to be associated with fluoroquinolone resistance (OR = 46).[63]

There are limited data available on the use of shorter regimens.[64-67] Interim results of the STREAM trial, presented at the IUATLD Conference in Guadalajara, demonstrated no inferiority of the shorter regimens in comparison with the individualized WHO longer regimen, favorable outcomes being achieved in approximately 78.1% of the patients treated with the shorter regimen, compared with 80.6% of those treated with the longer regimen.[68] The proportion of patients showing prolongation of the corrected QT was higher in the patients treated with the shorter regimen than in those treated with the longer regimen. The second stage of the trial is evaluating the role of bedaquiline within the shorter regimen.

In conclusion, after more than 40 years of neglect, the WHO and partner organizations are now giving greater attention to the need for new, better drugs and regimens to fight the "white plague". Favorable results are expected.

ACKNOWLEDGMENTS

The paper is part of a project organized jointly by the European Respiratory Society, the *Asociación Latinoamericana del Tórax* (Latin-American Thoracic Association), and the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association).

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Oct 30]. Global tuberculosis report 2017; [about 2 screens]. Available from: http://www.who.int/tb/publications/global_report/en/
2. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J. 2017;49(5). pii: 1700387. https://doi.org/10.1183/13993003.00387-2017
3. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J. 2013;42(1):169-179. https://doi.org/10.1183/09031936.00136312
4. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49(3). pii: 1602308. https://doi.org/10.1183/13993003.02308-2016
5. Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. Eur Respir J. 2015;46(5):1461-70. https://doi.org/10.1183/13993003.00649-2015
6. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. Eur Respir J. 2012;40(1):143-51. https://doi.org/10.1183/09031936.00204611
7. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014;43(2):554-65. https://doi.org/10.1183/09031936.00079413
8. D'Ambrosio L, Bothamley G, Caminero Luna JA, Duarte R, Guglielmetti L, Mu-oz Torrico M, et al. Team approach to manage difficult-to-treat TB cases: experiences in Europe and beyond. Rev Port Pneumol (2006). 2017. pii: S2173-5115(17)30163-X. [Epub ahead of print] https://doi.org/ 10.1016/j.rppnen.2017.10.005
9. Blasi F, Dara M, van der Werf MJ, Migliori GB. Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium. Eur Respir J. 2013;41(3):491-4. https://doi.org/10.1183/09031936.00196712
10. Caminero JA, Piubello A, Scardigli A, Migliori GB. Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases. Eur Respir J. 2017;50(1). pii: 1700648. https://doi.org/10.1183/13993003.00648-2017
11. Global Alliance for Public Relations and Communications Management [homepage on the Internet]. Lugano: the Alliance. [updated 2017 Nov 19; cited 2017 Nov 21]. Available from: http://www.globalalliancepr.org/
12. ClinicalTrials.gov [database on the Internet]. Bethesda: National Library of Medicine (US). [updated 2017 Nov 19; cited 2017 Nov 21]. Available from: https://clinicaltrials.gov/
13. World Health Organization. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. Geneva: World Health Organization; 2017.
14. Lu Y, Zheng M, Wang B, Fu L, Zhao W, Li P, et al. Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation. Antimicrob Agents Chemother. 2011;(55):5185-93. https://doi.org/10.1128/AAC.00699-11
15. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017;49(3). pii: 1602445. https://doi.org/10.1183/13993003.02445-2016
16. Tiberi S, Sotgiu G, D'Ambrosio L, Centis R, Abdo Arbex M, Alarcon Arrascue E, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(6):1758-66. https://doi.org/10.1183/13993003.00214-2016
17. Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016;47(4):1235-43. https://doi.org/10.1183/13993003.02146-2015
18. Diacon AH, van der Merwe L, Barnard M, von Groote-Bidlingmaier F, Lange C, García-Basteiro AL, et al. β-Lactams against Tuberculosis–New Trick for an Old Dog? N Engl J Med. 2016;375(4):393-4. https://doi.org/10.1056/NEJMc1513236
19. Tiberi S, D'Ambrosio L, De Lorenzo S, Viggiani P, Centis R, Sotgiu G, et al. Ertapenem in the treatment of multidrug-resistant tuberculosis: first clinical experience. Eur Respir J. 2016;47(1):333-6. https://doi.org/10.1183/13993003.01278-2015
20. Sotgiu G, Pontali E, Migliori GB. Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. Eur Respir J. 2015;45(1):25-9. https://doi.org/10.1183/09031936.00145014
21. Te Brake LHM, de Knegt GJ, de Steenwinkel JE, van Dam TJP, Burger DM, Russel FGM, et al. The Role of Efflux Pumps in Tuberculosis Treatment and Their Promise as a Target in Drug Development: Unraveling the Black Box. Annu Rev Pharmacol Toxicol. 2018;58:271-291. https://doi.org/10.1146/annurev-pharmtox-010617-052438
22. Amaral K, Viveiros M. Thioridazine: A Non-Antibiotic Drug Highly Effective, in Combination with First Line Anti-Tuberculosis Drugs, against Any Form of Antibiotic Resistance of Mycobacterium tuberculosis Due to Its Multi-Mechanisms of Action. Antibiotics (Basel). 2017;6(1). pii: E3. https://doi.org/10.3390/antibiotics6010003
23. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2016;47(2):394-402. https://doi.org/10.1183/13993003.01891-2015
24. Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J. 2017;49(3). pii: 1700146. https://doi.org/10.1183/13993003.00146-2017
25. DR-TB Scale-Up Treatment Action Team (DR-TB STAT) [homepage on the Internet]. [updated 2017 Sep; cited 2017 Nov 21]. Country Updates. Available from: http://drtb-stat.org/country-updates/
26. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J. 2017;50(5). pii: 1701462. https://doi.org/10.1183/13993003.01462-2017
27. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Jan 26; cited 2017 Nov 21]. A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug

Resistant Pulmonary Tuberculosis; Identifier NCT02333799; [about 13 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02333799?term=NCT02333799&rank=1

28. Conradie F, Diacon AH, Everitt D, Mendel C, van Niekerk C, Howell P, et al. The NIX-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. In: Conference on Retroviruses and Opportunistic Infections [proceedings on the Internet]; 2017 Feb 13-16; Seattle (WA), USA. Abstract Number 80LB. [cited 2017 Nov 21]. Available from: http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb
29. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Jan 11; cited 2017 Nov 21].The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB (STREAM); Identifier NCT02409290; [about 22 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02409290?term=NCT02409290&rank=1
30. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 Oct 26; cited 2017 Nov 21]. An Open-label RCT to Evaluate a New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis (NEXT); Identifier NCT02454205; [about 14 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02454205?term=NCT02454205&rank=1
31. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Jan 18; cited 2017 Nov 21]. Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL); Identifier NCT02589782; [about 14 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02589782?term=NCT02589782&rank=1
32. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Nov 17; cited 2017 Oct 15]. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB); Identifier NCT02754765; [about 16 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02754765?term=NCT02754765&rank=1
33. Dawson R, Harris K, Conradie A, Burger D, Murray S, Mendel C, et al. Efficacy Of Bedaquiline, Pretomanid, Moxifloxacin & PZA (BPAMZ) Against DS- & MDR-TB. In: Conference on Retroviruses and Opportunistic Infections [proceedings on the Internet]; 2017 Feb 13-16; Seattle, Washington. Abstract Number 724LB. [cited 2017 Oct 18]. Available from: http://www.croiconference.org/sessions/efficacy-bedaquiline-pretomanid-moxifloxacin-pza-bpamz-against-ds-mdr-tb
34. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2018 Feb 8; cited 2017 Oct 15]. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix); Identifier NCT03086486. [about 20 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT03086486
35. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2014 [cited 2017 Oct 18]. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance [Adobe Acrobat document, 80p.]. Available from: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf
36. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Respir J. 2016;48(3):938-43. https://doi.org/10.1183/13993003.00705-2016
37. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J. 2013;41(6):1393-400. https://doi.org/10.1183/09031936.00125812
38. McKay B. New Treatments for Drug-Resistant TB Get a Boost. Posted on October 23, 2017 The Wall Street Journal. 2017 Oct 13.
39. Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of multidrug- and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. Eur Respir J. 2017;50(5). pii: 1701105. https://doi.org/10.1183/13993003.01105-2017
40. Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. Eur Respir J. 2017 Jul 27;50(1). pii: 1700311. https://doi.org/10.1183/13993003.00311-2017
41. Hafkin J, Frias M, Hesseling A, Garcia-Prats AJ, Schaaf HS, Gler M, et al. Pharmacokinetics and safety of delamanid in pediatric MDR-TB patients: ages 6–17 years. In: Proceedings of the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2015 Sep 17-21; San Diego (CA), USA.
42. Hafkin J, Frias M, De Leon A, Hittel N, Geiter L, Wells C, et al. Long-term safety, tolerability and pharmacokinetics of delamanid in pediatric MDR-TB patients, ages 12–17 years. In: Proceedings of the 46th Union World Conference on Lung Health; 2015 Dec 2-6; Cape Town, South Africa.
43. Maryandyshev A, Pontali E, Tiberi S, Akkerman O, Ganatra S, Sadutshang TD, et al. Bedaquiline and Delamanid Combination Treatment of 5 Patients with Pulmonary Extensively Drug-Resistant Tuberculosis. Emerg Infect Dis. 2017;23(10). https://doi.org/10.3201/eid2310.170834
44. Tadolini M, Lingtsang RD, Tiberi S, Enwerem M, D'Ambrosio L, Sadutshang TD, et al. First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline. Eur Respir J. 2016;48(3):935-8. https://doi.org/10.1183/13993003.00637-2016
45. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Dec 7; cited 2017 Sep 28]. Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis; Identifier NCT02583048 [about 12 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT02583048?term=NCT02583048&rank=1
46. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2017 [cited 2017 Oct 5]. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. [Adobe Acrobat document, 9p.]. Available from: http://apps.who.int/iris/bitstream/10665/258941/1/WHO-HTM-TB-2017.20-eng.pdf
47. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2015 [cited 2017 Oct 5]. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. [Adobe Acrobat document, 28p.]. Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf
48. Santos G, Oliveira O, Gaio R, Duarte R. Effect of Isoniazid Resistance on the Tuberculosis Treatment Outcome. Arch Bronconeumol. 2018;54(1):48-51.
49. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first- line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Feb;17(2):223-234. https://doi.org/10.1016/S1473-3099(16)30407-8
50. Stagg HR, Lipman MC, McHugh TD, Jenkins HE. Isoniazid-resistant tuberculosis: a cause for concern? Int J Tuberc Lung Dis. 2017;21(2):129-139. https://doi.org/10.5588/ijtld.16.0716
51. Jindani A, Borgulya G, de Pati-o IW, Gonzales T, de Fernandes RA, Shrestha B, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. Int J Tuberc Lung Dis. 2016;20(6):832-8. https://doi.org/10.5588/ijtld.15.0577
52. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomized controlled trial. Lancet Infect Dis. 2017;17(1):39-49. https://doi.org/10.1016/S1473-3099(16)30274-2
53. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 Jul 11; cited 2017 Oct 15]. BTC Study 31: Rifapentine-containing Tuberculosis Treatment Shortening Regimens (S31/A5349); Identifier NCT02410772 Available from: https://www.clinicaltrials.gov/ct2/show/NCT02410772?term=NCT02410772&rank=1
54. Papineni P; Phillips P; Lu Q; Cheung YB; Nunn A; Paton N. TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. Int J Infect Dis. 2016;45 Suppl 1:404. https://doi.org/10.1016/j.ijid.2016.02.863
55. Lee H, Ahn S, Hwang NY, Jeon K, Kwon OJ, Huh HJ, et al. Treatment outcomes of rifabutin-containing regimens for rifabutin-sensitive multidrug-resistant pulmonary tuberculosis Int J Infect Dis. 2017;65:135-141. https://doi.org/10.1016/j.ijid.2017.10.013
56. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2017 Jul 18; cited 2017 Oct 20]. Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q); Identifier NCT01918397; [about 12 screens]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01918397?term=NCT01918397&rank=1

57. ClinicalTrials.gov [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2000. [updated 2016 May 3; cited 2017 Oct 20]. Treatment Shortening of MDR-TB Using Existing and New Drugs (MDR-END); Identifier NCT02619994; [about 10 screens]. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02619994?term=NCT02619994&rank=1
58. Aung K, Van Deun A, Declerq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014(18):1180-7. https://doi.org/10.5588/ijtld.14.0100
59. Piubello A, Harouna S, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuber Lung Dis. 2014(18):1188-94.
60. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Zumla A, Migliori GB. WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. Lancet. 2016;387(10037):2486-7. https://doi.org/10.1016/S0140-6736(16)30729-2
61. Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, et al. Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings. Int J Infect Dis. 2017;56:190-193. https://doi.org/10.1016/j.ijid.2016.10.021
62. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Alffenaar JW, Caminero JA, et al. Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. Eur Respir J. 2016;48(5):1503-1507. https://doi.org/10.1183/13993003.01249-2016
63. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J. 2017;50(1). pii: 1700061. https://doi.org/10.1183/13993003.00061-2017
64. van der Werf MJ, Ködmön C, Catchpole M. Shorter regimens for multidrug-resistant tuberculosis should also be applicable in Europe. Eur Respir J. 2017;49(6). pii: 1700463. https://doi.org/10.1183/13993003.00463-2017
65. Yassin MA, Jaramillo E, Wandwalo E, Falzon D, Scardigli A, Kunii O, et al. Investing in a novel shorter treatment regimen for multidrug-resistant tuberculosis: to be repeated. Eur Respir J. 2017;49(3). pii: 1700081. https://doi.org/10.1183/13993003.00081-2017
66. Barry PM, Lowenthal P, True L, Henry L, Schack G, Wendorf K, et al. Benefit of the Shorter Multidrug-Resistant Tuberculosis Treatment Regimen in California and Modified Eligibility Criteria. Am J Respir Crit Care Med. 2017;196(11):1488-1489. https://doi.org/10.1164/rccm.201701-0013LE
67. Chee CBE, KhinMar KW, Sng LH, Jureen R, Cutter J, Lee VJM, et al. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: are patients from South-East Asia eligible? Eur Respir J. 2017;50(2). pii: 1700753. https://doi.org/10.1183/13993003.00753-2017
68. Medical Research Council Clinical Trials Unit [homepage on the Internet]. London: MRC Clinical Trials Unit; c2014 [cited 2017 Oct 18]. Preliminary results from STREAM trial provide insight into shorter treatment for multidrug-resistant tuberculosis [about 3 screens]. Available from: http://www.ctu.mrc.ac.uk/news/2017/preliminary_results_from_stream_trial_provide_insight_into_shorter_treatment_for_multidrug_resistant_tuberculosis

J Bras Pneumol. 2018;44(2):161-166
http://dx.doi.org/10.1590/S1806-37562017000000459

REVIEW ARTICLE

Chest X-ray and chest CT findings in patients diagnosed with pulmonary tuberculosis following solid organ transplantation: a systematic review

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Submitted: 11 January 2018.
Accepted: 2 March 2018.

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ABSTRACT

The objective of this systematic review was to select articles including chest X-ray or chest CT findings in patients who developed pulmonary tuberculosis following solid organ transplantation (lung, kidney, or liver). The following search terms were used: "tuberculosis"; "transplants"; "transplantation"; "mycobacterium"; and "lung". The databases used in this review were PubMed and the Brazilian *Biblioteca Virtual em Saúde* (Virtual Health Library). We selected articles in English, Portuguese, or Spanish, regardless of the year of publication, that met the selection criteria in their title, abstract, or body of text. Articles with no data on chest CT or chest X-ray findings were excluded, as were those not related to solid organ transplantation or pulmonary tuberculosis. We selected 29 articles involving a collective total of 219 patients. The largest samples were in studies conducted in Brazil and South Korea (78 and 35 patients, respectively). The imaging findings were subdivided into five common patterns. The imaging findings varied depending on the transplanted organ in these patients. In liver and lung transplant recipients, the most common pattern was the classic one for pulmonary tuberculosis (cavitation and "tree-in-bud" nodules), which is similar to the findings for pulmonary tuberculosis in the general population. The proportion of cases showing a miliary pattern and lymph node enlargement, which is most similar to the pattern seen in patients coinfected with tuberculosis and HIV, was highest among the kidney transplant recipients. Further studies evaluating clinical data, such as immunosuppression regimens, are needed in order to improve understanding of the distribution of these imaging patterns in this population.

Keywords: Tomography, X-ray computed; Radiography; Tuberculosis, pulmonary; Lung/transplantation; Kidney/transplantation; Liver/transplantation.

INTRODUCTION

Pulmonary tuberculosis is an infection that is spread by airborne transmission and has a major impact on morbidity and mortality in several countries. In the year 2014, the global incidence of tuberculosis was approximately 133 cases/100,000 population, underdeveloped countries accounting for the majority of those cases, being 281 cases/100,000 population in Africa and approximately 33 cases/100,000 population in Brazil.[1,2]

Pulmonary tuberculosis occurs in two principal forms: primary, responsible for only 5% of cases, in which the inhaled tuberculosis bacillus infects the airway and is not immediately contained by the host immunity; and post-primary, responsible for 95% of cases, in which the principal focus of pulmonary infection is contained by the host immunity, with subsequent reactivation of the disease.

The incidence of pulmonary tuberculosis can be up to 20 times higher among recipients of solid organ transplants than among immunocompetent individuals in areas where tuberculosis is not endemic.[3,4]

The clinical manifestations of pulmonary tuberculosis in immunosuppressed patients, including solid organ transplant recipients, can often be attenuated, the typical signs and symptoms, including fever, productive cough, and night sweats, often being absent, which hinders and delays the correct diagnosis.

For immunosuppressed patients with acute or subacute respiratory symptoms, CT is the imaging modality of choice, often strongly suggesting the diagnostic hypothesis of pulmonary tuberculosis. Many radiological findings have been described in this disease, including the miliary pattern, consolidations, ground-glass attenuation opacities, cavitation with centrilobular "tree-in-bud" nodules, diffuse pulmonary infiltrates, mediastinal or hilar lymph node enlargement, and pleural effusion.[4-6]

There have been few studies reporting the tomographic findings of pulmonary tuberculosis in patients undergoing

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Financial support: None.

solid organ transplantation. The objective of the present study was to conduct a systematic review of the literature in order to identify the main radiological patterns of tuberculosis in this population.

METHODS

Search strategies

For this systematic review, we followed the precepts of the Cochrane Handbook for Systematic Reviews of Interventions,[7] which involve formulating the research question; locating and selecting scientific articles; and critically evaluating the articles selected. The research question used was as follows: What are the presentations of pulmonary tuberculosis on chest X-ray and chest CT in solid organ transplant recipients? The research was carried out by five researchers, four of whom carried out the searches for articles in an independent and blinded fashion, whereas the fifth was the reviewer, being consulted in cases of uncertainty in order to reach a consensus. The following search terms were used: "tuberculosis"; "transplants"; "transplantation"; "mycobacterium"; and "lung". Those search terms were selected from the list of descriptors available from the U.S. National Library of Medicine Medical Subject Headings and the Brazilian *Descritores em Ciências da Saúde da Biblioteca Virtual em Saúde* (Virtual Health Library Descriptors in the Health Sciences). For the research, the following online databases were used: PubMed, which includes Medline and the Cochrane Library; and the Virtual Health Library, which includes LILACS, the Spanish Bibliographic Index of the Health Sciences, and SciELO. The searches were conducted between January and October of 2016.

Selection criteria

We selected articles in English, Portuguese, or Spanish, published between January of 1980 and October of 2017, involving human subjects, in which the title, abstract, or body of the text had some relationship with the study objective. Duplicate articles were excluded, as were those for which abstracts were not available, those that did not contain information on chest X-ray or chest CT findings, and those that were not related to solid organ transplantation or pulmonary tuberculosis. No search filters were applied. The article selection process is depicted as a flow chart in Figure 1, according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses.[8]

Data analysis

On the basis of the reading of the abstracts of the studies identified, the full texts of the selected articles were retrieved. After the full texts of the articles had been read, the following data were extracted: author names, year of publication, the country where the research was conducted, sample size, patient age, patient genders, time from transplantation to diagnosis of tuberculosis, transplanted organ, chest CT findings, and chest X-ray findings. The selected articles were divided, by their study design, into case series and case reports.

The results obtained from the evaluation of the selected articles served as the basis for the evaluation of the demographic data related to the patients in the sample and chest imaging data. The chest imaging data were divided into five presentation groups, according to the predominant finding: miliary nodules; cavitation and centrilobular "tree-in-bud" nodular pattern; consolidation and ground-glass attenuation; mediastinal lymph node enlargement; and pleural effusion. This classification followed the criteria established by the Fleischner Society.[9]

For articles that discriminated the presentation of tuberculosis as pulmonary only, without additional details, the chest imaging data were classified as the

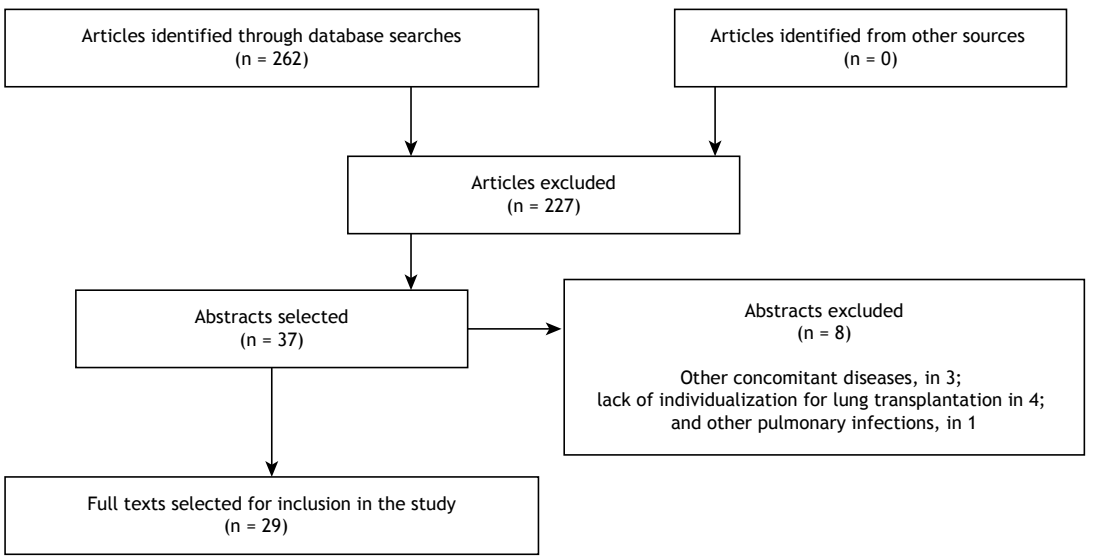

Figure 1. Selection of the articles analyzed in the present review.

typical presentation of tuberculosis and were inserted into the cavitation and centrilobular in "tree-in-bud" nodular pattern group, as were those for articles that described small pleural effusion, because the classification was based on the predominant pattern. Three abstracts were excluded because the pulmonary tuberculosis patients evaluated also had pulmonary Kaposi's sarcoma or pulmonary infection.[10-12] Four cases series were excluded for generalizing imaging findings to recipients of more than one solid organ transplant,[13-16] as was one case series for generalizing imaging findings to patients with tuberculosis or other respiratory infections.[17] The demographic data presented in two articles were censored, because they combined groups of interest (thoracic pathologies) with other groups (nonthoracic pathologies).[5,18]

RESULTS

From among the articles involving solid organ transplant recipients with pulmonary tuberculosis, we selected 16 case series[5,18-32] and 13 case reports[33-45] in which chest imaging findings were available, with a collective total of 219 patients. The data had been obtained in countries on all continents. Among the selected studies, the largest patient samples (78 and 35 patients, respectively) were in a study conducted in Brazil and a study conducted in South Korea, as can be seen in Table 1.[26,29,31,32]

Pulmonary tuberculosis occurs most commonly in men, who accounted for 65% and 72% of the sample, respectively, in the two most representative studies.[26,29] The majority of patients with pulmonary tuberculosis were between the fourth and sixth decades of life. The diagnosis of pulmonary tuberculosis was made 3-12 months after transplantation (Table 1).

The incidence of tuberculosis cases in relation to the number of transplants of a given organ at each institution ranged from 0.09% to 4.7% of the cases, with a mean incidence of 1.12%. We identified 53 cases of pulmonary tuberculosis among lung transplant recipients, with a predominance of the cavitation/tree-in-bud pattern in 35 (66%) of the cases (Table 2).

The largest patient sample was composed of kidney transplant recipients (96 patients); the most common pattern was cavitation and centrilobular nodules in a tree-in-bud pattern, which was seen in approximately one third of those patients, followed by the "lymph node enlargement" and "pleural effusion" categories, which together also accounted for a third of the cases (Table 3). We identified 51 liver transplant recipients, 62% of whom had cavitation and centrilobular nodules in a bud-tree pattern (Table 4).

DISCUSSION

To our knowledge, this is the first systematic review of chest imaging findings in solid organ transplant recipients diagnosed with pulmonary tuberculosis. A collective total of 219 cases were analyzed. Among the 219 cases analyzed, 96, 70, and 53 were in kidney, liver, and lung transplant recipients, respectively. This proportional distribution of cases of pulmonary tuberculosis probably reflects the similar proportional distribution of transplantations by organ.

In the articles selected (i.e., those that contained imaging findings), the prevalence of tuberculosis among transplant recipients ranged from 0.09% to 4.7%, thus not representing the total number of cases, which was not the purpose of the present study. These proportions allow us to infer only an approximate value for the true prevalence.

Table 1. Data obtained from the case series selected in the present systematic review.

Reference	Country	Organ transplanted	Cases, n	Time from transplantation to diagnosis of tuberculosis, months
		Lung	4	NA
Torre-Cisneros et al.[5]	Spain	Kidney	6	NA
		Liver	7	NA
Aslani et al.[18]	Iran	Kidney	16	NA
Kaaroud et al.[19]	Tunisia	Kidney	6	NA
Mortensen et al.[20]	USA	Lung	3	3.7
Kesten et al.[21]	USA	Lung	2	3
Schulma et al.[22]	USA	Lung	2	3
Ram et al.[23]	India	Kidney	16	NA
Shreeniwas et al.[24]	USA	Lung	1	3
Schulma et al.[25]	USA	Lung	2	11
Pereira et al.[26]	Brazil	Kidney	40	8.6
Malouf et al.[27]	Australia	Lung	12	NA
Jiang et al.[28]	China	Kidney	7	12
Lyu et al.[29]	South Korea	Liver	35	10
Meyers et al.[30]	USA	Liver	9	NA
Giacomelli et al.[31]	Brazil	Lung	19	3.2
Schuhmacher Neto et al.[32]	Brazil	Liver	19	2.6

NA: not available.

Table 2. Chest X-ray and chest CT findings in lung transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	1	9	10	18.9
Cavitation/tree-in-bud pattern	24	11	35	66.0
Mediastinal lymph node enlargement	0	4	4	7.5
Miliary pattern	0	2	2	3.8
Pleural effusion	2	0	2	3.8
Total	27	26	53	100

Table 3. Chest X-ray and chest CT findings in kidney transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	0	9	9	9.38
Cavitation/tree-in-bud pattern	5	29	34	35.4
Mediastinal lymph node enlargement	6	8	14	14.6
Miliary pattern	1	22	23	24
Pleural effusion	11	5	16	16.7
Total	23	73	96	100

Table 4. Chest X-ray and chest CT findings in liver transplant recipients.

Finding	X-ray	CT	n	%
Ground-glass opacity/ consolidations	0	1	1	1.4
Cavitation/tree-in-bud pattern	0	47	47	67.2
Mediastinal lymph node enlargement	0	10	10	14.3
Miliary pattern	0	12	12	17.1
Total	0	70	70	100

The studies with the highest numbers of patients included were conducted in Brazil, South Korea, India, and Iran. It is necessary to emphasize that tuberculosis is endemic only in certain countries, unlike most other opportunistic diseases, which are ubiquitous. The incidence of pulmonary tuberculosis among transplant recipients will always be related to the incidence of tuberculosis in the region in which the patient and donor reside.

Among the patient samples evaluated, there was a predominance of men, with an approximate male:female ratio of 2:1. However, it should be borne in mind that approximately half of the articles did not provide demographic data or extrapolated them to diseases other than tuberculosis and were therefore not included. The majority of the patients were between the fourth and sixth decades of life. A complete evaluation of demographic findings might be more appropriate if all articles on solid organ transplant recipients with tuberculosis were evaluated, rather than only those including chest imaging findings.

Data on the time from transplantation to the diagnosis of tuberculosis were present in approximately half of the studies of lung or kidney transplant recipients and most of those of liver transplant recipientsThe time from transplantation to the diagnosis of tuberculosis ranged from 3 to 11 months for lung transplant recipients, with medians between 3 and 4 months, compared with 8-12 months for kidney transplant recipients and 2.6-12 months for liver transplant recipients.

Approximately 66% of the lung transplant recipients with tuberculosis showed a typical pattern of pulmonary involvement (cavitations and the tree-in-bud pattern), atypical patterns occurring in approximately one third of cases. Unlike the lung transplant recipients, only 34 of the 96 kidney transplant recipients—approximately one third—showed the classic presentation of pulmonary tuberculosis, whereas approximately one quarter showed a miliary presentation and approximately one third showed a predominance of lymph node enlargement or pleural effusion.

Most (76%) of the data obtained for kidney transplant recipients were from CT findings, as were all (100%) of the data obtained for liver transplant recipients. In the latter case, the majority (67.2%) had the typical presentation of pulmonary tuberculosis. None of the liver transplant recipients showed a predominance of pleural effusion.

In patients with tuberculosis/HIV coinfection, pulmonary tuberculosis was found to be most often accompanied by lymph node enlargement and miliary disease.[46] Hilar and mediastinal lymph node enlargement occurred in 60% of such patients.[47,48]

On the basis of our results, we can infer that the presentation of pulmonary tuberculosis in kidney transplant recipients tend to be most similar to that of patients with tuberculosis/HIV coinfection (i.e., a greater proportion of cases of lymph node enlargement and miliary involvement); the same was not true for lung and liver transplant recipients, in whom the presentation tended to be more similar to that seen in the general population.

In the articles selected for this review, there were other presentations of pulmonary tuberculosis not defined in the classification described in the methods section. Boedefeld et al.[35] reported a case of pulmonary tuberculosis accompanied by pericardial involvement. There were also two reported cases of transplant recipients presenting with pulmonary tuberculosis in the form of masses.[39,45]

There were reports of pulmonary tuberculosis in solid organ transplant recipients with normal chest X-rays findings, as well as in healthy patients, with incidence rates that vary widely across studies. Lyu et al.[29] also identified patients with normal chest CT findings who developed pulmonary tuberculosis. Therefore, normal chest X-rays do not exclude a diagnosis of pulmonary tuberculosis in solid organ transplant recipients. The incidence of that combination might be better evaluated in clinical studies of tuberculosis in this population. In a case report, Carlsen et al.[42] stated that the presence of calcified mediastinal lymph nodes can raise the suspicion of a diagnosis of tuberculosis.

In summary, the majority of lung and liver transplant recipients with pulmonary tuberculosis show the classic cavitation and tree-in-bud nodular presentation (66.0 and 67.2%, respectively). However, that presentation is seen in only one third of kidney transplant recipients with pulmonary tuberculosis, in whom the presentation is similar to that seen in patients coinfected with tuberculosis and HIV. Studies evaluating sociodemographic differences and, in particular, the immunosuppressive regimen could help identify new hypotheses for the predominance of the atypical presentation of pulmonary tuberculosis in kidney transplant recipients.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; C2016 [cited 2016 Aug 7]. Media centre: Tuberculosis; [about 8 screens]. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. [homepage on the Internet]. Brasília: Ministério da Saúde; [cited 2016 Jun 10]. Tuberculose - 2015: Detectar, tratar e curar: desafios e estratégias brasileiras frente à tuberculose. Boletim Epidemiológico. 2015;46(09). [Adobe Acrobat document, 19p.]. Available from: http://portalarquivos2.saude.gov.br/images/pdf/2015/marco/27/2015-007---BE-Tuberculose---para-substitui---o-no-site.pdf
3. Subramanian A, Dorman S; AST Infectious Diseases Community of Practice. Mycobacterium tuberculosis in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S57-62. https://doi.org/10.1111/j.1600-6143.2009.02894.x
4. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27(5):1266-77. https://doi.org/10.1086/514993
5. Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis. 2009;48(12):1657-65. https://doi.org/10.1086/599035
6. Kiyono K, Sone S, Sakai F, Imai Y, Watanabe T, Izuno I, et al. The number and size of normal mediastinal lymph nodes: a postmortem study. AJR Am J Roentgenol. 1988;150(4):771-6. https://doi.org/10.2214/ajr.150.4.771
7. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
9. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. https://doi.org/10.1148/radiol.2462070712
10. Kalra V, Agarwal SK, Khilnani GC, Kapil A, Dar L, Singh UB, et al. Spectrum of pulmonary infections in renal transplant recipients in the tropics: a single center study. Int Urol Nephrol. 2005;37(3):551-9. https://doi.org/10.1007/s11255-005-4012-9
11. Rathi M, Gundlapalli S, Ramachandran R, Mohindra S, Kaur H, Kumar V, et al. A rare case of Cytomegalovirus, Scedosporium apiospermum and Mycobacterium tuberculosis in a renal transplant recipient. BMC Infect Dis. 2014;14:259. https://doi.org/10.1186/1471-2334-14-259
12. Krayem AB, Abdullah LS, Raweuily EA, Wali SO, Rawas MM, Samman YS, et al. The diagnostic challenge of pulmonary Kaposi's sarcoma with pulmonary tuberculosis in a renal transplant recipient: a case report. Transplantation. 2001;71(10):1488-91. https://doi.org/10.1097/00007890-200105270-00024
13. Tabarsi P. Farshidpour M, Marjani M, Baghaei P, Yoisefzadeh A, Najafizadeh K, et al. Mycobacterial infection and the impact of rifabutin treatment in organ transplant recipients: a single-center study. Saudi J Kidney Dis Transpl. 2015;26(1):6-11. https://doi.org/10.4103/1319-2442.148710
14. Schultz V, Marroni CA, Amorim CS, Baethgen LF, Pasqualotto AC. Risk factors for hepatotoxicity in solid organ transplants recipients being treated for tuberculosis. Transplant Proc. 2014;46(10):3606-10. https://doi.org/10.1016/j.transproceed.2014.09.148
15. Singh N, Patterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27(5):1266-77. https://doi.org/10.1086/514993
16. Lopez de Castilla D, Schluger NW. Tuberculosis following solid organ transplantation. Transpl Infect Dis. 2010;12(2):106-12. https://doi.org/10.1111/j.1399-3062.2009.00475.x
17. Eyüboğlu FÖ, Küpeli E, Bozbaş SS, Ozen ZE, Akkurt ES, Aydoğan C, et al. Evaluation of pulmonary infections in solid organ transplant recipients: 12 years of experience. Transplant Proc. 2013;45(10):3458-61. https://doi.org/10.1016/j.transproceed.2013.09.024
18. Aslani J, Einollahi B. Prevalence of tuberculosis after renal transplantation in Iran. Transplant Proc. 2001;33(5):2804-5. https://doi.org/10.1016/S0041-1345(01)02197-2
19. Kaaroud H, Beji S, Boubaker K, Abderrahim E, Ben Hamida F, Ben Abdallah TB, et al. Tuberculosis after renal transplantation. Transplant Proc. 2007;39(4):1012-3. https://doi.org/10.1016/j.transproceed.2007.02.032
20. Mortensen E, Hellinger W, Keller C, Cowan LS, Shaw T, Hwang S, et al. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. Transpl Infect Dis. 2014;16(1):67-75. https://doi.org/10.1111/tid.12171
21. Kesten S, Chaparro C. Mycobacterial infections in lung transplant recipients. Chest. 1999;115(3):741-5. https://doi.org/10.1378/chest.115.3.741
22. Schulma LL, Htun T, Staniloae C, McGregor CC, Austin JH. Pulmonary nodules and masses after lung and heart-lung transplantation. J Thorac Imaging. 2000;15(3):173-9. https://doi.org/10.1097/00005382-200007000-00004
23. Ram R, Swarnalatha G, Prasad N, Dakshinamurty KV. Tuberculosis in renal transplant recipients. Transpl Infect Dis. 2007;9(2):97-101. https://doi.org/10.1111/j.1399-3062.2006.00182.x
24. Shreeniwas R, Schulman LL, Berkmen YA, McGregor CC, Austin JH. Opportunistic bronchopulmonary infections after lung transplantation: clinical and radiographic findings. Radiology. 1996;200(2):349-56. https://doi.org/10.1148/radiology.200.2.8685324
25. Schulma LL, Scully B, McGregor CC, Austin JH. Pulmonary tuberculosis after lung transplantation. Chest. 1997;111(5):1459-62. https://doi.org/10.1378/chest.111.5.1459
26. Pereira M, Gazzoni FF, Marchiori E, Irion K, Moreira J, Giacomelli IL, et al. High-resolution CT findings of pulmonary Mycobacterium tuberculosis infection in renal transplant recipients. Br J Radiol. 2016;89(1058):20150686. https://doi.org/10.1259/bjr.20150686
27. Malouf MA, Glanville AL. The spectrum of mycobacterial infection after lung transplantation. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1611-6. https://doi.org/10.1164/ajrccm.160.5.9808113
28. Jiang T, Xue F, Zheng X, Yu H, Tao X, Xiao X, et al. Clinical data and CT findings of pulmonary infection caused by different pathogens after kidney transplantation. Eur J Radiol. 2012;81(6):1347-52. https://doi.org/10.1016/j.ejrad.2011.03.070
29. Lyu J, Lee SG, Hwang S, Lee SO, Cho OH, Chae EJ, et al. Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates. Liver Transpl. 2011;17(8):963-8. https://doi.org/10.1002/lt.22319
30. Meyers BR, Papanicolaou GA, Sheiner P, Emre S, Miller C. Tuberculosis in orthotopic liver transplant patients: increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. Transplantation. 2000;69(1):64-9. https://doi.org/10.1097/00007890-200001150-00013
31. Giacomelli IL, Schuhmacher Neto R, Nin CS, Cassano PS, Pereira M1, Moreira JDS, et al. High-resolution computed tomography findings of pulmonary tuberculosis in lung transplant recipients. J Bras Pneumol. 2017;43(4):270-273. https://doi.org/10.1590/s1806-37562016000000306
32. Schuhmacher Neto R, Giacomelli IL, Schuller Nin C, da Silva Moreira J, Comaru Pasqualotto A, Marchiori E, et al. High-resolution CT findings of pulmonary tuberculosis in liver transplant patients. Clin Radiol. 2017;72(10):899.e9-899.e14. https://doi.org/10.1016/j.crad.2017.05.006
33. Winthrop KL, Kubak BM, Pegues DA, Hufana C, Costamagna P,

Desmond E, et al. Transmission of mycobacterium tuberculosis via lung transplantation. Am J Transplant. 2004;4(9):1529-33. https://doi.org/10.1111/j.1600-6143.2004.00536.x

34. Ardalan MR, Shoja MM, Ghabili K. Concomitant pulmonary tuberculosis and tuberculous appendicitis in a recipient of a renal transplant: a case report. J Med Case Rep. 2011;5:191. https://doi.org/10.1186/1752-1947-5-191
35. Boedefeld RL, Eby J, Boedefeld WM 2nd, Stanley D, Lau LC, Kern JA, et al. Fatal Mycobacterium tuberculosis infection in a lung transplant recipient. J Heart Lung Transplant. 2008;27(10):1176-8. https://doi.org/10.1016/j.healun.2008.07.009
36. Shitrit D, Bendayan D, Saute M, Kramer MR. Multidrug resistant tuberculosis following lung transplantation: treatment with pulmonary resection. Thorax. 2004;59(1):79-80.
37. Miller RA, Lanza LA, Kline JN, Geist LJ. Mycobacterium tuberculosis in lung transplant recipients. Am J Respir Crit Care Med. 1995;152(1):374-6. https://doi.org/10.1164/ajrccm.152.1.7599848
38. Place S, Knoop C, Remmelinsk M, Baldassarre S, Van Vooren JP, Jacobs F, et al. Paradoxical worsening of tuberculosis in a heart-lung transplant recipient. Transpl Infect Dis. 2007;9(3):219-24. https://doi.org/10.1111/j.1399-3062.2006.00194.x
39. Lee J. Yew WW, Wong CF, Wong PC, Chiu CS. Multidrug-resistant tuberculosis in a lung transplant recipient. J Heart Lung Transplant. 2003;22(10):1168-73. https://doi.org/10.1016/S1053-2498(02)01189-0
40. Kumar D, Budev M, Koval C, Hellinger WC, Gordon SM, Tomford JW. Donor-derived tuberculosis (TB) infection in lung transplant despite following recommended algorithm. Am J Transplant. 2013;13(8):2225-6. https://doi.org/10.1111/ajt.12344
41. Kukrej N, Cook GJ, Pattison JM. Positron-emission tomography used to diagnose tuberculosis in a renal transplant patient. Am J Transplant. 2002;2(1):105-7. https://doi.org/10.1034/j.1600-6143.2002.020117.x
42. Carlsen SE, Bergin CJ. Reactivation of tuberculosis in a donor lung after transplantation. AJR Am J Roentgenol. 1990;154(3):495-7. https://doi.org/10.2214/ajr.154.3.2106211
43. Wong KK, Lim ST, Yeung CK, Ng WL, Ong GB. Disseminated tuberculosis in a renal transplant recipient. Aust N Z J Surg. 1983;53(2):173-5. https://doi.org/10.1111/j.1445-2197.1983.tb02422.x
44. Duggal R, Rajwanshi A, Gupta N, Lal A, Singhal M. Polymicrobial lung infection in postrenal transplant recipient diagnosed by fine-needle aspiration cytology. Diagn Cytopathol. 2010;38(4):294-6.
45. Tan BH, Cheah FK, Chew S, Ahmed Q. A renal transplant recipient with pulmonary nodules. Transpl Infect Dis. 2005;7(1):18-25. https://doi.org/10.1111/j.1399-3062.2005.00080.x
46. Saurborn DP, Fishman JE, Boiselle PM. The imaging spectrum of pulmonary tuberculosis in AIDS. J Thorac Imaging. 2002;17(1):28-33. https://doi.org/10.1097/00005382-200201000-00003
47. Castañer E, Gallardo X, Mata JM, Esteba L. Radiologic approach to the diagnosis of infectious pulmonary diseases in patients infected with the human immunodeficiency virus. Eur J Radiol. 2004;51(2):114-29. https://doi.org/10.1016/j.ejrad.2004.03.008
48. Almeida LA, Barba MF, Moreira FA, Bombarda S, Felice AS, Calore EE. Computed tomography findings of pulmonary tuberculosis in adult AIDS patients. Radiol Bras. 2011;44(1):13-9. https://doi.org/10.1590/S0100-39842011000100007

J Bras Pneumol. 2018;44(2):167-167
http://dx.doi.org/10.1590/S1806-37562018000000098

Giant pulmonary artery aneurysm in a patient with schistosomiasis-associated pulmonary arterial hypertension

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Dilatation of the pulmonary artery is a feature that is commonly present in pulmonary arterial hypertension, being even more pronounced in cases of schistosomiasis-associated pulmonary arterial hypertension.[1] Aneurysmal dilatations of the pulmonary artery, although less common, have a much greater potential for complications, causing anything from pulmonary artery dissection[2] to extrinsic compression of other regions.

We report the case of a 38-year-old male patient with a > 10-year history of schistosomiasis-associated pulmonary arterial hypertension, with compression of the aorta and coronary artery by a giant pulmonary artery aneurysm. Mean pulmonary artery pressure was 33 mmHg, pulmonary capillary pressure was 10 mmHg, and cardiac output was 6.9 L/min, without evidence of congenital heart disease or lung disease. The patient reported palpitations, dyspnea (categorized as functional class IV), and syncope on exertion. Chest X-ray and chest CT angiography showed a giant pulmonary artery aneurysm (Figures 1A and 1B), without evidence of thromboembolism but with calcifications in the main branches of the pulmonary artery, together with partial compression of the aorta and trunk of the left coronary artery (Figures 1C and 1D). Little is known about the dynamic behavior of such large vascular dilatations,[3] and their potential for complications should always be considered, especially for patients in whom the symptoms are disproportionate to the hemodynamic impairment.

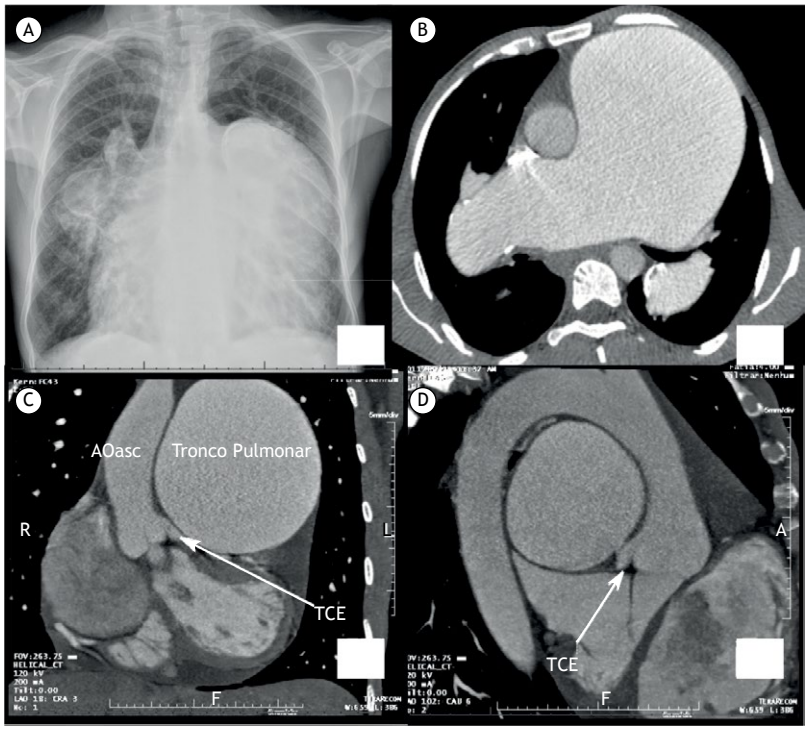

Figure 1. In A, chest X-ray; in B, chest CT scan showing aneurysmal dilatation of the pulmonary artery; and in C and D, CT image reconstruction showing extrinsic compression of the ascending aorta and (white arrows) by dilatation of the pulmonary artery. Designations in Portuguese: TCE, trunk of the left coronary artery; Tronco Pulmonar: pulmonary trunk; and AOasc: ascending aorta.

REFERENCES

1. Hoette S, Figueiredo C, Dias B, Alves JL Jr, Gavilanes F, Prada LF, et al. Pulmonary artery enlargement in schistosomiasis associated pulmonary arterial hypertension. BMC Pulm Med. 2015;15:118. https://doi.org/10.1186/s12890-015-0115-y
2. Corrêa Rde A, Silva LC, Rezende CJ, Bernardes RC, Prata TA, Silva HL. Pulmonary hypertension and pulmonary artery dissection. J Bras Pneumol. 2013;39(2):238-41. https://doi.org/10.1590/S1806-37132013000200016
3. Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: What can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol. 2012;110(6 Suppl):25S-31S. https://doi.org/10.1016/j.amjcard.2012.06.013

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J Bras Pneumol. 2018;44(2):168-170
http://dx.doi.org/10.1590/S1806-37562018000000019

Knowledge and perceptions of tuberculosis transmission and prevention among physicians and nurses in three Brazilian capitals with high incidence of tuberculosis

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TO THE EDITOR:

The Sustainable Development Goals[1] and the End TB Strategy[2] have set targets for tuberculosis elimination by 2050. Recent projections have shown that, in order to achieve interim targets for 2030, prevention through detection and treatment of latent tuberculosis infection (LTBI) is essential.[3] Major target groups for LTBI treatment include immunosuppressed patients[4] and close contacts of index cases,[5] because they are at high risk of progression to active tuberculosis. However, less than 5% of infected contacts are diagnosed and treated to prevent tuberculosis.[6] The reasons for that are not well understood.

In Brazil, major losses occur in the early steps of the cascade of care for LTBI: only 43% of all close contacts are identified, and, of those, only 3% are started on treatment.[7] Perceptions on the part of index patients and contacts do not seem to be at the root of this problem. Index patients fear that contacts will become ill and do tell them that they have tuberculosis. Contacts also fear TB and declare that they would take treatment to prevent it if prescribed.[7] In the present study, we used a knowledge, attitudes, and practices survey[8] in order to explore the perspectives of primary care physicians and nurses regarding TB transmission and prevention at 12 primary health care clinics in the cities of Recife, Manaus, and Rio de Janeiro, where the incidence of tuberculosis in Brazil is highest.[9] The present study is part of a larger study aimed at implementing solutions to the aforementioned problem (ClinicalTrials.gov identifier: NCT00931736 [http://www.clinicaltrials.gov/]). The aforementioned clinics are the same as those where we interviewed index patients and contacts.[7]

Between January of 2015 and July of 2016, a semi-structured questionnaire consisting of open-ended questions on tuberculosis transmission and prevention was administered by trained interviewers to the physicians and nurses who consented to participate in the study. The questionnaire used in the present study is a shortened version of a questionnaire that has previously been used in Indonesia,[10] having previously been translated to Portuguese and adapted for use in Brazil by our research group. A pilot study including 10 health professionals allowed us to make final refinements to the instrument. Participant answers were divided into predefined categories, and the categories were further classified as satisfactory (not necessarily 100% correct) if the answers included categories that were considered "compulsory" and no categories that were considered "unacceptable". For instance, prevention of tuberculosis disease in infected contacts was considered satisfactory if taking medicine, isoniazid, or any effective prophylactic regimen was mentioned and no religious belief was mentioned. A panel of three experts determined whether or not answers were satisfactory by judging whether or not slightly incorrect answers had a negative impact on contact management. The answers were compared between physicians and nurses, between health professionals with and without previous training in tuberculosis, and among the three cities involved in the study.

The study was approved by the local research ethics committees (Rio de Janeiro, Protocol no. CAAE 762,361; Manaus, Protocol no. CAAE 998,112; and Recife, Protocol no. CAAE 1,097,557). All participants gave written informed consent, and their answers remained anonymous.

Interviewers approached 55 physicians and 46 nurses, all of whom agreed to participate. Of the sample as a whole, 58% reported having recently received formal training in tuberculosis. Of those, 57% had received training in tuberculosis prevention and LTBI management. Despite having received formal training, less than 50% of the participants answered 7 of the 16 questions satisfactorily (Table 1). Knowledge gaps included prevention of LTBI among contacts (51%), prevention of progression to disease after infection (32%), LTBI diagnosis (43%), indications for LTBI treatment (62%), minimum duration of isoniazid treatment (44%), isoniazid dose (84%), and management of adverse events (57%). Of the sample

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ISSN 1806-3713

Table 1. Proportions of satisfactory answers to questions in a knowledge, attitudes, and practices survey among 55 physicians and 46 nurses in three cities in Brazil with high incidence of tuberculosis.

Question	Proportion of satisfactory answers
Knowledge	
How is a contact of an index patient with TB prevented from becoming infected?	50%
How can a person with LTBI be prevented from becoming ill?	68%
What tests are recommended for an asymptomatic contact?	57%
What tests are recommended for a contact with cough?	48%
How do you determine that a TB contact has been infected (with LTBI)?	46%
According to the recommendations of the Brazilian National Tuberculosis Control Program, what household contacts should receive treatment for LTBI?	38%
What is the minimum duration of LTBI treatment with isoniazid to prevent TB disease?	56%
What is the optimal duration of LTBI treatment with isoniazid to prevent TB disease?	7%
What is the recommended dose of isoniazid for the treatment of LTBI in children?	16%
What is the daily dose of isoniazid for the treatment of LTBI in adults?	7%
What are the most common side effects of isoniazid?	82%
What household contacts should be vaccinated with BCG?	15%
What do you do if an adult taking isoniazid for LTBI treatment has nausea and loss of appetite?	67%
What do you do if a child taking isoniazid for LTBI treatment has nausea and loss of appetite?	48%
What do you do if an adult taking isoniazid for LTBI treatment has jaundice?	69%
What do you do if a child taking isoniazid for LTBI treatment has jaundice?	65%
Attitudes	
Do you think it is important for a child who lives with a patient with active TB to be screened for active TB?	73%
Do you think it is important for a child who lives with a patient with active TB to be screened for LTBI?	54%
Do you think it is important for an adult who lives with a patient with active TB to be screened for active TB?	63%
Do you think it is important for an adult who lives with a patient with active TB to be screened for LTBI?	51%
Do you think that this health care clinic should be responsible for investigating adults and children living with a patient with active TB?	78%
Sometimes parents/legal guardians do not bring their child contacts to the clinic for LTBI/TB investigation. What do you think are the main reasons for that?	92%
Sometimes adult contacts do not come to the clinic to be investigated. What do you think are the main reasons for that?	93%
In this clinic, what are the difficulties in evaluating a child living with a patient with TB?	71%
In this clinic, what are the difficulties in evaluating an adult living with a patient with TB?	51%

TB: tuberculosis; and LTBI: latent tuberculosis infection.

as a whole, 46% stated that they did not think that it was important to screen child contacts for tuberculosis and LTBI and 49% stated that they did not think that it was important to screen adult contacts for tuberculosis and LTBI, attitudes that stand in contrast with the Brazilian National Guidelines for Tuberculosis Control.

Although physicians had better knowledge of management of adverse events than did nurses, there were no other significant differences in knowledge or perceptions between physicians and nurses (with or without previous training). With regard to the differences among the three cities, the proportions of satisfactory answers regarding tuberculosis transmission and investigation of contacts were lowest in Manaus, whereas the proportions of satisfactory answers regarding duration of isoniazid treatment and isoniazid dose were lowest in Rio de Janeiro. In Recife, none of the participants stated that it is important to screen child or adult contacts for LTBI (data on answers by professional category, training status, and city are not shown but are available upon request to the corresponding author, as is the questionnaire used in the present study).

In conclusion, there are major gaps in knowledge of and attitudes toward tuberculosis contact management among primary health care physicians and nurses, despite previous tuberculosis training. Inclusion of tuberculosis prevention in training sessions and motivation of health care workers are needed in order to overcome bottlenecks in LTBI treatment in Brazil. We propose standardized training as a solution to issues of LTBI treatment of close contacts of tuberculosis patients, as recommended by the Brazilian National Guidelines

for Tuberculosis Control. We believe that this approach can aid in determining priorities for LTBI management in settings in which the cascade of care of tuberculosis contacts is an issue for tuberculosis control.

REFERENCES

1. United Nations [homepage on the Internet]. New York City: United Nations; [cited 2017 Aug]. Sustainable Development Goals; [about 2 screens]. Available from: http://www.un.org/sustainabledevelopment/sustainable-development-goals/
2. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2017 Aug 25]. WHO End TB Strategy–Global strategy and targets for tuberculosis prevention, care and control after 2015; [about 2 screens]. Available from: http://www.who.int/tb/post2015_strategy/en/
3. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health. 2013;34:271-86. https://doi.org/10.1146/annurev-publhealth-031912-114431
4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2017 Aug 25]. Scaling up the Three I's for TB/HIV; [about 1 screen]. Available from: http://www.who.int/hiv/topics/tb/3is/en/
5. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2017 Aug 29]. Guidelines on the management of latent tuberculosis infection; [about 3 screens]. Available from: http://www.who.int/tb/publications/latent-tuberculosis-infection/en/
6. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269-1278. https://doi.org/10.1016/S1473-3099(16)30216-X
7. Salame FM, Ferreira MD, Belo MT, Teixeira EG, Cordeiro-Santos M, Ximenes RA, et al. Knowledge about tuberculosis transmission and prevention and perceptions of health service utilization among index cases and contacts in Brazil: Understanding losses in the latent tuberculosis cascade of care. PLoS One. 2017;12(9):e0184061. https://doi.org/10.1371/journal.pone.0184061
8. World Health Organization. Stop TB Partnership [homepage on the Internet]. Geneva: World Health Organization; [cited 2017 Aug 25]. Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys; 2008 [Adobe Acrobat document, 68p.]. Available from: http://apps.who.int/iris/bitstream/10665/43790/1/9789241596176_eng.pdf
9. Brasil. Ministério da Saúde [homepage on the Internet]. Brasília: o Ministério; [cited 2017 Aug 25]. Available from: http://portalsaude.saude.gov.br/
10. Rutherford ME, Ruslami R, Anselmo M, Alisjahbana B, Yulianti N, Sampurno H, et al. Management of children exposed to Mycobacterium tuberculosis: a public health evaluation in West Java, Indonesia. Bull World Health Organ. 2013;91(12):932-941A. https://doi.org/10.2471/BLT.13.118414

J Bras Pneumol. 2018;44(2):171-172
http://dx.doi.org/10.1590/S1806-37562017000000298

Rapidly growing pulmonary ground-glass nodule caused by metastatic melanoma lacking uptake on ^{18}F-FDG PET-CT

Giorgia Dalpiaz[1], Sofia Asioli[2], Stefano Fanti[3], Gaetano Rea[4], Edson Marchiori[5,a]

TO THE EDITOR:

In November of 2003, a 33-year-old man underwent surgical treatment for a malignant melanoma on the chest. The mitotic rate was 4 mitoses/mm^2, and tumor thickness was 1.35 mm, with no skin ulceration, lymphovascular invasion, or perineural invasion. After 5 years of follow-up, a CT scan showed a 15-mm subsolid nodule (pure ground-glass nodule) in the right lower lobe (Figure 1A). A follow-up CT scan performed 6 months later showed that the nodule had increased in size and had an eccentric solid component (Figure 1B). An ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) scan showed that the nodule lacked FDG uptake (Figure 1C). Nodal and distant metastases were absent. Surgical resection of the lung lesion was performed. Histological examination showed the spread of neoplastic melanoma cells along the alveolar walls, with lepidic growth (Figure 1D). No hemorrhage was detected around the lesion. Immunohistochemical analysis of S-100 protein showed that the neoplastic melanoma cells were in close proximity to cytokeratin 7-positive normal alveolar epithelium. Therefore, the patient was diagnosed with metastatic lung cancer from a primary cutaneous melanoma. He was started on chemotherapy with dacarbazine and cisplatin but showed no signs of improvement. He died a few months later as a result of disease progression.

Subsolid nodules are CT findings that can be classified as pure or partially solid ground-glass nodules. Subsolid pulmonary nodules have been reported in association with various lung diseases, including non-neoplastic diseases, primary neoplasms, and metastatic neoplasms. The CT patterns of pulmonary parenchymal involvement by malignant melanoma vary. Multiple solid nodules constitute the most common CT finding. Metastatic pulmonary melanoma appearing as a solitary ground-glass opacity nodule is very uncommon.[1-3] Negative FDG uptake on FDG-PET/CT is expected, as it is for other lesions with lepidic growth, such as peripheral lung adenocarcinomas (and their precursors) and metastases arising from adenocarcinoma of the gastrointestinal tract.[4] Subsolid nodules have various benign and malignant etiologies. When persistent, subsolid pulmonary nodules are very likely to represent part of the pathological spectrum of lung adenocarcinoma.[5] Although imaging findings were not pathognomonic in our patient, the rapid growth within a short period of time raised the suspicion of metastatic disease.[1,5] FDG-PET/CT has a major role in nodal staging for decisions pertaining to surgical resection; the use of limited surgical resection in patients with subsolid nodules but no documented nodal metastasis is under investigation.[4] Surgical resection is the preferred method for the histological diagnosis of subsolid nodules.[5] In conclusion, in patients with malignant melanoma, a solitary subsolid pulmonary nodule that shows rapid growth over a few months should raise the suspicion of metastasis, despite negative FDG uptake on FDG-PET/CT.

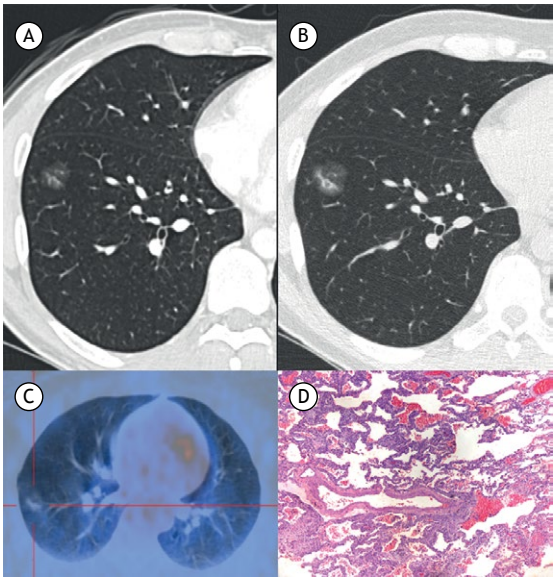

Figure 1. In A, axial CT scan of the chest showing a 15-mm subsolid nodule (pure ground-glass nodule) in the right lower lobe. In B, a CT scan of the chest taken 6 months after the first, showing that the nodule had increased in size and had an eccentric solid component. In C, ^{18}F-fluorodeoxyglucose positron emission tomography/CT scan showing that the nodule lacked ^{18}F-fluorodeoxyglucose uptake. In D, photomicrograph showing spread of neoplastic melanoma cells along the alveolar walls, with lepidic growth (H&E staining; magnification, ×50). Immunohistochemistry showed that the cells were positive for S-100 protein, which is a melanocytic marker (not shown).

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REFERENCES

1. Kang MJ, Kim MA, Park CM, Lee CH, Goo JM, Lee HJ. Ground-glass nodules found in two patients with malignant melanomas: different growth rate and different histology. Clin Imaging. 2010;34(5):396-9. https://doi.org/10.1016/j.clinimag.2009.10.036
2. Dalpiaz G, Kawamukai K, Parisi AM, La Torre L, Forcella D, Leuzzi G. Ground-glass opacity of the lung in a patient with melanoma: "The radiological seed of doubt". Rev Esp Med Nucl Imagen Mol. 2015;34(6):390-2. https://doi.org/10.1016/j.remn.2015.04.006
3. Mizuuchi H, Suda K, Kitahara H, Shimamatsu S, Kohno M, Okamoto T, et al. Solitary pulmonary metastasis from malignant melanoma of the bulbar conjunctiva presenting as a pulmonary ground glass nodule: Report of a case. Thorac Cancer. 2015;6(1):97-100. https://doi.org/10.1111/1759-7714.12124
4. Erasmus JJ, Macapinlac HA. Low-sensitivity FDG-PET studies: less common lung neoplasms. Semin Nucl Med. 2012;42(4):255-60. https://doi.org/10.1053/j.semnuclmed.2012.03.001
5. Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology. 2015;266(1):304-17. https://doi.org/10.1148/radiol.12120628

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3713, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

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Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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