Characterization of drug-resistant tuberculosis in Brazil, 2014*

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Abstract

Objective: to describe drug-resistant tuberculosis (DR-TB) notifications in Brazil. Methods: this is a descriptive study of clinical and epidemiological characteristics of DR-TB notifications in 2014 on SITETB and TBWeb, these being information systems on which cases involving special treatment regimens are registered. Results: there were 1,574 cases, 94.8% of which had the pulmonary form, 27.6% involved primary resistance, and 50.9% were multidrug-resistant; 70.6% of cases were male, 87.0% were between 20 and 59 years old, 60.9% were of Afro-Brazilian, and 68.0% had less than 8 years of schooling; as for comorbidities, 13.1% of patients had AIDS, 11.3% had diabetes, 25.8% made harmful use of alcohol, 21.0% were illegal drugs users, and 22.2% were tobacco users. Conclusion: the majority of DR-TB notifications were related to men, young people, Afro-Brazilian and people with low levels of education; there was a high percentage of primary resistance, as well as multidrug-resistance and comorbidities, with emphasis on substance use.

Keywords: Tuberculosis, Multidrug-Resistant; Communicable Diseases; Public Health; Epidemiology, Descriptive.

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Introduction

Tuberculosis (TB) is one of the ten leading causes of death worldwide, affecting mainly low and middle income countries. Inadequate, intermittent or interrupted treatments may select resistant strains, which are transmissible. Resistance to just one drug is classified as mono-resistance, while resistance to more than one drug is classified as poly-resistance. Multidrug-resistance (MDR-TB) is a form of poly-resistance characterized by resistance to, at least, isoniazid and rifampicin. Drug-resistant tuberculosis (DR-TB) is an increasingly frequent phenomenon and has the potential to make ineffectual the available therapeutic regimens.

Resistance to just one drug is classified as mono-resistance, while resistance to more than one drug is classified as poly-resistance. Multidrug-resistance (MDR-TB) is a form of poly-resistance characterized by resistance to, at least, isoniazid and rifampicin.

It is estimated that globally in 2017 rifampicin-resistant TB or MDR-TB occurred in 3.5% of new cases (primary resistance) and in 18.0% of previously treated cases (acquired resistance). According to the same estimates, 7.1% of new cases and 7.9% of previously treated cases had mono-resistance to isoniazid.

In the case of Brazil, the World Health Organization (WHO) estimated an incidence rate of 1.2 MDR-TB or rifampicin-resistant TB cases per 100,000 inhabitants in 2017. These patterns were related to 1.5% new TB cases and 8.0% previously treated cases. In 1997 in Brazil, 10.6% of pulmonary TB cases with a positive bacilloscopy result had some level of drug resistance, 2.2% of which were MDR-TB. In 2006, 1.4% of new TB cases and 7.5% of previously treated cases were MDR-TB.

When describing the epidemiological profile of DR-TB, recent Brazilian studies have used local data rather than national data.

The objective of this study was to describe notifications of DR-TB in Brazil.

Methods

This was a descriptive study of DR-TB notifications in 2014. We used data from the São Paulo Tuberculosis Patient Control System (TBWeb), for the Brazilian state of São Paulo, and data from the Tuberculosis Special Treatment Information System (SITETB) for the other Brazilian Federative Units. SITETB is used countrywide to monitor special TB treatments. TBWeb is exclusively used by the state of São Paulo for all TB cases there. We used both systems, because part of the monodrug-resistant cases in the state of São Paulo were only recorded on TBWeb.

The study population was comprised of DR-TB cases diagnosed in 2014, notified on the TBWeb for the state of São Paulo and on the SITETB for the rest of Brazil.

The variables analyzed were:

a) Federative Unit of residence;
b) sex (female; male);
c) ethnicity/skin color (white; black; brown/mixed race; indigenous; unknown), for analysis purposes, the black and brown/mixed race categories were grouped together into the Afro-Brazilian (negro, in Portuguese) category;
d) age group (in years: up to 19; 20 to 59; 60 or more);
e) education level (in years no schooling: illiterate; 1 to 3; 4 to 7, 8 to 11; 12 or more; unknown);
f) presence or absence of alcoholism, diabetes mellitus, AIDS, illegal drugs and tobacco use;
g) TB clinical form (pulmonary, extra-pulmonary, pulmonary and extra-pulmonary);
h) resistance type (acquired; primary); and

i) drug-resistance pattern (MDR; non MDR poly-resistance; mono-resistance to isoniazid; mono-resistance to rifampicin; mono-resistance to streptomycin; mono-resistance to ethionamide; mono-resistance to ethambutol; mono-resistance to pyrazinamide; unknown; not classified).

The resistance pattern was based on the resistance record of each drug, regardless of the diagnosis method applied. Cases classified as DR-TB on the information systems, but with no resistance record, were included in the analysis as “unknown” resistance pattern.

We described cases by means of absolute and relative frequencies. Data were analyzed using STATA version 12.0.
The study project was approved by the University of Brasília Health Sciences Faculty Human Research Ethics Committee: Report No. 1,431,237. The databases we analyzed were requested from the Ministry of Health and from the São Paulo State Health Department, in accordance with Law No. 12,527/201111 and São Paulo State Government Decree No. 58,052/2012.12

Results

In 2014, 1,574 DR-TB cases were reported in Brazil, most of them in the Southeast region (53.0%), in particular the states of São Paulo and Rio de Janeiro (Table 1). All state capital cities reported at least one case, except for Boa Vista, the capital of the only state with no reported cases: Roraima.

Table 1 – Distribution of drug-resistant tuberculosis cases per Federative Unit (FU), Brazil, 2014

| Region and FU       | Cases N (%) |
|---------------------|-------------|
| North               |             |
| Rondônia            | 6 (0.4)     |
| Acre                | 3 (0.2)     |
| Amazonas            | 55 (3.5)    |
| Pará                | 50 (3.2)    |
| Roraima             | –           |
| Amapá               | 2 (0.1)     |
| Tocantins           | 2 (0.1)     |
| Northeast           |             |
| Maranhão            | 23 (1.5)    |
| Piauí               | 3 (0.2)     |
| Ceará               | 95 (6.0)    |
| Rio Grande do Norte | 11 (0.7)    |
| Paraíba             | 16 (1.0)    |
| Pernambuco          | 71 (4.5)    |
| Alagoas             | 9 (0.6)     |
| Sergipe             | 10 (0.6)    |
| Bahia               | 114 (7.2)   |
| Southeast           |             |
| Minas Gerais        | 38 (2.4)    |
| Espírito Santo      | 9 (0.6)     |
| Rio de Janeiro      | 333 (21.2)  |
| São Paulo           | 454 (28.8)  |
| South               |             |
| Paraná              | 45 (2.9)    |
| Santa Catarina      | 42 (2.7)    |
| Rio Grande do Sul   | 137 (8.7)   |
| Midwest             |             |
| Mato Grosso do Sul  | 17 (1.1)    |
| Mato Grosso         | 7 (0.4)     |
| Goiás               | 9 (0.6)     |
| Federal District    | 1 (0.1)     |
| Unknown             | 12 (0.8)    |
| Brazil              | 1,574 (100.0) |
Table 2 – Type and resistance pattern of drug-resistant tuberculosis cases in Brazil, 2014

| Variables                      | Frequency N (%) |
|--------------------------------|-----------------|
| **Resistance type**           |                 |
| Primary                        | 434 (27.6)      |
| Acquired                       | 1,102 (70.0)    |
| Unknown                        | 38 (2.4)        |
| **Drug resistance pattern**   |                 |
| Multidrug-resistant (MDR)      | 801 (50.9)      |
| Non MDR poly-resistance        | 149 (9.5)       |
| Mono-resistance to isoniazid   | 342 (21.7)      |
| Mono-resistance to rifampicin  | 141 (9.0)       |
| Mono-resistance to streptomycin| 71 (4.5)        |
| Mono-resistance to ethionamide | –               |
| Mono-resistance to ethambutol  | 5 (0.3)         |
| Mono-resistance to pyrazinamide| 3 (0.2)         |
| Unknown                        | 44 (2.8)        |
| Not classified                 | 18 (1.1)        |

Of the total number of cases, 27.6% (434) had primary resistance (Table 2). Among the 801 MDR-TB cases, 159 (20.5%) had primary resistance and 615 (79.5%) had acquired resistance. Among the 774 pulmonary or pulmonary plus extra-pulmonary MDR-TB cases, 159 were new cases and 615 were previously treated ones.

Regarding personal characteristics, 70.6% (1,111) were male, 87.0% (1,370) were 20 to 59 years old, 60.9% (959) were Afro-Brazilian and 68.0% (1,070) had less than eight years of schooling (Table 3).

In relation to clinical characteristics, most of the cases were exclusively pulmonary, 94.8% (1,492), 13.1% (206) had AIDS and 11.3% (178) had diabetes. The use of illicit drugs, harmful use of alcohol and tobacco were reported, respectively, by 21.0% (330), 25.8% (406) and 22.2% (350) of cases (Table 3). Of the total cases, 56.5% (890) had some of the comorbidities studied, and the use of substances (alcohol, tobacco and/or illegal drugs) was reported in 42.0% (661) of cases.

All analyzed variables had more than 90% completeness.

**Discussion**

In Brazil, in 2014, almost one third of reported DR-TB cases had never been treated for TB and more than a half had MDR-TB. Most of them were men, were Afro-Brazilian, of working age, had a low education level and had at least one comorbidity, with emphasis on the use of substances. The relative frequency of primary resistance cases was higher than that described for Brazil in 2010 (between 6.0% and 8.0%),13 which may suggest transmission of resistant strains or improved DR-TB diagnosis. The latter hypothesis considers the expansion of sensitivity test supply, as well as expansion of rapid molecular testing for TB.14

MDR-TB predominance among DR-TB was also found in the Brazilian state of Espírito Santo: 47.7% between 2002 and 2012;9 the poly-resistance, reported by the same study was higher than the percentages we found (namely 14.0% and 9.5%).9 Regarding forms of mono-resistance, our results show predominance of mono-resistance to isoniazid, followed by mono-resistance to rifampicin. Similar results were found in previous studies.5,7,9 Notwithstanding, predominant mono-resistance to streptomycin had already been reported in the municipality of São José do Rio Preto, in the state of São Paulo, between 2009 and 2013.6

The number of pulmonary MDR-TB cases reported in 2014 accounted for 43.7% of those estimated by WHO for Brazil that year (19.4% of primary cases and 64.7% of acquired cases).15 The WHO estimates were based on reported cases, on underreporting estimated by specialists and on the most recent
Table 3 – Demographic and clinical characteristics of drug-resistant tuberculosis cases in Brazil, 2014

| Variable                        | Frequency N (%) |
|---------------------------------|-----------------|
| **Sex**                         |                 |
| Female                          | 463 (29.4)      |
| Male                            | 1,111 (70.6)    |
| **Age group (in years)**        |                 |
| ≤19                             | 83 (5.3)        |
| 20-59                           | 1,370 (87.0)    |
| ≥60                             | 121 (7.7)       |
| **Education level (in years of schooling)** |                 |
| None                            | 99 (6.3)        |
| 1-3                             | 507 (32.2)      |
| 4-7                             | 464 (29.5)      |
| 8-11                            | 255 (16.2)      |
| ≥12                             | 104 (6.6)       |
| Unknown                         | 145 (9.2)       |
| **Ethnicity/skin color**        |                 |
| White                           | 546 (34.7)      |
| Afro-Brazilian                  | 959 (60.9)      |
| Asian                           | 6 (0.4)         |
| Indigenous                      | 10 (0.6)        |
| Unknown                         | 53 (3.4)        |
| **Clinical form**               |                 |
| Pulmonary                       | 1,492 (94.8)    |
| Extra-pulmonary                 | 30 (1.9)        |
| Pulmonary + extra-pulmonary     | 52 (3.3)        |
| **Comorbidity**                 |                 |
| AIDS                            | 206 (13.3)      |
| Diabetes mellitus               | 178 (11.3)      |
| Illegal drugs use               | 330 (21.0)      |
| Harmful use of alcohol          | 406 (25.8)      |
| Tobacco use                     | 350 (22.2)      |

Brazilian survey on drug resistance. The difference found may arise from an overestimation by WHO, given the known limitations of the method, but it may also indicate a hidden endemic situation in the Brazil.

The predominance of men, Afro-Brasilian, young people, and people with low levels of education was also found in other municipal, state and local studies between 2000 and 2013; with an exception in the municipality of Porto Alegre, in the state of Rio Grande do Sul, between 2006 and 2007, when most DR-TB cases (64.3%) were white individuals. This variation is possibly due to regional differences in the ethnic composition of population. The DR-TB case profile is the same as that associated with treatment of drug-sensitive TB cases loss to follow-up. This convergence suggests the need to improve monitoring of these groups, to prevent resistant forms of the disease. One in nine DR-TB cases had AIDS (11.3%), a higher proportion than that found among MDR-TB cases in Espírito Santo between 2000 and 2004 (9.5%). HIV/AIDS and DR-TB co-infection is more complex due to how each infection is managed.
Diabetes has the potential to interfere with TB treatment, with higher risk of treatment failure, TB recurrence and death. The relative frequency of substance use is consistent with that found in São José do Rio Preto between 2009 and 2013, as well as among MDR-TB cases at the São Paulo State Referral Center in 2010. In Espírito Santo, among DR-TB cases reported between 2002 and 2012, a higher percentage of tobacco and alcohol users was reported. Exclusively in relation to alcohol, the result of our study is notably higher than the data for the state of Amazonas between 2000 and 2011 (6.2%). In general, the high percentages suggest that TB services need to be capable of providing care focused on DR-TB patients and psycho-social support. These are priorities of the End TB Strategy. The use of data from two information systems – TBWeb and SITETB – may indicate a limitation of this study, due to potential non-uniformity of data collection and recording. Underreporting of DR-TB cases may be another limitation, although their notification is compulsory in Brazil.

This study outlined the profile of DR-TB cases reported in Brazil in 2014, and found a relative frequency of primary DR-TB cases higher than previous levels and a lower number of pulmonary MDR-TB cases than that estimated by the WHO. We hope that these results will be able to inform programmatic decisions referring to DR-TB in Brazil, considering its magnitude, territorial distribution and specificities of the most affected groups.

Authors’ contributions

Jacobs MG and Pinto Junior VL contributed to the study conception. Jacobs MG analyzed the data and wrote the first version of the manuscript. Both authors revised the manuscript, wrote and approved the final version of the manuscript.

References

1. World Health Organization. Global tuberculosis report 2018 [Internet]. Geneva: World Health Organization; 2018 [cited 2019 Jul 18]. Available from: https://www.who.int/tb/publications/global_report/en/
2. Chiang CY. Basic concepts and definitions of drug resistance in tuberculosis. In: Caminero JA, editor. Guidelines for clinical and operational management of drug-resistant tuberculosis [Internet]. Paris: International Union Against Tuberculosis and Lung Disease (The Union); 2013 [cited 2019 Jul 18]. p.13-26. Available from: https://www.theunion.org/what-we-do/publications/technical/english/mdr-tbguide_6-19-13_web.pdf
3. Braga JU, Barreto AMW, Hijjar MA. Inquérito epidemiológico da resistência às drogas usadas no tratamento da tuberculose no Brasil 1995-1997, IEIRDTB. Parte III: principais resultados. Bol Pneumol Sanit [Internet]. 2003 Jul-dez [citado 2019 jul 18];11(1):76-81. Disponível em: http://scielo.iec.gov.br/pdf/bps/v10n2/v10n2a10.pdf
4. Kritski AL. Emergência de tuberculose resistente: renovado desafio. J Bras Pneumol [Internet]. 2010 mar-abr [citado 2019 jul 18];36(2):157-8. Disponível em: http://www.scielo.br/pdf/jbpeu/v36n2/a36n2a01. pdf. doi: 10.1590/S1806-3713201000020001
5. Micheletti VCD, Moreira JS, Ribeiro MO, Kritski AL, Braga JU. Drug-resistant tuberculosis in subjects included in the Second National Survey on Antituberculosis Drug Resistance in Porto Alegre, Brazil. J Bras Pneumol [Internet]. 2014 Mar-Apr [citado 2019 Jul 18];40(2):155-63. Available from: http://www.scielo.br/pdf/jbpeu/v40n2/1806-3713-jbpeu-40-02-00155.pdf. doi: 10.1590/S1806-37132014000200009
6. Pedro HSP, Nardi SMT, Pereira MIF, Oliveira RS, Suffys PN, Gomes HM, et al. Clinical and epidemiological profiles of individuals with drug-resistant tuberculosis. Mem Inst Oswaldo Cruz [Internet]. 2015 Apr [citado 2019 Jul 18];110(2):235-41. Available from: http://www.scielo.br/pdf/mioc/v110n2/0074-0276-mioc-01400316.pdf. doi: 10.1590/0074-02760140316
7. Nogueira JA, Marques RRC, Silva TR, França UM, Villa TCS, Palha PF. Caracterização clínico-epidemiológica dos pacientes com diagnóstico de tuberculose resistente às drogas em João Pessoa, PB. Rev Eletr Enf [Internet]. 2008 [citado 2019 jul 18];10(4):979-89. Disponível em: https://www.fen.ufg.br/revista/v10/n4/pdf/v10n4a10.pdf
8. Micheletti VCD, Kritski AL, Braga JU. Clinical features and treatment outcomes of patients with drug-resistant and drug-sensitive tuberculosis: a historical cohort study in Porto Alegre, Brazil. PLoS
9. Fregona G, Cosme LB, Moreira CMM, Bussular JL, Dettoni VV, Dalcolmo MP, et al. Risk factors associated with multidrug-resistant tuberculosis in Espírito Santo, Brazil. Rev Saúde Pública [Internet]. 2017 Apr [cited 2019 Jul 18];51:41. Available from: http://www.scielo.br/pdf/rsp/v51/0034-8910-rsp-S1518-87872017051006688.pdf. doi: 10.1590/s1518-8787.2017051006688

10. Brasil. Presidência da República. Lei no 12.288, de 20 julho de 2010. Institui o Estatuto da Igualdade Racial; altera as Leis n° 7.716, de 5 de janeiro de 1989, n° 9.029, de 13 de abril de 1995, n° 7.347, de 24 de julho de 1985, e n° 10.778, de 24 de novembro de 2003 [Internet]. Diário Oficial da União, Brasília (DF), 2010 jul 7 [citado 2019 jul 18]. Disponível em: http://planalto.gov.br/ccivil_03/_ato2007-2010/2010/lei/l12288.htm

11. Brasil. Presidência da República. Lei no 12.527, de 18 novembro de 2011. Regula o acesso a informações previsto no inciso XXXIII do art. 5o, no inciso II do § 3o do art. 37 e no § 2o do art. 216 da Constituição Federal; altera a Lei no 8.112, de 11 de dezembro de 1990; revoga a Lei no 11.111, de 5 de maio de 2005, e dispositivos da Lei no 8.159, de 8 de janeiro de 1991; e dá outras providências. Diário Oficial da União, Brasília (DF), 2011 nov 18 [citado 2019 jul 18]. Disponível em: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/lei/l12527.htm

12. Governo do Estado de São Paulo. Casa Civil. Decreto no 58.052 de 16 de maio de 2012. Regulamenta a Lei federal no 12.527, de 18 de novembro de 2011, que regula o acesso a informações, e dá providências correlatas. São Paulo, 2012 maio 16 [citado 2019 jul 18]. https://www.al.sp.gov.br/repositorio/legislacao/decreto/2012/decreto-58052-16.05.2012.html

13. Melo FAF. A experiência brasileira no controle da multidroga-resistência. Rev Port Pneumol [Internet]. 2010 jan [citado 2019 jul 18];7 Suppl 1A:16-23. Disponível em: https://www.sciencedirect.com/science/article/pii/S0873215915300878. doi: 10.1016/S0873-2159(15)30087-8

14. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Detectar, tratar e curar: desafios e estratégias brasileiras frente à tuberculose. Bol Epidemiol [Internet]. 2015 [citado 2019 jul 18];46(9):1-19. Disponível em: http://portalarquivos.saude.gov.br/images/pdf/2015/marco/25/Boletim-tuberculose-2015.pdf

15. World Health Organization. Global tuberculosis report 2015 [Internet]. 20th ed. Geneva: World Health Organization; 2015 [citado 2019 Jul 18]. 192 p. Available from: https://apps.who.int/iris/handle/10665/191102

16. Glaziou P, Simanidis C, Pretorius C, Timimi H, Floyd K. Global TB report 2015: technical appendix on methods used to estimate the global burden of disease caused by TB [Internet]. Geneva: World Health Organization; 2015 [citado 2019 Jul 18]. 34 p. Available from: https://www.who.int/tb/publications/global_report/gtbr15_online_technical_appendix.pdf

17. Almeida MG, Barbosa DRM, Almeida DFS. Epidemiologia e distribuição espacial de casos notificados de tuberculose multirresistente (TBMR) no Brasil, 2008-2012. Rev Epidemiool Controle Infecç [Internet]. 2014 out-dez [citado 2019 jul 18];3(4):117-22. Disponível em: https://online.unisc.br/seer/index.php/epidemiologia/article/download/356/3/3251

18. Vieira RCA, Fregona G, Palaci M, Dietze R, Maciel ELN. Perfil epidemiológico dos casos de tuberculose multirresistente do Espírito Santo. Rev Bras Epidemiol [Internet]. 2007 mar [citado 2019 jul 18];10(1):56-65. Disponível em: http://www.scielo.br/pdf/rbepid/v10n1/06.pdf. doi: 10.1590/S1415-790X2007000100007

19. Ferreira KR, Cavalcante EGR, De-La-Torre-Ugarte-Guaniolo MC, Bertal RAL, Bertolozzi MR. Portadores de tuberculose multirresistente em um centro de referência: perfil sócio-demográfico e clínico-epidemiológico. Rev Esc Enferm USP [Internet]. 2011 dez [citado 2019 jul 18];45(n. esp. 2):1685-9. Disponível em: http://www.scielo.br/pdf/reesusp/vi5nspe2/08.pdf. doi: 10.1590/S0080-62342011000800008
20. Garrido MS, Bührer-Sêkula S, Souza AB, Oliveira GP, Antunes IA, Mendes JM, et al. Multidrug-resistant tuberculosis in the Amazonas State, Brazil, 2000-2011. Int J Tuberc Lung Dis [Internet]. 2015 May [cited 2019 Jul 18];19(5):531-6. Available from: https://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000005/art00008%3bsessionid=1r6i6bh40zn8.x-ic-live-02. doi: 10.5588/ijtld.14.0291

21. Orofino RL, Brasil PEA do, Trajman A, Schmaltz CAS, Dalcolmto M, Rolla VC. Preditores dos desfechos do tratamento da tuberculose. J Bras Pneumol [Internet]. 2012 fev [citado 2019 jul 18];38(1):88-97. Disponível em: http://www.scielo.br/pdf/jbpneu/v38n1/a13.pdf. doi: 10.1590/S1806-37132012000100013

22. Sanchez M, Bartholomay P, Arakaki-Sanchez D, Enarson D, Bissell K, Barreira D, et al. Outcomes of TB treatment by HIV status in national recording systems in Brazil, 2003-2008. PLoS One [Internet]. 2012 Mar [cited 2019 Jul 18];7(3):e33129. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0033129. doi: 10.1371/journal.pone.0033129

23. Silva PF, Moura GS, Caldas AJM. Fatores associados ao abandono do tratamento da tuberculose pulmonar no Maranhão, Brasil, no período de 2001 a 2010. Cad Saúde Pública [Internet]. 2014 ago [citado 2019 jul 18];30(8):1745-54. Disponível em: http://www.scielo.br/pdf/csp/v30n8/a02-311X-csp-30-8-1745/pdf. doi: 10.1590/0102-311X00124513

24. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis – the perfect storm. J Infect Dis [Internet]. 2007 Aug [cited 2019 Jul 18];196 Suppl 1:S86-107. Available from: https://academic.oup.com/jid/article/196/Supplement_1/S86/807908. doi: 10.1093/518665

25. Han X, Wang Q, Wang Y, Cai J, Ma Y, Zhou X, et al. The impact of diabetes on tuberculosis treatment outcomes: evidence based on a cumulative meta-analysis. Int J Diabetes Dev Ctries [Internet]. 2016 Jul [cited 2019 Jul 18];36(4):490-507. Available from: https://link.springer.com/article/10.1007/s13410-016-0514-5

26. Walker IF, Baral SC, Wei X, Huque R, Khan A, Walley J, et al. Multidrug-resistant tuberculosis treatment programmes insufficiently consider comorbid mental disorders. Int J Tuberc Lung Dis [Internet]. 2017 Jun [cited 2019 Jul 18];21(6):603-9. Available from: https://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000006/art00004. doi: 10.5588/ijtld.17.0135

27. World Health Organization. The end TB strategy: global strategy and targets for tuberculosis prevention, care and control after 2015 [Internet]. Geneva: World Health Organization; 2015 [cited 2019 Jul 18]. Available from: https://www.who.int/tb/post2015_strategy/en/

28. Brasil. Ministério da Saúde. Portaria no 204, de 17 de fevereiro de 2016. Define a Lista Nacional de Notificação Compulsória de doenças, agravos e eventos de saúde pública nos serviços de saúde públicos e privados em todo o território nacional, nos termos do anexo, e dá outras providências [Internet]. Diário Oficial da União, Brasília (DF), 2016 fev 18 [citado 2019 jul 18]; Seção 1:23. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gnm/2016/prt0204_17_02_2016.html