Published in final edited form as:

Int J Tuberc Lung Dis. 2020 February 01; 24(2): 207–213. doi:10.5588/ijtld.19.0186.

The fourth national anti-tuberculosis drug resistance survey in Peru

Neyda Quispe¹, Luis Asencios¹, Cristian Obregon¹, Gustavo E. Velásquez^{2,3}, Carole D. Mitnick^{3,4,5}, Michael Lindeborg⁶, Hector Jave⁷, Lely Solari^{1,8}

¹Instituto Nacional de Salud, Lima, Peru

²Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA

³Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

⁴Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA

⁵Partners In Health, Boston, MA, USA

⁶Harvard Medical School, Boston, MA, USA

⁷Hospital Nacional Dos de Mayo, Lima, Peru

⁸Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Lima, Peru

SUMMARY

Setting—Peru is one of the 30 countries with the highest burden of multidrug-resistant tuberculosis (MDR-TB), however, universal drug susceptibility testing (DST) has not yet been achieved.

Objective—To estimate the proportion of drug resistance among smear-positive tuberculosis patients in Peru.

Design—From September 2014 to March 2015, we performed a national drug resistance survey. We included patients aged 15 years and older with tuberculosis diagnosed with a positive sputum smear. We performed DST at the National Reference Laboratory of the Peruvian National Institute of Health, using the proportion method in Middlebrook 7H10 agar for 4 first-line drugs and 6 second-line drugs, and the Wayne method for pyrazinamide.

Results—1,908 new and 272 previously treated patients were included in the analysis. 638 (29.3%) patients had resistance to at least one first-line drug. MDR-TB was diagnosed in 7.3% of new and 16.2% of previously treated patients ($p < 0.001$). There were 5 (0.2%) patients with extensively drug-resistant tuberculosis.

Conclusion—Resistance to anti-tuberculosis drugs is increasing in Peru. MDR-TB has increased to 7.3% in new patients, compared to 5.3% in the previous survey. Ongoing community

Corresponding Author: Lely Solari, M.D., Ph.D., Capac Yupanqui 1400, Jesus Maria, Lima, Peru, Telephone: 051-1-999128241, lelysol@hotmail.com.

Conflicts of interest: None of the authors declares conflicts of interests.

transmission of resistant strains highlights an urgent need for early diagnosis, optimized treatment and effective contact tracing of MDR-TB.

Keywords

Multidrug-resistant; *Mycobacterium tuberculosis*; Peru; surveillance

INTRODUCTION

Peru is a middle-income country in South America with a high incidence of tuberculosis (116 cases per 100,000 adult population).¹ It is currently included among the 30 countries in the world with the highest burden of multidrug-resistant tuberculosis (MDR-TB), having reported 3,500 cases in 2018.¹ Extensively drug resistant tuberculosis (XDR-TB) is an additional challenge, with around a hundred annual cases detected countrywide.² Diagnosis of tuberculosis and drug susceptibility testing (DST) rely on the national network of laboratories. This network performs, from microscopy for acid-fast bacilli (AFB) in sputum at primary care centers, to molecular diagnosis of susceptibility to first and second-line drugs at the National Reference Laboratory of Mycobacteriology in the Peruvian National Institute of Health (INS).³

National policy mandates DST for first line anti-tuberculosis drugs in all patients with a positive result for AFB on sputum smear.⁴ This has been progressively implemented since the early 2000s through different DST assays, such as the nitrate reductase assay (Griess),⁵ microscopic observation of drug susceptibility (MODS),⁶ and more recently, molecular testing with Genotype MTBDR*plus* (Hain Lifescience).⁷ However, the scale up of these tests is still not ideal. Among 31,052 cases of tuberculosis reported in 2013, only 9,390 patients (30.2%) were tested with molecular DST methods.⁸ Factors such as lack of an efficient sample transport system, irregular procurement of supplies for the tests, and high turnover of specialized personnel are important obstacles to universal DST.

Achieving adequate control of drug-resistant tuberculosis requires correct estimates of the disease burden, which allows adequate programming and purchase of the drugs required and appropriate projection of the resources needed for control interventions.⁹ Correct estimates can also signal possible gaps in the diagnosis of drug resistance at a programmatic level, in case the estimates based on surveillance systems differ from the ones based on research studies or surveys. This can occur when certain geographical areas have lower DST coverage compared to others.¹⁰

Resistance to first line drugs has steadily increased in Peru, from the first national survey in 1995–1996, when the percentage of MDR-TB among all tuberculosis cases was estimated to be 5.6%,¹¹ to 8.3% in 2006.¹² Here, we report the results of the fourth national anti-tuberculosis drug resistance survey. Our objective was to estimate the proportion of drug resistance among smear-positive tuberculosis patients and to compare the results with those of previous surveys. In doing so, we aimed to identify avenues for programmatic improvement, and describe an experience that could be useful for similar settings.

MATERIALS AND METHODS

Sample design

To calculate the sample size, we used the number of smear-positive cases (which in Peru are considered to be representative of all cases) reported in 2012, which was 14,917.¹³ We stratified the sample according to geography and health system distribution, and by prior treatment history. For geography we considered 7 regions: Lima east, Lima center, Lima south, Callao, the rest of the coast, the Andean highlands or “sierra,” and the jungle or “selva.” For prior treatment history we classified participants as either new (never having received anti-tuberculosis drugs) or previously treated (having received at least 4 weeks of anti-tuberculosis treatment, but not in the 4 weeks prior to enrollment). We excluded patients who had received anti-tuberculosis treatment in the 4 weeks prior to enrollment or those who had received less than 4 weeks of treatment at any time. We assumed a 19% prevalence of isoniazid resistance (the drug with highest proportion of resistance),¹² a precision of $\pm 5\%$, a design effect of 2, and 10% loss to follow up. With these parameters, we established a target sample size of 2,355 for new cases and 471 for previously treated cases, divided among the seven regions proportionally to the number of smear-positive cases diagnosed in 2012.

Study subjects and laboratory procedures

Patients 15 years or older with a positive sputum AFB smear were included from primary and secondary health care facilities and hospitals all over the country. They completed a questionnaire including basic demographic information and provided a second sputum sample. Sputum samples were preserved at 4°C and sent within 72 hours to the national reference laboratory at the INS, where they were cultured in Löwenstein-Jensen medium according to standard procedures. The immune-chromatographic test Capilia TB-Neo (TAUNS Lab) was performed for species identification in all samples.¹⁴ DST was performed using the proportion method in Middlebrook 7H10 agar.^{15,16} The critical concentrations used for first-line drugs were: isoniazid 0.2 µg/mL, rifampin 40 µg/mL, streptomycin 4 µg/mL, and ethambutol 2 µg/mL. For second-line drugs we used ethionamide 5 µg/mL, kanamycin sulfate 5 µg/mL, para-aminosalicylic acid 8 µg/mL, levofloxacin 1 µg/mL, capreomycin 10 µg/mL and cycloserine 30 µg/mL. In the case of pyrazinamide, we used the Wayne assay,¹⁷ and the results are reported separately. The questionnaires and laboratory results were double-entered into Microsoft Excel (Microsoft Corporation). Patient confidentiality was protected using identification codes for data analysis.

Data management and analysis

We report drug resistance according to 2009 World Health Organization (WHO) guidelines¹⁸ but also following the Global Tuberculosis Report.¹ We present means and medians (with corresponding standard deviations and interquartile ranges, respectively) for continuous variables and frequencies and percentages for categorical variables. We performed no imputation of data. We explored the factors associated with MDR-TB with the Student's *t*-test for continuous variables and the Pearson's chi-squared test or Fisher's exact test as appropriate for categorical variables, and considered significant association as having a *p* value ≤ 0.05 . We used Stata 15 (StataCorp LLC) for the statistical analysis.

Ethical considerations

The study was approved by the ethics committee of the INS. Permission from the health authorities of the included regions and the participating health facilities was ensured. Personnel trained for the study obtained written informed consent from participants of age 18 years and older and from parents of children of age 15–17. DST results were reported to the attending physicians as soon as they were available.

RESULTS

From September 2014 to March 2015, 2,916 smear-positive patients met the inclusion criteria and agreed to participate in the study. 52 patients (1.8%) were excluded because *Mycobacterium tuberculosis* infection was not confirmed (either they had positive culture for non-tuberculous mycobacteria or indeterminate results on the Capilia test). Among the 2,864 patients with confirmed tuberculosis, 684 (23.9%) patients were excluded due to missing DST results, either because the cultures were contaminated, no growth was present, or no report was available (Figure 1).

The final analysis included 2,180 patients; of these, 1,908 were new and 272 were previously treated cases. The median age was lower among new patients (32.2; interquartile range [IQR], 23.0–50.5), than in previously treated patients (37.6; IQR, 27.5–52.3) ($p=0.001$ in Mann-Whitney *U* test). Most patients (63.1%) were male and 70.5% lived in Lima and Callao. The median number of days that samples took to reach the reference laboratory was 4 (IQR, 2–4). Table 1 shows the characteristics of patients included in the analysis.

There were 638 (29.3%, 95%CI 27.4–31.2) patients with resistance to at least one first-line drug. Table 2 shows the resistance patterns to first-line drugs. Monoresistance (exclusive resistance to one drug) was uncommon for isoniazid, rifampin, and ethambutol, but was found in 10% (95%CI 8.8–11.3) for streptomycin. Any resistance to the first line drugs, defined as resistance to a drug on its own or in combination with other first-line drugs, was more frequent. MDR-TB was diagnosed in 8.4% (95%CI 7.3–9.6) of all patients: 7.3% (95%CI 6.2–8.5) among new and 16.2% (95%CI 12.8–21.1) among previously treated patients ($p<0.001$) and MDR/RR-TB was found in 9.5% (95%CI 8.3–10.8) of patients. Resistance to pyrazinamide was found in 2.7% (95%CI 2.1–3.5) of new and 8.4% (95%CI 7.3–9.6) of previously treated patients ($p<0.001$).

We explored the association between patient characteristics and diagnosis of MDR-TB, in comparison to patients with pan-susceptible strains, that is, patients with susceptibility to the 5 first-line drugs (patients with mono-resistance or with patterns of resistance other than MDR-TB were excluded from this analysis). Results are shown in Table 3. Only geographic region of provenance and previous treatment were associated with MDR-TB. All regions of Lima had higher proportions of MDR-TB patients.

Table 4 shows the resistance patterns to second-line drugs. Among all patients, the proportion of resistance to second-line drugs was around 1%, except for ethionamide, with 8.3% resistance. We found 27 patients with pre-XDR-TB due to second-line injectable resistance (there were no patients with pre-XDR due to fluoroquinolone resistance) and 5

patients with XDR-TB (11.5% and 2.7% of MDR-TB patients, respectively), 16 and 4 of whom were new patients. The 5 patients with XDR-TB had resistance to both levofloxacin and capreomycin. One patient was resistant to levofloxacin but sensitive to rifampin. There were no significant differences in resistance patterns to second-line drugs between new and previously treated patients (the numbers being very small), but MDR-TB patients showed significantly more resistance to second line drugs.

Figure 2 presents the prevalence of MDR-TB in the four national anti-tuberculosis drug surveys. The proportion of MDR-TB among new cases continues to rise, having increased from 2.5% (95% CI: 1.7–3.3) in 1996 to 7.3% (95% CI 6.2–8.5) in less than 20 years.

DISCUSSION

Our study shows that the prevalence of resistance to anti-tuberculosis drugs is gradually increasing in Peru, with 8.4% MDR-TB among smear-positive cases. Alarmingly, this increase is mostly driven by patients with no prior history of tuberculosis. In this group, the 2006 survey showed 5.3%¹² MDR-TB, now estimated at 7.3%. We consider this finding quite relevant, as it mostly reflects transmission of resistant strains in the community, rather than development of resistance during an inadequate course of treatment.¹⁹ We believe these findings may also reflect transmission dynamics among smear-negative cases. At the same time, this information poses an opportunity for MDR-TB control, as it should urge the reinforcement of interventions specifically oriented to the early detection and immediate treatment of MDR-TB cases with optimized regimens, to the exhaustive identification of their contacts, ensuring their treatment completion for latent infection if present, and close follow-up for early disease detection.^{4,20,21} National policies regarding the need for a special committee to decide on treatment of MDR-TB patients should be re-evaluated.

Another important finding is the high proportion of resistance to isoniazid: 17.9% overall and 16.8% in new patients, which is concordant with our previous survey showing 14.7% overall resistance.¹² Resistance to isoniazid is associated with worse outcomes²² and requires a special treatment containing fluoroquinolones, so it needs to be promptly detected. High isoniazid resistance supported the selection of molecular tests that evaluate susceptibility to both rifampin and isoniazid in Peru,²³ such as GenoType MTBDR^{plus} (Hain Lifescience), instead of options that offered only rifampin testing such as Xpert MTB/RIF (Cepheid). Xpert MTB/RIF has been widely deployed in other Latin-American countries that do not have this proportion of isoniazid resistance.⁴ Rifampin resistance continues being a good proxy for MDR-TB in Peru (9.5% and 8.4% prevalence, respectively). Finally, resistance to streptomycin has stalled since the last survey (20.7% in 2006 vs. 21.1% in 2015), but we expect it to decline in the coming years, as it has not been in use since 2013. All these considerations should be taken into account when establishing Peru's future diagnostic standards and therapeutic guidelines, the latter of which has provided considerations regarding the use of shorter regimens for the treatment of MDR-TB.²⁵ Standardized regimens have also been considered in this update.

With regards to XDR-TB, we found that around 0.2% of all smear-positive patients and 2.7% of all patients with MDR-TB in Peru have XDR-TB, which is concordant with current

surveillance reports.¹ Consistency in information obtained through surveillance systems and surveys is ideal, as it points to no further need of the latter²⁶. Interestingly, 4/5 of the patients with XDR-TB and 20/27 of those with pre-XDR-TB were new tuberculosis patients, which underscores the concept of resistant strains circulating in the community and the need for public health strategies to contain their transmission. These have to be implemented both in communities, through the strict evaluation of their contacts, as well as in health facilities where these patients seek attention, through the reinforcement of infection control measures which are currently suboptimally implemented.²⁷

Our study has some limitations. We were only able to include 1,908/2,355 (81%) of the new and 272/471 (58%) of the previously treated patients in our predefined sample size. This could significantly affect the precision of our estimate for previously treated patients and prevents us from drawing direct conclusions about the prevalence of drug resistance in this subgroup. This suboptimal sample size was due to many reasons, including the high rate of specimens with contamination or no growth on DST (24%), which can occur in studies with a nationwide scope.²⁸ Other aspect to consider is that we did not use statistical techniques to account for potential clustering in the estimation of the resistance proportions.

An additional limitation was the lack of information concerning factors associated to anti-tuberculosis drug resistance, such as HIV infection, substance abuse, and other comorbidities, among others, to better illustrate the dynamics of our epidemic.²⁹ We can only conclude previously treated patients and those living in urban regions such as Lima and Callao had a greater proportion of MDR-TB cases in comparison to the rest of the coast, the Andean region, and the jungle. This “concentration” of tuberculosis in the capital city, most of all in the crowded slums, has already been described.² Factors such as high population density and overcrowding, low socioeconomic status, impaired nutrition, and barriers to diagnosis due to a weak health system contribute to uninterrupted transmission. Unlike other places in which an inadequately monitored private sector can jeopardize the efforts of the public health sector to control the emergence of resistance to anti-tuberculosis drugs,³⁰ Peru has regulatory bodies that preclude the private sector from treating tuberculosis. However, the fragmentation of its public health system into many disintegrated subsystems (ministry of health, social security for health, penitentiary, and armed services) could be a factor jeopardizing the control of the MDR-TB epidemic.

The increasing prevalence of MDR-TB in new patients could reflect the transition from a situation, during the decades of 1990s and early 2000s, in which inadequate treatment adherence and low availability of DST led to the development and amplification of resistance, to our current situation, in which we have a wider deployment of DST and a broader spectrum of drugs and regimens,²³ but drug-resistant strains are already circulating in the community and are being identified in patients diagnosed with tuberculosis for the first time. This is seen both for first as for second-line drugs, reflecting our persisting gaps in the control of the disease, most of all in the prompt diagnosis and treatment initiation of drug-resistant patients. Of note, some cases detected among previously treated patients could also represent new transmission events (reinfections) as opposed to relapsed disease, so the prevalence of MDR-TB among new patients could underestimate the background transmission of drug-resistant strains.

CONCLUSION

The fourth national anti-tuberculosis drug resistance survey in Peru shows an increase in the percentage of patients with MDR-TB, most of all in patients diagnosed with tuberculosis for the first time. This prompts us to reinforce the current interventions directed to early diagnosis and treatment of MDR-TB, contact tracing, and adequate management of latent infection. This is essential to decelerate community transmission of drug-resistant strains, particularly, but not exclusively, in the capital city of Lima. Achieving universal DST through laboratory strengthening is a priority, so that future estimates of drug-resistance can be based on laboratory surveillance systems so that no further surveys are required.

Acknowledgements:

To Juan Ramirez, Rosario Salazar, Carlos Bartra, Eddy Valencia for their contribution in data collection.

N.Q., L.A. and L.S. conceived and designed the study. N.Q. and L.A. participated in the acquisition of data and drafting of the manuscript. L.S. participated in the conception and design of the study, data analysis and interpretation and drafting of the manuscript. C.O. participated in data analysis and interpretation and revision of the manuscript. G.E.V., C.D.M., M.L., H.J. and V.A. participated in data interpretation and revision of the manuscript. All authors approved the final version and agree to be accountable for the study.

Funding: This study was fully funded by the Peruvian National Institute of Health: Instituto Nacional de Salud (INS).

G.E.V. received support from the National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health (grant numbers K08 AI141740, L30 AI120170, P30 AI060354, and UM1 AI068636), the Ronda Stryker and William Johnston Fellowship in Global Health and Social Medicine and the Dr. Lynne Reid/Drs. Eleanor and Miles Shore Fellowship at Harvard Medical School, the Burke Global Health Fellowship at the Harvard Global Health Institute, the AIDS Clinical Trials Group Minority HIV Investigator Mentoring Program, and the Harvard University Center for AIDS Research (CFAR). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the institutions with which the authors are affiliated.

REFERENCES

1. Global Tuberculosis Report, . World Health Organization, Geneva. Available at https://www.who.int/tb/publications/global_report/en/. Accessed February 4, 2019.
2. Alarcón V, Alarcón E, Figueroa C, Mendoza-Ticona A. Tuberculosis en el Perú: situación epidemiológica, avances y desafíos para su control. *Rev Peru Med Exp Salud Publica*. 2017;34(2):299–310. [PubMed: 29177392]
3. Vargas-Herrera J, Segovia-Juarez J, Garro G. Sistema de información de la red nacional de laboratorios de salud pública en el Perú (Netlab). *Rev Peru Med Exp Salud Publica*. 2015;32(2):378–84. [PubMed: 26338402]
4. Norma técnica de salud para la atención integral de las personas afectadas por tuberculosis. Lima: Ministerio de Salud, 2013 Available at <http://www.tuberculosis.minsa.gob.pe/portaldpctb/recursos/20180308083418.pdf>. Accessed December 2, 2018.
5. Shin S, Yagui M, Asencios L, Yale G. Scale-up of Multidrug-Resistant Tuberculosis Laboratory Services, Peru. *Emerg Infect Dis*. 2008; 14(5): 701–708. [PubMed: 18439349]
6. Mendoza A, Castillo E, Gamarra N, et al. Reliability of the MODS assay decentralisation process in three health regions in Peru. *Int J Tuberc Lung Dis*. 2011; 15(2): 217–i. [PubMed: 21219684]
7. Asencios L, Galarza M, Quispe N, et al. Molecular test Genotype® MTBDRplus, an alternative to rapid detection of multidrug resistance tuberculosis. *Rev Peru Med Exp Salud Publica*. 2012;29(1):92–98. [PubMed: 22510913]
8. Puyén ZM, Acosta J, Obregon G, et al. Use and evaluation of a line probe assay in patients with tuberculosis in Peru: 2011–2013. *Rev Panam Salud Publica*. 2016;39(1):19–25. [PubMed: 27754534]

9. Maama-Maime LB, Mareka M, Ershova JV, et al. Antituberculosis Drug Resistance Survey in Lesotho, 2008–2009: Lessons Learned. *PLoS One*;10(7):e0133808.
10. Impacto socioeconómico de la tuberculosis en el Perú 2010: documento técnico. Lima: Ministerio de Salud, 2012 Available at: <http://bvs.minsa.gob.pe/local/minsa/1820.pdf>. Accessed December 2, 2018.
11. Vásquez L, Asencios L, Quispe N, et al. Vigilancia de la resistencia a los medicamentos antituberculosos en el Perú, 1995–96. *Rev Med Exp*. 1997; 14(1): 5–14.
12. Asencios L, Quispe N, Mendoza-Ticona A, et al. Vigilancia nacional de la resistencia a medicamentos antituberculosos, Perú 2005–2006. *Rev Peru Med Exp Salud Publica*. 2009; 26(3): 278–87.
13. Informe Operacional de Tuberculosis. Lima: Estrategia Sanitaria Nacional de Tuberculosis, Ministerio de Salud, 2012 Available at <http://www.tuberculosis.minsa.gob.pe/DashboardDPCTB/recursos/20180213171931.pdf>. Accessed December 2, 2018
14. Gomathi N, Devi S, Lakshmi R, et al. Capilia test for identification of *Mycobacterium tuberculosis* in MGIT™-positive cultures. *Int J Tuberc Lung Dis*. 2012;16(6):788–92. [PubMed: 22409876]
15. Canetti G, Fox W, Khomenko A, Mahler HT, Menon NK, Mitchison DA, Rist N, Smelev NA. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. *Bull World Health Organ*. 1969;41(1):21–43. [PubMed: 5309084]
16. Kent PT, Kubica GP. Public Health Microbiology, a Guide for the Level III Laboratory Centers for Disease Control, Division of Laboratory Training and Consultation. Atlanta, GA, US Department of Health and Human Services, US Government Printing Office, 1985.
17. Wayne L Simple pyrazinamidase and urease tests for routine identification of mycobacteria. *Am Rev Respir Dis*. 1974; 109:147–151. [PubMed: 4203284]
18. Guidelines for surveillance of drug resistance in tuberculosis – 4th edition Geneva: World Health Organization, 2009 Report number WHO/HTM/TB/2009.422. Accessed December 2, 2018
19. Outhred AC, Britton PN, Marais BJ. Drug-Resistant tuberculosis - primary transmission and management. *J Infect*. 2017;74(S1):S128–S135. [PubMed: 28646952]
20. Menzies H, Moalosi G, Anisimova V, et al. Increase in anti-tuberculosis drug resistance in Botswana: results from the fourth national drug resistance survey. *Int J Tuberc Lung Dis*. 2014;18(9):1026–33. [PubMed: 25189548]
21. Grandjean L, Gilman R, Martin L, et al. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. *PLoS Med*. 2015;12(6):e1001843. [PubMed: 26103620]
22. Villegas L, Otero L, Sterling TR, et al. Prevalence, Risk Factors, and Treatment Outcomes of Isoniazid- and Rifampicin-Mono-Resistant Pulmonary Tuberculosis in Lima, Peru. *PLoS One*. 2016;11(4):e0152933. [PubMed: 27045684]
23. Plan estratégico multisectorial de la respuesta nacional a la tuberculosis en el Perú 2010– 2019. Lima: Ministerio de Salud, 2010 Accessed December 2, 2018.
24. Pinto MFT, Steffen R, Entringer A, Costa ACCD, Trajman A. Budget impact of the incorporation of GeneXpert MTB/RIF for diagnosis of pulmonary tuberculosis from the perspective of the Brazilian Unified National Health System, Brazil, 2013–2017. *Cad Saude Publica*. 2017;33(9):e00214515. [PubMed: 29019524]
25. Modificatoria de la Norma técnica sanitaria No. 104. Lima: Ministerio de Salud, 2018 Available at <http://www.tuberculosis.minsa.gob.pe/portaldpctb/recursos/20190404114640.PDF> Accessed June 29, 2019.
26. Nhung NV, Hoa NB, Sy DN, Hennig CM, Dean AS. The fourth national anti-tuberculosis drug resistance survey in Viet Nam. *Int J Tuberc Lung Dis*. 2015;19(6):670–5. [PubMed: 25946357]
27. Escombe AR, Huaroto L, Ticona E, 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. [PubMed: 20819256]
28. Zhao Y, Xu S, Wang L, et al. National Survey of Drug-Resistant Tuberculosis in China. *N Engl J Med*. 2012; 366:2161–2170. [PubMed: 22670902]

29. Otero L, Krapp F, Tomatis C, et al. High prevalence of primary multidrug resistant tuberculosis in persons with no known risk factors. PLoS One. 2011;6(10):e26276. [PubMed: 22046266]
30. Almeida D, Rodrigues C, Udwadia ZF, et al. Incidence of multidrug-resistant tuberculosis in urban and rural India and implications for prevention. Clin Infect Dis. 2003;36(12):e152–4. [PubMed: 12802779]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Flowchart of patients included in the fourth national anti-tuberculosis drug resistance survey, Peru, 2014–2015. DST = drug susceptibility testing; TB = tuberculosis.

Figure 2. Proportion of patients with MDR-TB in the four national surveys (lines show 95% confidence intervals). MDR-TB = multidrug-resistant tuberculosis.

Table 1.

Characteristics of patients included in the fourth national anti-tuberculosis drug resistance survey, Peru, 2014–2015

Characteristic	New patients (n= 1,908)	Previously treated patients (n=272)	Total (n= 2,180)
Male sex	1183 (62.0%)	193 (71.0%)	1376 (63.1%)
Age group			
15–24	544 (28.5%)	43 (15.8%)	587 (26.9%)
25–34	421 (22.0%)	69 (25.4%)	490 (22.5%)
35–54	433 (22.7%)	81 (29.8%)	514 (23.6%)
55	358 (18.8%)	49 (18.0%)	407 (18.7%)
Unknown	152 (8.0%)	30 (11.0%)	182 (8.3%)
Source			
Primary care facilities	294 (15.4%)	29 (10.7%)	323 (14.8%)
Secondary care facilities	1183 (62.0%)	184 (67.6%)	1367 (62.7%)
Hospital/ regional lab	431 (22.6%)	59 (21.7%)	490 (22.5%)
Region			
Lima East	387 (20.3%)	64 (23.5%)	451 (20.7%)
Lima Center	348 (18.2%)	76 (28.0%)	424 (19.4%)
Lima South	348 (18.2%)	36 (13.2%)	384 (17.6%)
Callao	250 (13.1%)	27 (9.9%)	277 (12.7%)
Rest of coast	209 (11.0%)	26 (9.6%)	235 (10.8%)
Selva	181 (9.5%)	13 (4.8%)	194 (8.9%)
Sierra	185 (9.7%)	30 (11.0%)	215 (9.9%)
Smear result			
1+	728 (38.1%)	93 (34.2%)	821 (37.7%)
2+	604 (31.7%)	83 (30.5%)	687 (31.5%)
3+	557 (29.2%)	96 (35.3%)	653 (30.0%)
Others	19 (1.0%)	0 (0.0%)	19 (0.9%)

Table 2.

Resistance patterns to first-line anti-tuberculosis drugs in the fourth national anti-tuberculosis drug resistance survey, Peru, 2014–2015

Susceptibility pattern*	New patients (n=1,908)	Previously treated patients (n=272)	Total (n= 2,180)	Previously treated/New Prevalence ratio	P value *
Pansusceptible (n=2174)	1361 (71.5%) (69.1%–73.9%)	175 (64.6%) (57.5%–71.7%)	1536 (70.7%) (68.4%–73.0%)	0.90 (0.82–0.99)	0.02
Monoresistance					
Isoniazid (n=2180)	58 (3.0%) (2.4%–3.9%)	8 (2.9) (1.5%–5.8%)	66 (3.0%) (2.4%–3.8%)	0.97 (0.47–2.00)	0.9
Rifampin (n=2180)	10 (0.5%) (0.3%–1.0%)	9 (3.3%) (1.7%–6.2%)	19 (0.9%) (0.6%–1.4%)	6.60 (2.59–15.40)	<0.001
Ethambutol (n=2172)	5 (0.3) (0.1%–0.6%)	2 (0.7%) (0.2%–2.9%)	7 (0.3%) (0.2%–0.7%)	2.33 (0.55–14.45)	0.2
Streptomycin (n=2179)	199 (10.4%) (9.1%–11.9%)	18 (6.6%) (4.2%–10.3%)	217 (10.0%) (8.8%–11.3%)	0.63 (0.40–1.01)	0.05
Any resistance (n= 2180)					
Isoniazid	321 (16.8%) (15.2%–18.6%)	65 (23.9%) (19.2%–29.3%)	386 (17.7%) (16.2%–19.4%)	1.42 (1.12–1.80)	0.004
Rifampin [†]	152 (7.8%) (6.8%–9.3%)	55 (20.2%) (15.9%–25.4%)	207 (9.5%) (8.3%–10.8%)	2.59 (1.92–3.36)	<0.001
Etambutol	101 (5.3%) (4.4%–6.4%)	30 (11.0%) (7.8%–15.4%)	131 (6.0%) (5.1%–7.1%)	2.08 (1.41–3.07)	<0.001
Streptomycin	404 (21.2%) (19.4%–23.1%)	56 (20.6%) (16.2%–25.8%)	460 (21.1%) (19.4%–22.9%)	0.97 (0.76–1.25)	0.8
MDR	139 (7.3%) (6.2%–8.5%)	44 (16.2%) (12.5%–21.1%)	183 (8.4%) (7.3%–9.6%)	2.22 (1.62–3.04)	<0.001

Values shown are number (percent) on the first row, and (95% confidence interval) on the second row.

* Pearson's chi square test/ Fisher's exact test as appropriate.

[†] Equivalent to MDR/RR-TB.

Table 3.

Factors associated with multidrug-resistant tuberculosis, Peru, 2014–2015

Susceptibility pattern	MDR-TB (n= 183) n (%)	Pan-susceptible TB (n=1,536) n (%)	<i>P</i>
Male sex	122 (66.7)	973 (63.4)	0.4 [*]
Median age (interquartile range)	34.2 (23.8–49.5)	33.4 (23.6–52.0)	0.51 [†]
Type of health facility			
Primary care facilities	30 (12.5)	211 (87.5)	0.2 [*]
Secondary care facilities	118 (11.0)	956 (89.0)	
Hospital/ regional lab	35 (8.7)	369 (91.3)	
Region of provenance			
Lima East	46 (12.9)	312 (87.1)	<0.001 [*]
Lima Center	50 (14.6)	292 (85.4)	
Lima South	37 (12.9)	251 (87.1)	
Callao	24 (12.5)	168 (87.5)	
Rest of coast	5 (2.5)	192 (97.5)	
Selva	8 (5.2)	145 (94.8)	
Sierra	13 (6.9)	175 (93.1)	
Previously treated	44 (24.0)	175 (11.4)	<0.001 [*]

* Pearson's chi square test/ Fisher's exact test as appropriate.

[†] Student t test

Table 4.

Resistance patterns to second-line anti-tuberculosis drugs in the fourth national anti-tuberculosis drug resistance survey, Peru, 2014–2015

Any resistance	New patients (n = 1,886)	Previously treated patients (n =269)	<i>p</i> value *	Non-MDR-TB (n=1,997)	MDR-TB (n = 183)	<i>p</i> value *	Total (n = 2,156)
Ethionamide (n=2,176)	155 (8.1%)	25 (9.2%)	0.56	128 (6.4%)	52 (28.7%)	<0.001	180 (8.3%)
Para-aminosalicylic acid (n=2,176)	11 (0.6%)	1 (0.4%)	1.0	7 (0.4%)	5 (2.7%)	0.002	12 (0.6%)
Cycloserine (n=2,176)	18 (1.0%)	5 (1.8)	0.20	0 (0.0%)	23 (12.6%)	<0.001	23 (1.1%)
Levofloxacin (n=1,595)	5 (0.4%)	1 (0.5%)	0.54	1 (0.1%)	5 (3.7%)	<0.001	6 (0.4%)
Kanamycin (n=2,178)	29 (1.1%)	7 (2.6%)	0.07	12 (0.6%)	15 (8.2%)	<0.001	27 (1.2%)
Capreomycin (n=2,179)	20 (1.1%)	5 (1.8%)	0.23	0 (0.0%)	25 (13.7%)	<0.001	25 (1.2%)
Second line injectable- preXDR (n=2,177)	20 (1.1%)	7 (1.8%)	0.07	Not applicable	27 (14.8%)	Not applicable	27 (1.3%)
XDR (n=1,595)	4 (0.3%)	1 (0.5%)	0.89	Not applicable	5 (3.7%)	Not applicable	5 (0.3%)

Values shown are number (percent)

* Pearson's chi square test/ Fisher's exact test as appropriate.