Journal of Tuberculosis Research, 2022, 10, 75-86
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Effectiveness and Safety of 9-Month Treatment Regimen for Multidrug-Resistant Tuberculosis in the Philippines

Vivian S. Lofranco[1*], Vincent M. Balanag Jr[1], Lawrence O. Raymond[1], Noel G. Macalalad[2], Alex Golubkov[3], Mary Rosary T. Santiago[4], Anna Marie Celina G. Garfin[4]

[1]National Center for Pulmonary Research-Lung Center of the Philippines, Quezon City, Philippines
[2]National TB Reference Laboratory-Research Institute for Tropical Medicine, Muntinlupa City, Philippines
[3]Global Health Bureau, Infectious Diseases Office, TB Division, U.S. Agency for International Development (USAID), Washington, USA
[4]Disease Prevention and Control-Department of Health, Manila, Philippines
Email: *vivslofranco5000@gmail.com

How to cite this paper: Lofranco, V.S., Balanag Jr, V.M., Raymond, L.O., Macalalad, N.G., Golubkov, A., Santiago, M.R.T. and Garfin, A.M.C.G. (2022) Effectiveness and Safety of 9-Month Treatment Regimen for Multidrug-Resistant Tuberculosis in the Philippines. *Journal of Tuberculosis Research*, **10**, 75-86.
https://doi.org/10.4236/jtr.2022.102006

Received: May 26, 2022
Accepted: June 26, 2022
Published: June 29, 2022

Abstract

Background: The Philippines has a burden of drug-resistant tuberculosis (DR-TB). One of the key challenges in the programmatic management of DR-TB (PMDT) is the high rate of loss to follow-up (38% in the 2010 cohort). An urgent need for a shorter, more tolerable, less expensive treatment regimen exists. The aim of the operational study is to determine the efficacy and safety of the short treatment regimen among drug resistant TB. **Methods**: This is a prospective single-arm cohort study evaluating the effectiveness and safety of a shorter 9 - 11-month treatment regimen (9MTR) for rifampicin-resistant/multi-drug resistant TB (RR/MDR-TB) in 10 PMDT facilities. All eligible consenting adult patients with rifampicin-resistant TB were enrolled and received the standardized 9-month treatment regimen (9MTR), including injectables, with a follow-up after 12 months of treatment completion. **Results**: A total of 329 patients were enrolled from July 2015 to December 2016. At the 6th month post-enrollment, 256 (77.8%) of them had culture-negative test results. The end-of-treatment success rate was 74.1% (224 [68.0%] were cured and 20 [6.1%] completed the treatment). On the other hand, 10 (3.0%) died, 41 (12.5%) lost to follow-up, 33 (10.0%) withdrawn, 1 (0.3%) treatment failure. In the 12th month after 9MTR completion, among the 244 patients with successful treatment, 198 (81.1%) had culture-negative results, while there were 46 patients whose culture tests were not done. One patient developed TB relapse with fluoroquinolone resistance. The majority of the adverse events were mild that occurred mostly during the first 6

months of treatment. **Conclusion**: The 9-month treatment regimen had a high treatment success rate with a favorable safety profile. The loss to follow-up was reduced; however, it was still a challenge. The introduction of the 9MTR via operational research had a major impact on building national capacity and infrastructure for the programmatic adoption of a new regimen. Ten PMDT centers received training and experience, created diagnostic pathways, and active drug safety monitoring and management were built.

Keywords

MDR-TB, Short Treatment Regimen, Treatment Outcomes, Prospective Studies

1. Introduction

The Philippines is one of the 30 countries with a high burden of tuberculosis (TB) and drug-resistant TB rates according to the World Health Organization (WHO) [1]. In 2018, the country had an estimated annual incidence of 554/100,000 [2]. The results of the 2018 Drug Resistance Survey in the Philippines demonstrated 1.8% of the new cases and 16.6% of the retreatment cases to be rifampicin-resistant, and the total estimated incidence of rifampicin-resistant/multidrug-resistant-TB (RR/MDR-TB) in 20,000 cases [3].

A high proportion of patients were lost to follow-up (LTFU) during drug-resistant TB (DR-TB) treatment due to the following reasons: adverse drug reactions, need to work, personal challenges, geographical barriers, and the long duration of the standard regimen [4]. Loss to follow-up reached 31% for the DR-TB cohort of 2015 [5].

Given the large burden of RR/MDR-TB in the Philippines and the high LTFU rate, there was an urgent need for a shorter, more tolerable, and less expensive treatment regimen. The 9-month treatment regimen (9MTR) with an injectable agent was seen as an alternative treatment option for RR/MDR-TB. This prospective single-arm cohort study was conducted in 10 programmatic management of DR-TB (PMDT) treatment facilities to measure the effectiveness and safety of the 9-month treatment regimen in the Philippines.

2. Methods

2.1. Study Population and Setting

The study was conducted in 10 programmatic management of DR-TB (PMDT) treatment facilities. These were selected based on the site inclusion criteria: at least 1 year of experience in managing patients with DR-TB; suitable staff and facilities for close supervision of patients; access to diagnostic and laboratory examinations and a network of TB laboratories; and has expressed commitment to participate in the study.

2.2. Study Design and Methodology

This prospective single-arm cohort study evaluated the effectiveness (interim and final treatment outcomes) and safety of the 9MTR with injectable prescribed to patients with RR/MDR-TB who met all the inclusion criteria and none of the exclusion criteria in 10 PMDT treatment facilities. The protocol was approved by the National Ethics Committee of the Philippines (PCHRD, Philippines) and the Lung Center of the Philippines Institutional Review Board, Quezon City Philippines. Patients enrolled had confirmed RR/MDR-TB were FQ-sensitive and had no resistance to injectable agents. All patients have signed the informed consent and have been enrolled from July 2015 to December 2016. Other inclusion criteria were: 1) no previous use of the second-line anti-TB drugs for 1 month or more; 2) at least 18 years old at the time of enrollment in the 9MTR, and 3) willingness to visit the study site during the entire treatment duration of the study or a local treatment site during the continuation phase of treatment and post-treatment follow-up period.

Exclusion criteria for the study were: 1) pregnant or breastfeeding women; 2) age less than 18 years; 3) extra-pulmonary TB, and 4) human Immunodeficiency Virus (HIV) co-infection with a CD4 count of <50.

Before data collection, permission from the respective ethics committee was obtained from the regional health offices where the 10 PMDT facilities were located and from the heads of the PMDT health facilities.

The composition of the short treatment regimen had an intensive phase of 4 to 6 months with kanamycin, high dose moxifloxacin, prothionamide, high-dose isoniazid, clofazimine, ethambutol, and pyrazinamide; and a continuation phase of 5 months with moxifloxacin, clofazimine, ethambutol, and pyrazinamide. Capreomycin and levofloxacin were used to replace kanamycin or moxifloxacin, respectively in a few selected cases.

The regimen is summarized as:

4-6m (Cm) Cfz Mfx^{h} (Lfx) E H^{h} Z Pto/5m Cfz Mfx (Lfx) E Z

Post-treatment follow-up was done at the end of 6 and 12 months after completing the 9-month regimen to determine the relapse rate.

2.3. Data Management and Analysis

Data were collected and reviewed as recorded from DR-TB registers, clinical reporting forms, PMDT medical records including treatment cards, screening forms, patient progress report forms, and TB Medical Advisory Committee presentation forms using a formulated standard data collection tool. These collected data were checked for completeness, quality, and accuracy before they were encoded. Double data entry was done for verification.

General descriptive data, including frequencies of basic demographic and clinical variables, were calculated. The proportion of successful treatment are those cured and treatment completed and those patients that did not finish treatment such as loss to follow up, and failed are considered as poor treatment

outcomes, the frequency of adverse drug reactions, total aggregate and for each study site were consolidated and analyzed. The analyses were stratified by relevant demographic and clinical variables.

The interim outcome during the 4th and 6th month of treatment were analyzed that served as an important indicator if the effectivity of the short treatment regimen through its conversion of the sputum culture from the initial positive to negative culture. Most importantly a 12-month post follow-up after the treatment was closely monitored to determine its relapse rate among those drug resistant tuberculosis who have been successfully treated with short treatment regimen.

3. Results

A total of 1100 rifampicin-resistant TB cases were detected between June 2015 to December 2016 in 10 treatment sites and 948 (86%) were screened for study eligibility. A total of 530 (56%) patients had provided verbal consent for the line probe assay test and 523 (98.7%) have been tested. Among 523 patients tested, 372 (71.1%) were susceptible to both FQ and SLI and 47 (8.9%) had resistance to either FQ or SLI; 7 out of 47 (14.9%) had FQ resistance, and 40 out of 47(85.1%) had aminoglycoside resistance. Among 372 eligible patients, 329 (88.4%) have provided consent for the treatment (see Figure 1).

The baseline demographics of the patients treated with the 9MTR showed that 216 (65.7%) were males and the majority of the patients were aged 35 - 54 years (54.1%). Most of the patients (94.6%) had a previous history of tuberculosis treatment and 76 (23.1%) had comorbidities. At the start of treatment, 238 (72.3%) had smear-positive test results. The baseline audiometry showed 149 (45.3%) with normal findings, 127 (38.6%) with hearing impairment, and 53 (16.1%) were not done (Table 1).

Interim treatment outcomes were evaluated at the end of the 4th and 6th months. The interim outcome at the end of the 4th month demonstrated that 261 patients (79.3%) had negative culture results, 17 (5.2%) lost to follow-up, 7 (2.1%) died, 15 (5.0%) were withdrawn, and 1 (0.3%) failed from treatment. At

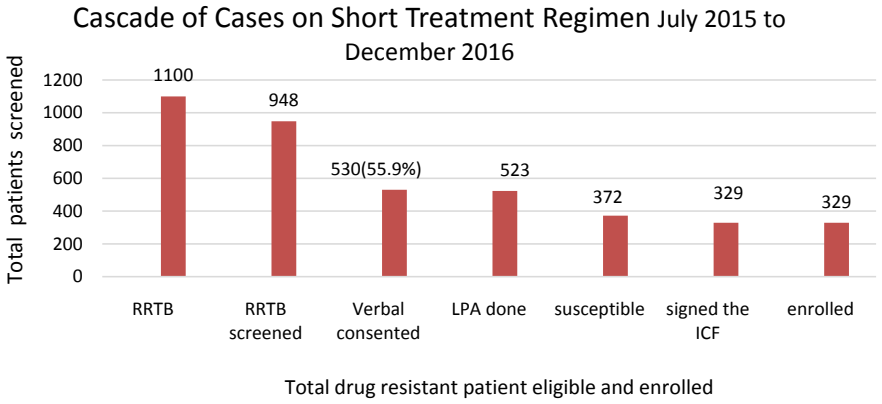

Figure 1. Cascade of cases on 9MTR from July 2015 to December 2016.

Table 1. Baseline demographics of patients treated with the short treatment regimen.

Characteristics	Number (N = 329)	Percentage
Age		
15 - 34	103	31.3
35 - 54	178	54.1
55 - 76	48	14.6
Sex		
Male	216	65.7
Female	113	34.3
History of previous TB treatment		
Yes	311	94.6
No	18	5.5
Comorbidities[1]		
Yes	76	23.1
No	253	76.9
Body mass index		
Underweight (<18.4 kg)	146	44.4
Normal/overweight/obese (18.5 kg or more)	183	55.6
Baseline Smear result		
Negative	77	23.4
Positive	238	72.3
Not done	14	4.3
Baseline culture result		
Negative	121	36.8
Positive	191	58.1
Not done	17	5.2
Audiometry		
Normal	149	45.3
Abnormal	127	38.6
Not done	53	16.1

the end of the 6th month, 256 patients (78.0%) had negative culture results, 26 (8.0%) lost to follow-up, 7(2.1%) died, 22 (7.0%) were withdrawn and 1 (0.3%) failed from treatment (Table 2).

Of the 329 patients enrolled in the study, final treatment outcomes (Table 3) showed 224 (68.1%) cured, 20 (6.1%) completed, 10 (3.0%) died, 41 (12.5%) loss to follow-up, 33 (10.0%) withdrawn, and 1(0.3%) failed.

All deaths in the study were reported within 24 hours to the Philippines Food

[1]Comorbidities: Diabetes mellitus, renal insufficiency, liver disease, HIV, and cancer.

Table 2. Interim outcome at the end of 4th and 6th months, N = 329.

Interim Outcome	4th month	Percentage	6th month	Percentage
Culture negative	261	79.3	256	78
Still culture positive	0	0	0	0
Failed	1	0.3	1	0.3
LTFU	17	5.2	26	8
Died	7	2.1	7	2.1
Withdrawn[2]	15	5	22	7
Not evaluated[3]	28	8.5	17	5.2

Table 3. Final treatment outcome under the short treatment regimen, N = 329.

Treatment outcome	Cured	Treatment completed	Died	Loss to follow up	Withdrawn[4]	Failed
N = 329	224 (68.1%)	20 (6.1%)	10 (3.0%)	41 (12.5%)	33 (10.0%)	1 (0.3%)

and Drug Administration (FDA) and the National TB Control Program of the Department of Health (NTP-DOH). The causes of death were: acute respiratory failure (2, 20.0%), hepatic encephalopathy (1, 10.0%) with acute hepatic failure secondary to drug-induced hepatitis, pneumonia (1, 10.0%), acute cardiac syndrome (1, 10.0%), sepsis (2, 20.0%), hypovolemic shock due to massive hemoptysis (1, 10.0%), and terminal cases of multidrug-resistant TB (2, 20.0%).

Adverse drug reactions were collected prospectively through the patient progress clinical report form. The side effects of varying degrees were observed in all 329 patients enrolled in the study although most of the side effects were mild and were treated with ancillary drugs. The top 10 most common adverse reactions were vomiting (296, 89.9%), nausea (234, 71.1%), hypokalemia (165, 50.1%), increased SGOT (151, 45.9%), dizziness (149, 45.3%), headache (148, 44.9%), arthralgia (139, 42.2%), increased SGPT (133 (40.4%), discoloration of the skin (133, 40.4%), and increased creatinine (125 (37.9%). These adverse reactions occurred mostly during the first 6 months of treatment (**Figure 2**). A total of 210 AEs of grade ≥ 3 were reported (**Figure 3**).

The frequency of each adverse drug reaction was recorded and showed symptoms based on system organ classification [6] wherein 2500 were gastrointestinal, 1614 hepatic, 844 metabolism/nutrition, 813 musculoskeletal, 763 dermatological/hypersensitivity, 750 ototoxicity/vestibular toxicity, 527 nephrotoxicity, 499 neurotoxicity, others 447, and psychiatric 250 (**Figure 4**).

A total of 244 (74.1%) patients were followed up for 12 months after the end of treatment. At the end of the 6th-month post-treatment follow-up, 189 (77.0%)

[2]Reasons for withdrawal: refused treatment, ADRs, enrolled in the long-term regimen.

[3]Reasons for not being evaluated: unable to submit a specimen for sputum culture, refused treatment.

[4]Reasons for withdrawal: ADRs, refused treatment, pregnant, FQ/SLI.

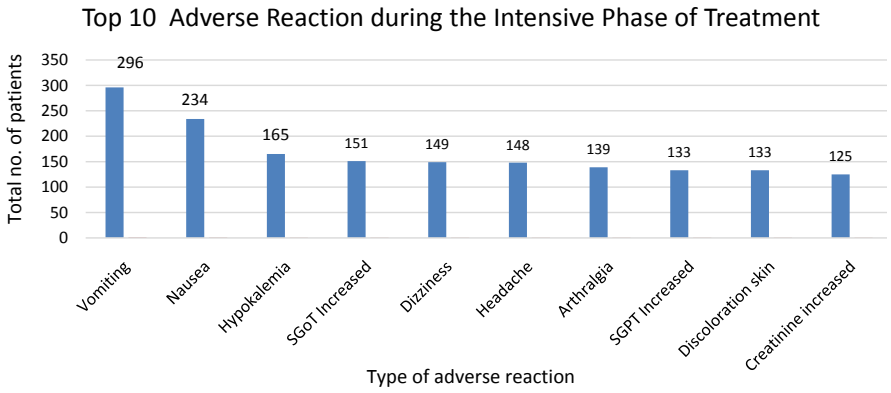

Figure 2. Top 10 most common adverse reactions.

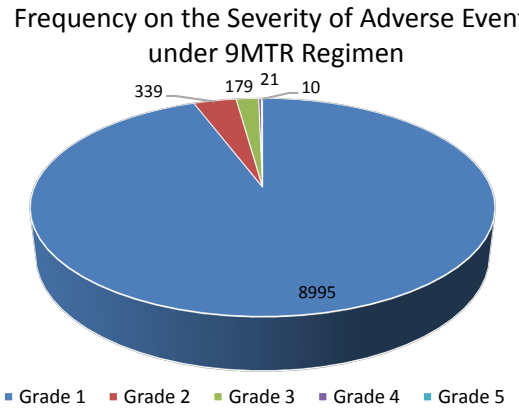

Figure 3. Frequency of the severity of adverse events.

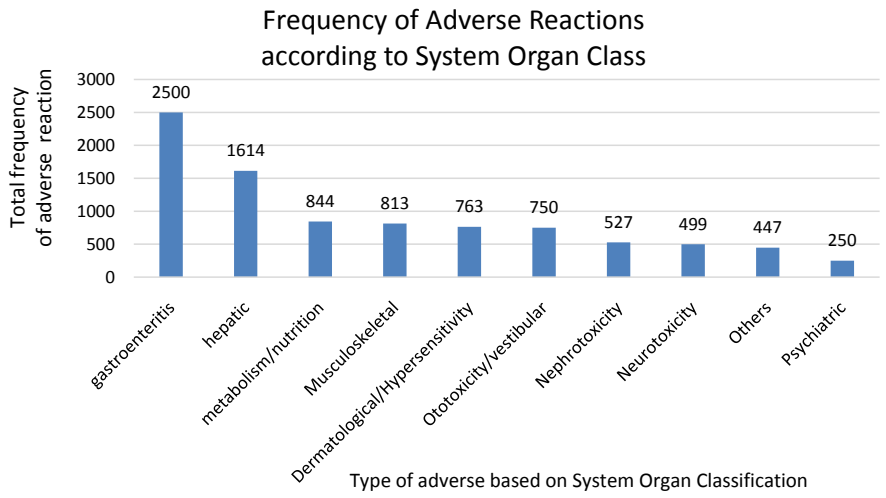

Figure 4. Frequency of adverse events[5].

had negative culture results, and 1 (0.4%) had positive culture results. At the end of the 12th-month post-treatment follow-up, 198 (81.0%) had negative culture results, while the post-treatment follow-up tests were not done on 46 (18.8%) patients (Table 4). The reasons for some patients who had not received follow-up

[5]Others: vehicular accidents, and those not listed in the system organ system.

Table 4. Post treatment follow-up of patients after short treatment regimen (n = 244).

Follow-up	Negative	Positive	Not done
At end of 6 months	189 (77.5%)	1 (0.4%)	54 (22.1%)
At end of 12 months	198(81.1%)	0 (0.0%)	46 (18.8%)

examinations at the end of 12 months were: work conflicts (14, 30.4%), loss of contact (12, 26.1%), relocation to other places for livelihood (12, 26.1%), refusal to sputum collection (6, 13.0%), death (1, 2.2%), and enrollment to new treatment (1, 2.2%). One patient who was detected as culture-positive during the follow-up was tested resistant to fluoroquinolone.

4. Discussion

The introduction of 9-month treatment regimen (9MTR) was first implemented in Bangladesh using a combination of 7 drugs with support from the Damien Foundation and reported treatment outcome in 2010 by Van Deun, *et al.* [7] In 2015, the World Health Organization recommended the 9MTR for patients diagnosed with DR-TB under operational research conditions for patients who are usually treated with conventional 20 - 24 months regimen. At that time, the average treatment success rate for DR-TB cohorts was only 50% worldwide [8]. The study of Van Deun [9], *et al.* requiring 7 types of drugs with pyrazinamide throughout treatment regimen had given a cure rate of more than 85% and occurrence of major adverse drug reactions were infrequent and manageable.

In our study, the treatment regimen that consisted of a combination of 7 first-line and second-line anti-TB medications was essentially the same as the Bangladesh regimen [9] except for the use of high-dose moxifloxacin or levofloxacin instead of gatifloxacin. Pyrazinamide, with sterilizing activity, and clofazimine, a well-tolerated companion drug. [10] [22] were given throughout treatment. The regimen was given for 4 - 6 months during the intensive phase, followed by a 5-month continuation of 4 oral medications.

We used both sputum smear tests as well as a culture conversion to determine treatment progress and also used it as an important interim indicator of the efficacy of anti-TB treatment for RR/MDRTB [11] [12]. In the study, early sputum culture conversion was achieved among 79% at the end of the 4th month and 78% at the end of the 6th month [13].

Adverse drug reactions were experienced during the initial 6 months by a majority of patients. Gastrointestinal events were common symptoms. In our study, the frequency of vomiting and nausea occurred in two-thirds of our patients during the first 6 months and has been managed through appropriate treatment actions, including counseling and ancillary medications.

Ototoxicity was predominantly associated with the use of parenteral anti-tuberculous agents like aminoglycosides and aminopeptides [14]-[19]. In the study, the frequency of ototoxicity was among the top 10 adverse events. Among 149 patients with normal audiometry findings on the baseline, 33 (22%) devel-

oped hearing impairment while on treatment, and 9 (27%) were shifted from kanamycin to capreomycin.

In the Bangladesh study described by Van Deun, of the 21 patients who died during the treatment, 20 of them had culture conversion within 3 months before death [9]. In our study, 10 (3%) died during the treatment, 7 (70%) died during the intensive phase, and 3 (30%) during the continuation phase. In all of these patients, preceding culture results had been negative.

The treatment success rate of (>80%) and the low relapse rate of (<1%) in our study were favorable as compared to a longer treatment regimen which had a 50% success rate worldwide (for the 2013 cohort) [20]. In the Philippines, the treatment success rate for DR-TB patients placed on a longer regimen was 41% in 2000, [21] and slightly increased to 55% in 2015 [5]. The treatment success rate under a short treatment regimen in our cohort was similar to the one reported for Niger [22] and South Africa [23] that had 89.2% and 78.8% respectively.

While it was a requirement for all clinical trials, it was therefore considered a best practice for operational research studies to follow up with patients after the end of the treatment for a 6- or 12-month period. Such observation allows to capture early replacements and to confirm treatment success rate results, especially for patients who did not have culture confirmation at the end of the treatment (people who registered as treatment completed). In our study, we strived to monitor patients for 12 months, however, it was difficult to obtain patient cooperation for follow-up tests, and only 244 (74.1%) patients received evaluation at the end of 12 months of observation. During the follow-up period, only 1 patient had a sputum culture-positive result at the 6-month mark. A line probe assay was done and revealed fluoroquinolone resistance. The patient was subsequently enrolled under a new regimen.

Active drug pharmacovigilance was part of the protocol implementation and all adverse events were documented. However, the study has limitations. First, it was an operational study done only in 10 selected facilities and protocol-guided management was strictly followed. Second, the turn-around time of the line probe assay result came longer than the expected schedule resulting in a limited number of enrolled patients in the study. Our study did not administer genotyping or DNA fingerprinting to differentiate the origin of acquired drug resistance TB. Given the low incidence of HIV co-infected in the country which is <1%, we need further study as to what extent this short treatment regimen is effective for the HIV-infected population.

5. Conclusion

The effect of the short treatment regimen for the treatment of multidrug-resistant tuberculosis showed a high treatment success rate with a favorable safety profile. Loss to follow up was much reduced but still is a challenge. The introduction of 9MTR via operational research had a major impact on building national capacity and infrastructure for programmatic adoption of the new regimen. Ten centers

throughout the country received training and experience, diagnostic pathways were created, and capacity for drug safety monitoring and management was built. When WHO recommended the programmatic use of 9MTR at the end of 2016, the Philippines was able to scale it up quickly to cover 80% of all DR-TB treatments in the country by the end of 2017.

Acknowledgements

This study is made possible by the generous support provided by the Philippine Department of Health-National Tuberculosis Control Program and Philippine Business for Social Progress-ACCESS TB Project under the Global Fund. The authors would like to extend their gratitude to the following partners: Dr. Mariquita M. Mantala, Technical Assistance Support Coordination (TASC) funded by USAID; Research staff from PBSP-Global Fund namely Ms. Patrice Jamie E. Cabasis, Ms. Katherine E. Asence, Ms. Maria Rhoda Torres-Cervas, Mr. Joey S. Cabanalan, Ms. Khrizza Marianne D. Casuncad, and Mr. Ryan Paulo B. Sardona. The authors would also like to acknowledge all the staff (nurses, and support staff) and physicians of the study sites: Dr. Joan Samoy-Tuy, Lung Center of the Philippines-National Center for Pulmonary Research; Dr. Chiqui Villegas-Torres, Dr. Jose N. Rodriguez Memorial Hospital and Sanitarium; Dr. Luisa Ticsay, Batangas Medical Center; Dr. Nancy Rose Labarete, Sorsogon Medical Mission Group Hospital and Health Services Cooperative; Dr. Chester Directo, Ilocos Regional Training and Research Medical Center; Dr. Sheryll Magayanes, Jose B. Lingad Memorial General Hospital; Dr. Alimar Nassaie, Eversley Childs Sanitarium and General Hospital; Dr. Leonnie Fortin, Western Visayas Medical Center; Dr. Leslie Christine Magsayo-Salon, Xavier University-Community Health Care Center of German Doctors; and Dr. Marcelino Medina, Zamboanga City Medical Center.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the U.S. Agency for International Development or the U.S. Government.

Ethics Approval

The study protocol was approved by the Lung Center of the Philippines Institutional Ethics Review Board.

Conflicts of Interest

None declared.

References

[1] World Health Organization (2017) Global Tuberculosis Report 2017. WHO, Geneva. http://www.who.int/tb/publications/global_report/en/

[2] World Health Organization (2019) Global Tuberculosis Report 2019. WHO, Geneva. https://www.who.int/tb/publications/global_report/en/

[3] Department of Health (2018) Third National Drug Resistance Survey on Tuberculosis in the Philippines, Technical Report. Department of Health, National TB Control Program, Infectious Diseases Office, Manila.

[4] Tupasi, T.E., Garfin, A.M.G., Kurbatova, E.V., *et al.* (2016) Factors Associated with Loss to Follow up during Treatment for MDR-TB, the Philippines 2012-2014. *Emerging Infectious Diseases*, **22**, 491-502. https://doi.org/10.3201/eid2203.151788

[5] Philippines Department of Health (2015) National Tuberculosis Control Program (Unpublished) 2015 Accomplishment Report. Philippines Department of Health, Manila.

[6] U.S. Department of Health and Human Services (2010) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

[7] World Health Organization (2016) WHO Treatment Guidelines for Drug-Resistant Tuberculosis. WHO, Geneva. http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

[8] Falzon, D., Mirzayev, F., Wares, F., *et al.* (2015) Multidrug-Resistant Tuberculosis around the World: What Progress Has Been Made? *European Respiratory Journal*, **45**, 150-160. https://doi.org/10.1183/09031936.00101814

[9] Van Deun, A., Maug, A.K.J., Salim, A.H., *et al.* (2010) Short, Highly Effective and Inexpensive Standardized Treatment of Multidrug-Resistant Tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, **182**, 684-692. https://doi.org/10.1164/rccm.201001-0077OC

[10] Chang, K.C., Leung, C.C., Yew, W.W., *et al.* (2012) Pyrazinamide May Improve Fluoroquinolone-Based Treatment of Multidrug-Resistant Tuberculosis. *Antimicrobial Agents and Chemotherapy*, **56**, 5465-5475. https://doi.org/10.1128/AAC.01300-12

[11] Nagaraja, C., Shashibhushan, B.L., Asif, M., Manjunath, P.H. and Sagar, C. (2012) Pattern of Drug-Resistance and Treatment Outcome in Multidrug-Resistant Pulmonary Tuberculosis. *The Indian Journal of Chest Diseases and Allied Sciences*, **54**, 23-26.

[12] Grosset, J.H., Tyagi, S., Almeida, D.V., *et al.* (2013) Assessment of Clofazimine Activity in a Second-Line Regimen for Tuberculosis in Mice. *American Journal of Respiratory and Critical Care Medicine*, **188**, 608-612. https://doi.org/10.1164/rccm.201304-0753OC

[13] Holtz, T.H., Sternberg, M., Kammerer, S., *et al.* (2006) Time to Sputum Culture Conversion in Multidrug-Resistant Tuberculosis: Predictors and Relationship to Treatment Outcome. *Annals of Internal Medicine*, **144**, 650-659. https://doi.org/10.7326/0003-4819-144-9-200605020-00008

[14] De Jaget, P. and Van Altena, R. (2002) Hearing Loss and Nephrotoxicity in Long-Term Aminoglycoside Treatment in Patients with Tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, **6**, 622-627.

[15] Duggal, P. and Sarkar, M. (2007) Audiologic Monitoring of the Multi-Drug Resistant Tuberculosis Patients on Aminoglycoside Treatment with Long Term Follow-Up. *BMC Ear, Nose and Throat Disorders*, **7**, Article No. 5. https://doi.org/10.1186/1472-6815-7-5

[16] Brumett, R.E. and Fox, K.E. (1989) Aminoglycoside-Induced Hearing Loss in Humans. *Antimicrobial Agents and Chemotherapy*, **33**, 797-800. https://doi.org/10.1128/AAC.33.6.797

[17] Nadol Jr., J.B. (1993) Medical Progress: Hearing Loss. *The New England Journal of Medicine*, **329**, 1092-1102. https://doi.org/10.1056/NEJM199310073291507

[18] Tan, K.H.V., Mulheran, M., Knox, A.J. and Smyth, A.R. (2003) Aminoglycoside Prescribing and Surveillance in Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, **167**, 819-823. https://doi.org/10.1164/rccm.200109-012CC

[19] Selimoglu, F. (2007) Aminoglycoside-Induced Ototoxicity. *Current Pharmaceutical Design*, **13**, 119-126. https://doi.org/10.2174/138161207779313731

[20] World Health Organization (2015) Global Tuberculosis Report 2015. WHO, Geneva.

[21] Philippines Department of Health (2000) National Tuberculosis Control Program (Unpublished) 2000 Accomplishment Report. Philippines Department of Health, Manila.

[22] Trebucq, A., Schwoebel, V., Kashongwe, Z., *et al.* (2017) Treatment Outcome with a Short Multi-Drug-Resistant Tuberculosis Regimen in Nine African Countries. *The International Journal of Tuberculosis and Lung Disease*, **22**, 17-25. https://doi.org/10.5588/ijtld.17.0498

[23] Nunn, A.J., Phillips, P.P.J., Meredith, S.K., *et al.* (2019) A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. *The New England Journal of Medicine*, **380**, 1201-1213. https://doi.org/10.1056/NEJMoa1811867

Appendix

The final most effective treatment regimen required a minimum of nine months duration with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout, supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of four months, giving a relapse-free cure of 87.9% (95% confidence interval 82.7% to 91.6%) among 206 patients. Major adverse drug reactions were infrequent and manageable. Compared to the 221 patients treated with regimens based on ofloxacin and commonly prothionamide throughout, the hazard ratio of any adverse outcome was 0.39 (95% confidence interval 0.26 - 0.59). CONCLUSIONS: Serial regimen formulation guided by overall treatment effectiveness ultimately resulted in treatment outcomes comparable to those obtained with first-line treatment. Confirmatory formal trials in populations with high levels of human immunodeficiency virus co-infection and in populations with a higher initial prevalence of resistance to second-line drugs are required.