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# Management of multidrug-resistant tuberculosis with shorter treatment regimen in Niger: Nationwide programmatic achievements

Alberto Piubello [a,b,*], Mahamadou Bassirou Souleymane [a], Souleymane Hassane-Harouna [a], Abdourahamane Yacouba [c], Pauline Lempens [d], Mourtala Mohamed Assao-Neino [e], Ibrahim Maman-Lawan [a], Sala Attaher [f], Boubacar Moustapha [e], Alphazazi Soumana [g], Assiatou Gagara-Issoufou [h], Nimer Ortuño-Gutiérrez [i], Alberto Roggi [i], Mourad Gumusboga [d], Zelika Hamidou-Harouna [j], Jeroen Dockx [d], Saïdou Mamadou [k], Bouke C. de Jong [d], Tom Decroo [l,m], Armand Van Deun [b,c,d]

[a] Damien Foundation, Niamey, Niger
[b] International Union Against Tuberculosis and Lung Disease, Paris, France
[c] Regional Hospital Agadez, Niger
[d] Unit of Mycobacteriology, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[e] National Tuberculosis Programme, Niamey, Niger
[f] Regional Hospital, Maradi, Niger
[g] National Anti-Tuberculosis Centre, Niamey, Niger
[h] University Hospital Lamorde, Niamey, Niger
[i] Damien Foundation, Brussels, Belgium
[j] National Reference Laboratory of Tuberculosis, Niamey, Niger
[k] Abdou Moumouni University, Niamey, Niger
[l] Unit of HIV & Co-infections, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[m] Research Foundation Flanders, Brussels, Belgium

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ABSTRACT

*Background:* In Niger, the Shorter Treatment Regimen (STR) has been implemented nationwide for rifampicin resistant tuberculosis (RR-TB), since 2008. No previous publication has shown the results from countrywide programmatic implementation using few exclusion criteria, nor exhaustively assessed the effect of initial resistance to companion drugs on outcomes.

*Methods:* The National Tuberculosis Programme and the Damien Foundation conducted a retrospective observational study to evaluate the management of RR-TB from 2008 to 2016. Baseline resistance to drugs was assessed phenotypically, complemented by screening the *inhA, katG* and *pncA* genes. Cured patients were followed-up for a period of one year after cure.

*Findings:* Among 1044 patients tested for rifampicin resistance, mainly previously treated patients, 332 were diagnosed with pulmonary RR/TB, 288 were enrolled on treatment and 255 started on STR. Six patients received a modified STR.

Among 249 patients on standardised STR, 207 (83·1%) were cured relapse-free, eight (3·2%) had failure, 23 (9·2%) died, seven (2·8%) were lost to follow-up and four (1·6%) relapsed.

The risk of unfavourable outcome was higher in patients with initial resistance to fluoroquinolones (aOR 20·4, 95%CI:5·6–74·6) and very severely underweight (aOR 3·9, 95%CI:1·5–10·1). Successful outcome was not affected by initial resistance to companion drugs. Serious ototoxicity was reported in eight patients (3·2%).

*Interpretation:* A comprehensive nationwide approach to multidrug-resistant tuberculosis management using the STR was feasible and successful. Outcomes were not affected by initial resistance to companion drugs. Our study confirms the effectiveness and safety of the STR.

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* Corresponding author. Damien Foundation and International Union Against Tuberculosis and Lung Disease, B.P. 1065, Niamey, Niger.
*E-mail address:* apiubello@theunion.org (A. Piubello).

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## 1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) threatens effective TB control with an estimated 484,000 new cases harbouring resistance to rifampicin (RR) in 2018. Overall treatment success was 56% according to the 2019 World Health Organization (WHO) report [1].

In 2011, the WHO guidelines recommended a 20-month regimen with an 8-month intensive phase including a second-line injectable (SLI) [2].

Van Deun et al. showed 87·9% relapse-free treatment success using a 9-month gatifloxacin-based regimen in Bangladesh [3]. These results were confirmed in a larger cohort in Bangladesh [4] and also in Niger [5] and Cameroon [6], where 12-month regimens were used. A large observational study conducted in Central and West Africa, including Niger, showed 81·6% success [7]. Preliminary results coming from this study and other settings together with available published results [4–6] informed the 2016 WHO recommendation for the use of a standardised Shorter Treatment Regimen (STR) [8].

A recent meta-analysis of individual patient data from observational studies informed the 2019 WHO RR/MDR-TB guidelines [9]. The choice is left between the STR, a longer individualised all-oral regimen, depending on the expected effect of individual drugs and all-oral shorter regimens under operational research conditions.

Niger adopted the STR as operational research in 2008 and as the nationally recommended regimen in 2016. After nine years of implementation, this is the first study to report of the comprehensive approach to countrywide RR/MDR-TB management, including the number of persons tested for RR, diagnosed with RR/MDR-TB, enrolled on treatment, and their treatment outcomes. In addition, we estimate predictors of unfavourable outcome, including the effect of initial resistance to STR companion drugs on outcomes, not yet exhaustively reported.

## 2. Methods

### 2.1. Design and study population

This retrospective cohort study was conducted to evaluate the performance of MDR-TB management in Niger, from 2008 to 2016. All patients tested for RR were included.

### 2.2. Setting

Niger is a challenging operational environment. Health staff are scarce, access to care is limited due to long distances between communities and health facilities and security threats. Since 2008, the National Tuberculosis Programme (NTP) and the Damien Foundation (DF) have collaborated closely to provide a comprehensive MDR-TB management.

DF supplied Second-Line Drugs (SLD), provided transport fees and nutritional support, and assured monitoring and management of Adverse Events (AEs), home visits and family counselling. Medical staff were provided by the DF and NTP and trained by The Union and DF. Career advancements were offered to retain skilled staff.

Nationwide patients with presumptive MDR-TB were screened, including failures and relapses of retreatment from 2008 to 2014 and all retreatments from 2015 onwards. Since 2008, MDR/RR-TB contacts with presumptive TB were systematically tested. A sputum transportation system from TB facilities to Xpert sites using public transport, allowed a full coverage of the country.

### 2.3. Bacteriological investigations

Sputum specimens were collected before treatment initiation and monthly for smear and culture during treatment. Follow-up after cure continued up to one year after treatment completion with smear and culture performed every 6 months (Table 1). Initially the National TB laboratory in Niamey performed cultures on solid medium and Drug Susceptibility Testing (DST) to diagnose RR/MDR-TB. From October 2013, Xpert® MTB/RIF (Xpert; Cepheid, Sunnyvale, CA, USA) testing was introduced and in 2014, three additional Xpert machines were installed across the country. Second-Line Line Probe Assay (SL-LPA; GenoType MTBDRsl; Hain Lifesciences, Nehren, Germany) testing became available in January 2016.

To determine the initial resistance profile a posteriori, pre-treatment samples in cetylpyridinium chloride were systematically referred to the Supra-National TB Reference Laboratory of Antwerp for culture and DST (proportion method) for rifampicin, isoniazid, ofloxacin, kanamycin, ethambutol and ethionamide/prothionamide, following the standardised WHO recommended techniques [10,11]. SL-LPA testing and Sanger DNA sequencing were performed from 2012 onwards. Preserved strains were used for genotypic DST, identifying mutations in the *inhA, katG* and *pncA* genes [12].

Failures and relapses were distinguished from reinfection by comparing the initial with the failure or relapse strain using fingerprinting techniques [13].

### 2.4. Treatment regimen

Individuals with confirmed MDR/RR-TB were treated in the three national Units, in Niamey, Maradi and Zinder. The regimens comprised high doses of gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout, supplemented by kanamycin, prothionamide and medium-high doses of isoniazid during the intensive phase, lasting a minimum of 4 months, with a maximum of 6 months, according to sputum smear conversion. The continuation phase lasted eight months between 2008 and 2010 and was shortened to five months from January 2011 onwards, after the publication of Bangladesh results [3]. In October 2013 high-dose gatifloxacin was replaced by normal-dose moxifloxacin when gatifloxacin became unavailable on the market (Table 2). Since 2017 high-dose moxifloxacin was used.

From October 2015, a modified STR, with linezolid replacing kanamycin during the intensive phase was used in patients with hearing loss on audiometry.

### 2.5. Clinical management

A system to track patients between TB facilities, Xpert sites and MDR-TB Units was set up. Clinically stable patients received ambulatory care with daily directly observed treatment during the intensive phase. Hospital care was offered to patients with severe comorbidities or living more than 5 km from the MDR-TB Units. During the continuation phase, patients living close to facilities continued their attendances whereas patients from further away visited the clinics weekly. Patient education covered issues related to the disease and treatment adherence. Patients' characteristics, bacteriological follow-up, test results, drug intake and AEs were recorded on national treatment cards.

Diabetes mellitus was an exclusion criterion for the gatifloxacin-based STR. Patients with corrected QT (QTc) interval prolongation beyond 500 ms were excluded from the moxifloxacin-based STR. They were treated with individualised longer regimens, as were patients with previous exposure to SLD or with confirmed resistance to fluoroquinolones and/or SLI at baseline. Having extensive or advanced disease, clinically or on chest X-Ray, was not exclusion criteria for the STR.

### 2.6. Monitoring and management of adverse events

Systematic clinical and laboratory monitoring of patients on treatment was introduced in 2008 (Table 1). AEs were graded according to the National Agency for the Research on AIDS and hepatitis (ANRS) scale [14]. From 2008 to September 2013, hearing loss was monitored clinically and with audiometry at the end of the intensive phase.

Thereafter, bimonthly audiometry has been carried out in all patients given SLIs.

Ototoxicity was managed by replacing kanamycin with capreomycin from 2008 to 2011, reducing the frequency of kanamycin from daily to thrice a week from 2012 to September 2015 and replacing kanamycin with linezolid from October 2015 onwards. Hearing aids were provided to all patients with moderate to serious hearing loss.

ECGs were performed at baseline, at week one and one month after treatment initiation to check the QTc interval.

### 2.7. Definitions

The WHO treatment outcome definitions [15] were used except for treatment failure. We defined treatment failure when treatment was terminated or at least two anti-TB drugs were permanently changed due to either a positive culture after ≥ six months of treatment (except for an isolated positive culture), or at least 2 consecutive positive sputum smears with grade ≥ 2 + after ≥ six months of treatment (if cultures were not available) [16].

Relapse was declared if patients had a positive culture during 12-month follow-up after cure or completion, except if molecular tests showed reinfection. Relapse-free cure was declared if patients were cured with no evidence of relapse at the end of the 12-month follow-up.

### 2.8. Data management and analysis

Data were collected from the standardised patient forms and registers and double entered in a database. Inconsistencies were resolved by analysing the source documents.

We employed univariable and multivariable logistic regression to estimate predictors of unfavourable outcomes of either death, failure, relapse, or lost to follow-up (LTFU). Independent variables included age, gender, HIV status, type of TB, bacillary load, extent of disease, Body Mass Index (BMI), and the initial resistance pattern. Factors associated with outcomes ($P$-value <0.1) were included in a multivariable model which was simplified by stepwise backwards elimination until all variables had a $P$-value < 0.05. To have a better understanding of the effect of companion drugs, we repeated the same analysis in patients with fluoroquinolone-susceptible TB. For the latter analysis we excluded those LTFU. Analyses were performed with Stata (Version 14.1, Stata Corp LP, College Station, TX, USA).

**Table 2**
Daily dosage by weight band, among patients treated with the shorter treatment regimen.

| *Drug* | *30–39* | *40–54* | 55–70 | >70 |
|---|---|---|---|---|
| Kanamycin[a] | 0·5 | 0·75 g | 1 g | 1 g |
| Isoniazid (300 mg)[a] | 1 | 1.5 | 2 | 2 |
| Prothionamide (250 mg) [a] | 2 | 2 | 3 | 4 |
| Moxifloxacin (400 mg)[b] | 0·5 | 1 | 1 | 1 |
| Clofazimine (50 mg) | 1 | | | |
| Clofazimine (100 mg) | | 1 | 1 | 1 |
| Ethambutol (400 mg) | 1·5 | 2 | 3 | 3·5 |
| Pyrazinamide (400 mg) | 2 | 3 | 4 | 5 |

The continuation phase lasted eight months between 2008 and 2010 and was shortened to five months from January 2011 onwards.

[a] Used during the intensive phase only (4–6 months, depending of sputum smear conversion).

[b] Gatifloxacin 800 mg was used from 2008 to October 2013.

### 2.9. Ethics

This study was approved by the Niger National Ethics Committee and by the Institutional Review Board of the Institute of Tropical Medicine of Antwerp, which waived the requirement to obtain informed consent.

## 3. Results

### 3.1. Patients eligible and analysed for treatment outcome

Countrywide, from 2008 to 2016, a total of 1044 patients were tested. The proportion of retreatment cases tested increased from 11·2% in 2008 to 42·6% in 2016. A total of 332 patients were diagnosed with pulmonary RR/MDR-TB (Fig. 1). Thirty-two (9·6%) died, 12 (3·6%) were not retrieved before treatment, and 288 (86·7%) started MDR-TB treatment. Of 32 patients who died before starting treatment, ten (31·3%). were diagnosed in 2008. Of 288 patients enrolled on treatment, 33 (11·5%) patients were treated with longer individualised regimens because of previous use of SLD or diabetes mellitus, with a success rate of 69·7%. Six (2·1%) patients were treated with a modified STR because of serious AEs or ototoxicity of any grade at baseline or during

**Table 1**
Clinical, bacteriological and laboratory assessment at baseline and during treatment and follow-up.

| | Month 0 | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 | Month 7 | Month 8 | Month 9 | Month 15 | Month 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinical assessment | x | x | x | x | x | x | x | x | x | x | x | x |
| Sputum smear | x | x | x | x | xx[a] | x(x)[a] | x(x)[a] | x | x | xx[a] | x | x |
| Xpert[b] | x | | | | | | | | | | | |
| LPA 2nd line[c] | x | | | | | | | | | | | |
| Sputum culture[d] | x | x | x | x | x | x | x | x | x | x | x | x |
| DST (1st and 2nd line) | x | | | | | | | | | | | |
| Chest X Ray | x | | | | | | | | x | | | |
| Audiogram[b] | x | | x | | x | | | | | | | |
| ECG | xx | x | | | | | | | | | | |
| Blood count | x | | | | | | | | | | | |
| Blood glucose[e] | x | x | x | x | x | x | x | x | x | x | | |
| Serum creatinine | x | x | x | x | x | | | | | | | |
| Serum potassium | x | x | x | x | x | | | | | | | |
| Serum liver enzymes[f] | x | x | x | x | x | | | | | | | |
| Thyroid Stimulating Hormone | x | | | | x | | | | | | | |
| Pregnancy test (female) | x | | | | | | | | | | | |
| HIV test | x | | | | | | | | | | | |

[a] xx: test performed twice; x(x): test performed twice if the smear of the previous month was positive.

[b] Available from October 2013.

[c] Available from January 2016.

[d] Performed bimonthly from 2008 to 2010 and monthly from 2011 to 2016.

[e] For patients treated with gatifloxacin.

[f] Bimonthly from 2008 to 2010 and monthly from 2011 to 2016.

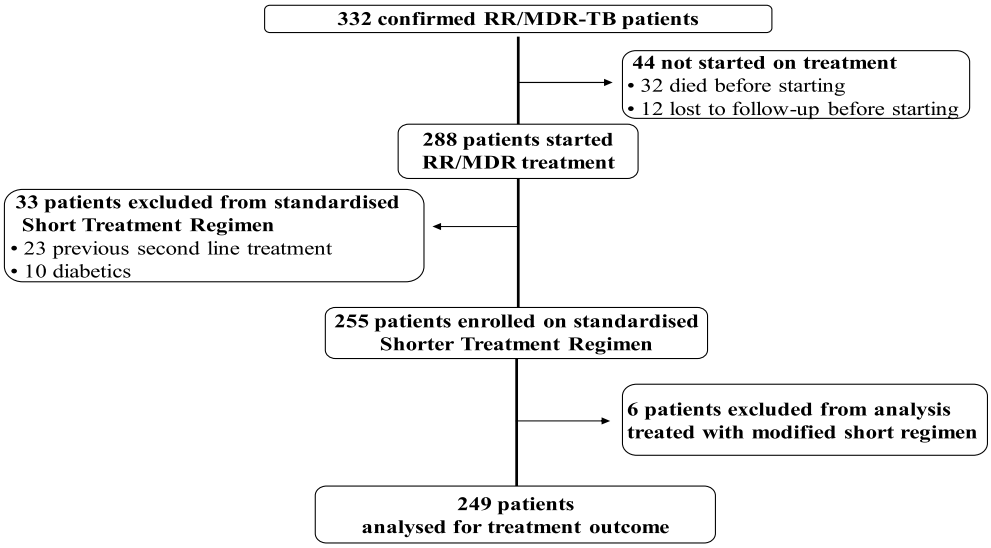


**Fig. 1.** Patients eligible for second-line treatment with exclusion from enrolment and analysis of the study regimens.

treatment. Of these, five (83·3%) were cured and one died.

The remaining 249 (86·5%) were treated with the standardised (unmodified) STR. The median interval between MDR-TB suspicion and treatment start decreased from 138 days (IQR: 50–201) in 2006 to 11 days (IQR: 7–17) in 2016. Their baseline characteristics are shown in Table 3. The median age was 32 years (IQR: 25–40). Most patients were in poor clinical condition at the treatment initiation, with a median BMI of 17·2 kg/m$^2$ (IQR:15·2–19·4). Baseline resistance is shown in Table 3.

Among 28 (11·2%) of 249 patients the intensive phase was extended (15 patients to 5 months and 13 to 6 months).

### 3.2. Culture conversion on the standardised STR

Nine patients died and one was LTFU before having culture conversion. Of the remaining 239 patients, 229 (95·8%) converted at the end of a 4-month intensive phase, three (1·3%) converted on culture at the end of an extended (plus one or two months) intensive phase, and seven (2·9%) remained culture-positive.

### 3.3. Treatment outcomes

Of 249 patients on the standardised STR, 207 (83·1%, 95% CI:78·5–87·8) were cured relapse-free, and 42 had an unfavourable treatment outcome: eight (3·2%) were diagnosed with treatment failure, 23 (9·2%) died, seven (2·8%) were LTFU and four (1·6%) relapsed.

Among the eight patients with treatment failure, seven never converted and one had culture reversion. A posteriori analysis of the initial resistance profile showed that six had initial resistance to fluoroquinolones (three high-level and three low-level) and two had susceptible strains. Subsequently, five died before they could start a treatment and three patients were cured with bedaquiline-based regimens.

Of 23 patients who died during treatment, all had extensive and bilateral pulmonary lesions at baseline, 14 were severely underweight and three of them were HIV positive (two were non-adherent to ART). Three patients died because of cerebral malaria and one was diabetic with poor metabolic control.

Nine patients (39·1%) died during the intensive phase (eight during the first eight treatment weeks) before culture conversion. Fourteen patients (60·9%) died in the continuation phase after bacteriological conversion.

Seven patients were LTFU, three during the intensive phase and four in the continuation phase. All but one had culture conversion.

Of 214 patients with fluoroquinolone-susceptible strains, 84·6% were cured relapse-free.

Most (87·2%) of cured patients had bacteriological documented follow-up one year after cure. Five had a recurrent episode. In one patient the recurrent strain was different than the initial one (thus reinfection). Of four true relapses, three had strains with initial resistance to fluoroquinolone (two high-level and one low-level) while one strain was susceptible at baseline.

The median interval between treatment completion and relapse was 73·5 days, ranging from 30 to 301 days. All patients with recurrence were afterward treated and cured with bedaquiline-based regimens.

Seven patients died because of respiratory failure with extensive sequelae. The details on patients' follow-up after cure are provided in Table 4.

### 3.4. Predictors of unfavourable outcomes

The risk of programmatic unfavourable outcome was significantly higher in patients with initial resistance to fluoroquinolones (69·2% vs. 15·0%; aOR 20·4, 95%CI:5·6–74·6) and very severely underweight (BMI $<$ 15 kg/m$^2$) (30·0% vs. 12·0%; aOR 3·9, 95%CI:1·5–10·1). No significant association was found between outcome and extent of disease, HIV status, initial resistance to isoniazid, ethambutol, pyrazinamide and prothionamide (Table 5).

Double mutation *inhA* and *katG* didn't affect outcomes. On a total of 14 patients, 12 of them with additional resistance to pyrazinamide and one with additional low-level resistance to fluoroquinolones, 13 (92·9%) were cured with no relapse and one died because of septic shock.

Among patients with confirmed fluoroquinolone-susceptible MDR/RR-TB, the only predictor for having an unfavourable outcome (either death, failure or relapse) was very severe underweight (28·9% vs. 6·0%; aOR 6·4, 95%CI:1·9–21·2) No other significant association was found (Table 6).

After excluding patients with treatment failure or relapse and those LTFU, mortality was only associated with very severe underweight (27·1% vs. 3·9%; aOR 10·5, 95%CI:2·7–40·6).

### 3.5. Acquisition of resistance

Of 214 patients with initially fluoroquinolone-susceptible MDR/RR-TB, three (1·4%) acquired high-level fluoroquinolone resistance (two mutations D94G and one D94 N on gyrase A). One had initial resistance to prothionamide and pyrazinamide, one had a strain susceptible to both

**Table 3**
Baseline patients' characteristics.

| | N | % |
|---|---|---|
| **Total** | 249 | 100·0 |
| **Gender** | | |
| F | 43 | 17·3 |
| M | 206 | 82·7 |
| **Age** | | |
| <18 | 7 | 2·8 |
| 18–24 | 42 | 16·9 |
| 25–34 | 94 | 37·8 |
| 35–44 | 65 | 26·1 |
| 45–54 | 32 | 12·9 |
| 55–64 | 8 | 3·2 |
| ≥65 | 1 | 0·4 |
| **Type of patient** | | |
| New Case | 3 | 1·2 |
| Failure | 179 | 71·9 |
| Relapse | 66 | 26·5 |
| Return after LTFU | 1 | 0·4 |
| **Bacillary load (on SS)** | | |
| Low | 66 | 26·5 |
| High | 183 | 73·5 |
| **Extent of disease (on CXR)** | | |
| One lung | 16 | 6·4 |
| Bilateral | 233 | 93·6 |
| **BMI** | | |
| <15 (very severely underweight) | 50 | 20·1 |
| 15-16 (severely underweight) | 39 | 15·7 |
| >16–18·5 (underweight) | 73 | 29·3 |
| >18·5 (normal or overweight) | 83 | 33·3 |
| Missing | 4 | 1·6 |
| **HIV status** | | |
| Negative | 230 | 92·4 |
| Positive | 12 | 4·8 |
| Not tested | 7 | 2·8 |
| **Fluoroquinolone type** | | |
| Gatifloxacin | 119 | 47·8 |
| Moxifloxacin | 130 | 52·2 |
| **Resistance to FQ (phenotypic)** | | |
| No | 214 | 85·9 |
| Yes | 13 | 5·2 |
| Missing | 22 | 8·8 |
| **Resistance to Km (phenotypic)** | | |
| No | 227 | 91·2 |
| Missing | 22 | 8·8 |
| **Resistance to H** | | |
| No (wild type) | 5 | 2·0 |
| *katG* mutation (only) | 200 | 80·3 |
| *inhA* mutation (only) | 6 | 2·4 |
| *katG* and *inhA* mutation | 14 | 5·6 |
| Phenotypic DST (only) | 14 | 5·6 |
| Missing | 10 | 4·0 |
| **Resistance to Z – *pncA* (molecular)** | | |
| No (wild type) | 122 | 49·0 |
| Yes | 110 | 44·2 |
| Missing | 17 | 6·8 |
| **Resistance to E (phenotypic)** | | |
| No | 72 | 28·9 |
| Yes | 162 | 65·1 |
| Missing | 15 | 6·0 |
| **Resistance to Pto (phenotypic)** | | |
| No | 177 | 71·1 |
| Yes | 50 | 20·1 |
| Missing | 22 | 8·8 |

F: Female; M: Male; LTFU: Lost to Follow-Up; SS: Sputum Smear; CXR: Chest X-Ray; BMI: Body Mass Index in kg/m$^2$
FQ: fluoroquinolones; Km: Kanamycin; H: isoniazid; DST: Drug Susceptibility Testing; Z: pyrazinamide; E: ethambutol; Pto: prothionamide.

**Table 4**
Status of cured patients at 6 and 12 months of follow-up.

| | 6-month follow-up | | 12-month follow-up | |
|---|---|---|---|---|
| Status | N | % | N | % |
| Culture negative | 188 | 89·1 | 179 | 84·8 |
| Lost to follow-up after treatment | 14 | 6·6 | 20 | 9·5 |
| Died | 4 | 1·9 | 7 | 3·3 |
| Relapse | 4 | 1·9 | 4 | 1·9 |
| Reinfection (different strain) | 1 | 0·5 | 1 | 0·5 |
| Total | 211 | 100 | 211 | 100 |

and one had resistance to prothionamide only. Two patients were underweight and one had normal weight. All three were treated with a moxifloxacin-based STR. There was no acquisition of resistance to fluoroquinolone in patients treated with gatifloxacin.

Among 227 patients with initial susceptible strains to kanamycin, two (0·9%) developed resistance to the drug. Both had initial resistance to fluoroquinolone (one high-level and one low-level) and were also treated with moxifloxacin.

### 3.6. Adverse events

Most patients (78·7%) had at least one AE, and 5·6% had a serious one (Grade 3–4) (Table 7). None had to stop treatment definitively or to change more than one drug.

The most frequent serious AE was ototoxicity, which was reported in eight cases (3·2%) and decreased over time. No patient developed serious hearing loss in 2016, after the introduction of the modified STR with linezolid (Table 8). All patients with ototoxicity were HIV-negative and seven of them had been treated with streptomycin in the past. Six patients with serious ototoxicity were detected through clinical monitoring and audiometry at the end of the intensive phase from 2008 to September 2013 and two through bimonthly audiometry from October 2013 onwards. Hyperglycaemia was recorded in eight patients treated with gatifloxacin. It was manageable with oral antidiabetic drugs, except for one patient for whom gatifloxacin was switched to high-dose levofloxacin. Hyperglycaemia was reversible in all patients after the completion of treatment. No patient developed hypoglycaemia. Among subjects treated with moxifloxacin, one QTc prolongation (>500 ms) without symptoms was recorded and reverted after correction of hypokalaemia. No other QTc disorders were reported.

Ethambutol was stopped in one patient due to optic neuritis in the continuation phase. He had been treated with ethambutol for 20 months before STR initiation.

Mild or moderate gastro-intestinal disorders were frequent (54·6%), appeared within a median of one month (IQR: 1–2), were manageable with food intake and anti-emetic drugs (metoclopramide and ondansetron). Serious hepatic disorders were recorded in three patients and one of them had also hepatitis C and died. Other minor AEs were rare, mild to moderate and subsided after the completion of treatment.

Six patients were excluded in the final treatment outcome analysis because they received a modified STR. For one, ethambutol was stopped and replaced with cycloserine because of optic neuritis during the intensive phase. This patient had undergone several first-line treatments in the past with a total of 32-months of ethambutol. One patient had severe Achilles' tendonitis. The fluoroquinolone was stopped and replaced by linezolid as bedaquiline was unavailable at that time. He was cured. Three patients had moderate to severe ototoxicity during treatment and kanamycin was replaced by linezolid. One patient had moderate hearing loss at baseline and was started on a modified STR where the injectable was replaced with linezolid. None had Grade 4 hearing loss at the end of treatment.

**Table 5**
Predictors of a programmatically unfavourable outcome[a], among 249 MDR/RR-TB patients treated with the standardised Shorter Treatment Regimen.

| | Total | Programmatic favourable outcome | | Programmatic unfavourable outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | OR | [95% CI] | p value £ | aOR | [95% CI] | p value & |
| Total | 249 | 207 | 83·1 | 42 | 16·9 | | | | | | |
| **Gender** | | | | | | | | 0·22 | | | NA |
| F | 43 | 33 | 76·7 | 10 | 23·3 | 1 | | | | | |
| M | 206 | 174 | 84·5 | 32 | 15·5 | 0·6 | [0·3, 1·4] | | | | |
| **Age, median (IQR)** | 32 (25–40) | 32 | (25–40) | 34 | (27–45) | 1·3[b] | [0·9, 1·7] | 0·14 | | | NA |
| **Type of patient** | | | | | | | | 0·13 | | | NA |
| New Case | 3 | 2 | 66·7 | 1 | 33·3 | 2·1 | [0·2, 23·3] | | | | |
| Failure | 179 | 144 | 80·4 | 35 | 19·6 | 1 | | | | | |
| Relapse | 66 | 60 | 90·9 | 6 | 9·1 | 0·4 | [0·2, 1·0] | | | | |
| Return after LTFU | 1 | 1 | 100·0 | 0 | 0·0 | NA | | | | | |
| **Bacillary load (on SS)** | | | | | | | | 0·66 | | | NA |
| Low (scanty and 1+) | 66 | 56 | 84·8 | 10 | 15·2 | 1 | | | | | |
| High (2 + and 3+) | 183 | 151 | 82·5 | 32 | 17·5 | 1·2 | [0·5, 2·6] | | | | |
| **Extent of disease (on CXR)** | | | | | | | | 0·63 | | | NA |
| One lung | 16 | 14 | 87·5 | 2 | 12·5 | 1 | | | | | |
| Bilateral | 233 | 193 | 82·8 | 40 | 17·2 | 1·5 | [0·3, 6·6] | | | | |
| **BMI** | | | | | | | | **0·007** | | | **0·001** |
| <15 | 50 | 35 | 70·0 | 15 | 30·0 | **3·1** | **[1·3, 7·7]** | | **3·9** | **[1·5, 10·1]** | |
| 15–16 | 39 | 35 | 89·7 | 4 | 10·3 | 0·8 | [0·2, 2·8] | | 0·8 | [0·2, 3·1] | |
| >16–18·5 | 73 | 63 | 86·3 | 10 | 13·7 | 1·2 | [0·5, 3·0] | | 0·9 | [0·3, 2·7] | |
| >18·5 | 83 | 73 | 88·0 | 10 | 12·0 | 1 | | | 1 | | |
| Missing | 4 | 1 | 25·0 | 3 | 75·0 | **21·9** | **[2·1, 231·4]** | | **27·4** | **[2·5, 296·2]** | |
| **HIV status** | | | | | | | | 0·31 | | | NA |
| Negative | 230 | 193 | 83·9 | 37 | 16·1 | 1 | | | | | |
| Positive | 12 | 8 | 66·7 | 4 | 33·3 | 2·6 | [0·7, 9·1] | | | | |
| Not tested | 7 | 6 | 85·7 | 1 | 14·3 | 0·9 | [0·1, 7·4] | | | | |
| **Fluoroquinolone type** | | | | | | | | 0·30 | | | NA |
| Gatifloxacin | 119 | 102 | 85·7 | 17 | 14·3 | 1 | | | | | |
| Moxifloxacin | 130 | 105 | 80·8 | 25 | 19·2 | 1·4 | [0·7, 2·8] | | | | |
| **Resistance to FQ (phenotypic)** | | | | | | | | **<0·001** | | | **<0·001** |
| No | 214 | 182 | 85·0 | 32 | 15·0 | 1 | | | 1 | | |
| Yes | 13 | 4 | 30·8 | 9 | 69·2 | **12·8** | **[3·7, 44·1]** | | **20·4** | **[5·6, 74·6]** | |
| Missing | 22 | 21 | 95·5 | 1 | 4·5 | 0·3 | [0·04, 2·1] | | 0·3 | [0·04, 2·7] | |
| **Resistance to H** | | | | | | | | 0·9 | | | NA |
| No (wild type) | 5 | 5 | 100·0 | 0 | 0·0 | 1 | | | | | |
| *katG* mutation (only) | 200 | 164 | 82·0 | 36 | 18·0 | 2·4 | [0·1, 45·1] | | | | |
| *inhA* mutation (only) | 6 | 5 | 83·3 | 1 | 16·7 | 3·0 | [0·1, 91·0] | | | | |
| *katG* & *inhA* mutation | 14 | 13 | 92·9 | 1 | 7·1 | 1·2 | [0·0, 34·9] | | | | |
| Phenotypic DST (only) | 14 | 11 | 78·6 | 3 | 21·4 | 3·3 | [0·1, 76·8] | | | | |
| Missing | 10 | 9 | 90·0 | 1 | 10·0 | 1·7 | [0·1, 50·4] | | | | |
| **Resistance to Z (*pncA* mutation)** | | | | | | | | 0.49 | | | NA |
| No (wild type) | 122 | 101 | 82·8 | 21 | 17·2 | 1 | | | | | |
| Yes | 110 | 90 | 81·8 | 20 | 18·2 | 1·1 | [0·5, 2·1] | | | | |
| Missing | 17 | 16 | 94·1 | 1 | 5·9 | 0·3 | [0·04, 2·4] | | | | |
| **Resistance to E (phenotypic)** | | | | | | | | 0·36 | | | NA |
| No | 72 | 62 | 86·1 | 10 | 13·9 | 1 | | | | | |
| Yes | 162 | 131 | 80·9 | 31 | 19·1 | 1·5 | [0·7, 3·2] | | | | |
| Missing | 15 | 14 | 93·3 | 1 | 6·7 | 0·4 | [0·1, 3·7] | | | | |
| **Resistance to Pto (phenotypic)** | | | | | | | | **0·04** | | | 0·14 |
| No | 177 | 150 | 84·7 | 27 | 15·3 | 1 | | | | | |
| Yes | 50 | 36 | 72·0 | 14 | 28·0 | **2·2** | **[1·03, 4·5]** | | | | |
| Missing | 22 | 21 | 95·5 | 1 | 4·5 | 0·3 | [0·03, 2·0] | | | | |

£ variables with $p < 0.1$ were included in the saturated multivariable regression model.
& p-values are only shown for variables included in the multivariable regression model. For variables not included we show p = NA (Not Applicable).
F: Female; M: Male; IQR: Inter Quartile Range; LTFU: Lost To Follow-Up; SS: Sputum Smear; CXR: Chest X-Ray; BMI: Body Mass Index in $kg/m^2$.
FQ: fluoroquinolones; H: isoniazid; DST: Drug Susceptibility Testing; Z: pyrazinamide; E: ethambutol; Pto: prothionamide.
[a] Programmatically unfavourable outcome: either death, lost to follow-up, failure or relapse; programmatically favourable outcome: relapse-free cure after 12-months post-treatment follow-up.
[b] For every increase with 10 years.

**Table 6**
Predictors of unfavourable outcome (either death, failure or relapse), among 208 MDR/RR-TB fluoroquinolone susceptible patients treated with the standardised Shorter Treatment Regimen.

| | Total | Favourable outcome | | Unfavourable outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | OR | [95% CI] | p value[£] | aOR [95%CI] | p value[&] |
| **Total** | 208 | 182 | 87·5 | 26 | 12·5 | | | | | |
| **Gender** | | | | | | | | 0·08 | | 0·12 |
| F | 38 | 30 | 78·9 | 8 | 21·1 | 1 | | | | |
| M | 170 | 152 | 89·4 | 18 | 10·6 | 0·4 | [0·2, 1·1] | | | |
| **Age, median (IQR)** | 32 (26–40) | 32 | (25–40) | 35 | (30–44) | 1·4[a] | [0·9, 2·1] | 0·09 | | 0·07 |
| **Type of patient** | | | | | | | | 0·23 | | NA |
| New Case | 2 | 1 | 50·0 | 1 | 50·0 | 6·3 | [0·4, 104·8] | | | |
| Failure | 146 | 126 | 86·3 | 20 | 13·7 | 1 | | | | |
| Relapse | 59 | 54 | 91·5 | 5 | 8·5 | 0·6 | [0·2, 1·6] | | | |
| Return after LTFU | 1 | 1 | 100·0 | 0 | 0·0 | NA | | | | |
| **Bacillary load (on SS)** | | | | | | | | 0·62 | | NA |
| Low (scanty and 1+) | 48 | 43 | 89·6 | 5 | 10·4 | 1 | | | | |
| High (2 + and 3+) | 160 | 139 | 86·9 | 21 | 13·1 | 1·3 | [0·5, 3·7] | | | |
| **Extent of disease (on CXR)** | | | | | | | | 0·75 | | NA |
| One lung | 13 | 11 | 84·6 | 2 | 15·4 | 1 | | | | |
| Bilateral | 195 | 171 | 87·7 | 24 | 12·3 | 0·8 | [0·2, 3·7] | | | |
| **BMI** | | | | | | | | **<0·001** | | **<0·001** |
| <15 | 45 | 32 | 71·1 | 13 | 28·9 | **6·4** | **[1·9, 21·2]** | | [b] | |
| 15–16 | 31 | 29 | 93·5 | 2 | 6·5 | 1·1 | [0·2, 6·3] | | | |
| >16–18·5 | 61 | 57 | 93·4 | 4 | 6·6 | 1·1 | [0·3, 4·6] | | | |
| >18·5 | 67 | 63 | 94·0 | 4 | 6·0 | 1 | | | | |
| Missing | 4 | 1 | 25·0 | 3 | 75·0 | **47·2** | **[4·0, 564·4]** | | | |
| **HIV status** | | | | | | | | 0·32 | | NA |
| Negative | 191 | 169 | 88·5 | 22 | 11·5 | 1 | | | | |
| Positive | 11 | 8 | 72·7 | 3 | 27·3 | 2·9 | [0·7, 11·7] | | | |
| Not tested | 6 | 5 | 83·3 | 1 | 16·7 | 1·5 | [0·2, 13·8] | | | |
| **Fluoroquinolone type** | | | | | | | | 0·23 | | NA |
| Gatifloxacin | 111 | 100 | 90·1 | 11 | 9·9 | 1 | | | | |
| Moxifloxacin | 97 | 82 | 84·5 | 15 | 15·5 | 1·7 | [0·7, 3·8] | | | |
| **Resistance to H**[c] | | | | | | | | 0·90 | | NA |
| No (wild type) | 4 | 4 | 100·0 | 0 | 0·0 | 1 | | | | |
| *katG* mutation (only) | 177 | 155 | 87·6 | 22 | 12·4 | 1·3 | [0·1, 25·0] | | | |
| *inhA* mutation (only) | 5 | 4 | 80·0 | 1 | 20·0 | 3·0 | [0·1, 95·2] | | | |
| *katG* and *inhA* mutation | 11 | 10 | 90·9 | 1 | 9·1 | 1·3 | [0·0, 38·0] | | | |
| Phenotypic DST (only) | 11 | 9 | 81·8 | 2 | 18·2 | 2·4 | [0·1, 60·3] | | | |
| **Resistance to Z (*pncA* mutation)** | | | | | | | | 0·11 | | NA |
| No (wild type) | 111 | 93 | 83·8 | 18 | 16·2 | 1 | | | | |
| Yes | 93 | 85 | 91·4 | 8 | 8·6 | 0·5 | [0·2, 1·2] | | | |
| Missing | 4 | 4 | 100·0 | 0 | 0·0 | NA | | | | |
| **Resistance to E (phenotypic)** | | | | | | | | 0·95 | | NA |
| No | 63 | 55 | 87·3 | 8 | 12·7 | 1 | | | | |
| Yes | 145 | 127 | 87·6 | 18 | 12·4 | 1·0 | [0·4, 2·4] | | | |
| **Resistance to Pto (phenotypic)** | | | | | | | | 0·60 | | NA |
| No | 168 | 148 | 88·1 | 20 | 11·9 | 1 | | | | |
| Yes | 40 | 34 | 85·0 | 6 | 15·0 | 1·3 | [0·5, 3·5] | | | |

[£] variables with $p < 0.1$ were included in the saturated multivariable regression model.
[&] p-values are only shown for variables included in the multivariable regression model. For variables not included we show p = NA (Not Applicable).
F: Female; M: male; IQR: Inter Quartile Range; LTFU: Lost To Follow-Up; SS: Sputum Smear; CXR: Chest X-Ray; BMI: Body Mass Index in $kg/m^2$.
H: isoniazid; DST: Drug Susceptibility Testing; Z: pyrazinamide; E: ethambutol; Pto: prothionamide.
[a] For every increase with 10 years.
[b] aOR not shown as the multivariable model includes only one variable (BMI).
[c] Firth logistic regression was used, as one group had no events.

## 4. Discussion

This is a population-based study assessing countrywide management of MDR/RR-TB with the STR over a period of nine years. Moreover, we show comprehensive data on the effect of initial resistance to companion drugs included in the STR on outcomes, not exhaustively previously reported.

During programmatic implementation in a challenging setting, nine out of ten patients were treated with the unmodified STR, obtaining a high relapse-free cure (83·1%). Most of patients had an initial resistance profile and records of bacteriological follow-up to 12 months after cure. Initial resistance to fluoroquinolones was strongly associated with unfavourable outcomes. However, initial resistance to the companion drugs (isoniazid, ethambutol, pyrazinamide and prothionamide), did not affect the outcomes. SLI resistance was absent in this setting.

Our results are consistent with the 78·8% success rate obtained with the STR in the STREAM trial, stage 1, the world's first randomised phase III clinical trial on MDR-TB which showed that the STR was non-inferior to longer individualised regimens with a duration of 20–24 months [17]. Our findings are also consistent with the 81·6% success rate reported by an observational study conducted in programmatic conditions in nine African countries [7].

**Table 7**
Frequency and severity of reported adverse effects during treatment according to the most severe effect recorded.

| | No AE | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Type | N | % | N | % | N | % | N | % | N | % |
| Any type | 53 | 21·3 | 76 | 30·5 | 106 | 42·6 | 8 | 3·2 | 6 | 2·4 |
| Gastro-intestinal | 113 | 45·4 | 67 | 26·9 | 69 | 27·7 | 0 | | 0 | |
| Hepatic | 164 | 65·9 | 61 | 24·5 | 21 | 8·4 | 2 | 0·8 | 1 | 0·4 |
| Hearing loss | 186 | 74·7 | 39 | 15·7 | 16 | 6·4 | 3 | 1·2 | 5 | 2·0 |
| Renal | 227 | 91·2 | 18 | 7·2 | 3 | 1·2 | 1 | 0·4 | 0 | |
| Peripheral neuropathy | 230 | 92·4 | 11 | 4·4 | 8 | 3·2 | 0 | | 0 | |
| Hyperglycaemia[a] | 111 | 93·3 | 6 | 5·0 | 1 | 0·8 | 1 | 0·8 | 0 | |
| Osteoarticular | 237 | 95·2 | 11 | 4·4 | 1 | 0·4 | 0 | | 0 | |
| Dermatological | 242 | 97·2 | 5 | 2·0 | 2 | 0·8 | 0 | | 0 | |
| Hypothyroidism | 244 | 98·0 | 4 | 1·6 | 1 | 0·4 | 0 | | 0 | |

[a] In 119 patients treated with gatifloxacin.

**Table 8**
Proportion and severity of hearing loss in 249 patients with unmodified STR at the end of the intensive phase, stratified according with the strategy of detection and management.

| Strategies | Period | Patients | No Hearing loss | | Grade 1 | | Grade 2 | Grade 3 | | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | N | % | N | % | N | % | N | % | N | % |
| **Clinical monitoring of hearing loss and audiometry at the end of the intensive phase.** *If hearing loss, kanamycin replaced by capreomycin or frequency of kanamycin reduced from daily to thrice-weekly.* | 2008–Sept/2013 | 119 | 97 | 81·5 | 8[a] | 6·7[a] | 8 | 6·7 | 2 | 1·7 | 4 | 3·4 |
| **Bimonthly audiometry.** *If hearing loss, frequency of kanamycin reduced from daily to thrice-weekly.* | Oct/2013–Sept/2015 | 74 | 47 | 63·5 | 19 | 25·7 | 6 | 8·1 | 1 | 1·4 | 1 | 1·4 |
| **Bimonthly audiometry**. *If hearing loss, kanamycin replaced by linezolid.* | Oct/2015–2016 | 56 | 42 | 75·0 | 12 | 21·4 | 2 | 3·6 | 0[b] | | 0 | |

[a] Mild hearing loss may have been underestimated as audiometry was performed at the end of the intensive phase only for patients with clinical signs of ototoxicity in this period.

[b] Severe hearing loss (Grade 3) was detected in two patients having been switched to a modified STR with linezolid in the last quarter of 2015. Both patients were switched after the development of a Grade 2. From 2016 onwards, all patients with a hearing loss of Grade 1 were switched to linezolid.

A meta-analysis of individual patient data from observational studies informed the current WHO guidelines [9]. There are three approaches to treat RR-TB. First, an individualised all-oral longer regimen, combining the most effective individual drugs identified by the meta-analysis with a conditional recommendation based on a very low certainty in the estimate of effect. Second, the STR, based on a conditional recommendation with a low certainty in the estimate of effect. Third, an all-oral shorter regimen under operational research conditions. The meta-analysis showed that the STR was associated with a higher proportion of programmatic success, mainly explained by a statistically significant lower proportion of LTFU, but suggested a higher risk of failure and relapse in the presence of resistance to companion drugs in patients with fluoroquinolone and SLI-susceptible MDR-TB [9].

Our data do not support this finding. In patients with fluoroquinolone-susceptible MDR/RR-TB, we found a very low incidence of failure/relapse, even though the initial resistance to the companion drugs was frequent. Some of our patients had high-level resistance to isoniazid combined with resistance to prothionamide (double mutation *inhA* and *katG*). Moreover, phenotypic DST for ethambutol and thioamides is not reliable and poorly reproducible [18]. Although the detection of mutations in the *inhA* gene to establish the resistance to thioamides may be feasible in the field [19], *ethA* mutations can only be tested using DNA sequencing [20].

Studies showing higher failure/relapse rates in patients treated with the STR were conducted in settings with a high prevalence of initial resistance to SLD [21]. In such settings patients need a baseline molecular test to identify resistance to fluoroquinolones. However, as the pooled sensitivity of the direct SL-LPA is 86·2% [22], initial hetero-resistance to fluoroquinolone may be missed. Relying on a posteriori determination of initial resistance (before the implementation of SL-LPA), our data showed that the strongest predictor of unfavourable outcome was fluoroquinolone resistance. Therefore, missed initial resistance to fluoroquinolone, the core drug of the STR, may explain higher failure/relapse rates shown.

Acquisition of resistance to fluoroquinolones was very uncommon. Acquired resistance was identified in three patients treated with the moxifloxacin-based STR, and in none of the patients treated with the gatifloxacin-based STR. Indeed, gatifloxacin is associated with a lower risk of failure, relapse and acquisition of resistance [23].

Since 2012, when bedaquiline became available in Niger, we have applied the principle of 'cascade of regimens' [24], meaning that after an unsuccessful fluoroquinolone-based STR, seven patients were enrolled on a bedaquiline-based regimen with a 100% cure.

All patients who died presented with a poor clinical condition at diagnosis. Severe underweight was an important predictor of mortality, consistent with findings from other settings [25,26]. We speculate that reducing the delay in treatment initiation will decrease mortality in the future [27].

We provide a detailed description of AEs in a real-life setting. The STR proved to be safe, with 5·6% of patients developing serious AEs. Although mild hearing loss have may been underestimated because of the unavailability of systematic audiometry until 2013, the cumulative rate of serious ototoxicity was low (3·2%), with no serious hearing loss detected from 2016 to date. Several factors may have contributed to this decrease, such as the earlier detection of RR-TB and thus shorter exposure to the streptomycin-based regimen, the systematic monitoring with

audiometry since October 2013, and the switch from the injectable to linezolid when audiometry abnormalities were detected.

Our study was conducted in a setting with a low prevalence of resistance to fluoroquinolones and SLI limiting the generalization of our findings.

Although our study was not documented with the rigor of a clinical trial, we believe that its programme embeddedness is in fact a strength.

## 5. Conclusion

Our results show that a comprehensive approach to RR/MDR-TB diagnosis and management is feasible and can be can be implemented with good treatment outcomes even in resource-limited settings. The treatment outcomes were not affected by initial resistance to the companion drugs used in the standardised STR. Our study confirms the effectiveness and the safety of the STR on the long run and complements the report on its efficacy documented by the STREAM trial.

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## Authors contributions

AP wrote the study protocol, supervised the study and wrote the first draft; MBS and SHH conducted the study, supervised the data collection and quality control; TD conducted the data analysis with contributions of AY, NOG and AR; MMA, IML, SA, BM, AS and AGI conducted the study; PL, MG, ZHH, JD and BdJ conducted the laboratory tests; SM and AVD verified the methods and the results; all authors contributed to the final manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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