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# Prevalence and risk factors of multidrug-resistant tuberculosis in Cubal, Angola: a prospective cohort study

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SUMMARY

**BACKGROUND**: Although the Republic of Angola is one of the 14 countries figuring in the three high tuberculosis (TB) burden country lists, the true multidrug-resistant TB (MDR-TB) situation is unknown.

**MATERIAL AND METHODS**: Patients aged ⩾16 years with a diagnosis of pulmonary TB were prospectively enrolled from June 2014 to July 2015. Sputum samples were collected for culture and drug susceptibility testing in all patients, and for Xpert® MTB/RIF testing in all previously treated patients and in new patients whose sputum remained smear-positive after 2 months of treatment.

**RESULTS**: A total of 422 patients were included; *Mycobacterium tuberculosis* was isolated in 308 sputum samples. The prevalence of MDR-TB was 8.0% (18/225) in new patients and 71.1% (59/83) in previously treated patients. Male sex (OR 2.95, 95%CI 1.35–6.44, $P = 0.007$), previous anti-tuberculosis treatment (OR 20.86, 95%CI 9.53–45.67, $P < 0.001$), presence of pleural thickening (OR 7.68, 95%CI 1.57–37.43, $P = 0.012$) and duration of illness >4 months (OR 3.34, 95%CI 1.45–7.69, $P = 0.005$) were independent risk factors for MDR-TB.

**CONCLUSIONS**: The prevalence of MDR-TB in Cubal, Angola, was higher than estimated by the World Health Organization for Angola and one of the highest worldwide. Facilities to diagnose and treat MDR-TB are urgently needed in Angola.

**KEY WORDS**: Xpert MTB/RIF; treatment outcomes; Africa; rural setting

TUBERCULOSIS (TB) REMAINS a major cause of morbidity and mortality worldwide, particularly in Asia and sub-Saharan Africa.[1] Multidrug-resistant TB (MDR-TB) is particularly difficult to treat. According to the World Health Organization (WHO) 2017 global tuberculosis report, an estimated 4.1% of new TB cases and 19% of previously treated cases have MDR-TB.[2]

The Republic of Angola is one of the 14 countries figuring in the WHO's three high TB burden country lists.[2] The estimated annual incidence of TB, including human immunodeficiency virus (HIV) infected cases, is 370 per 100 000 population (95% confidence interval [CI] 230–543), with 54% of notified pulmonary TB cases bacteriologically confirmed.[3] The WHO estimates that 2.6% of new cases and 18% of previously treated cases are MDR-TB;[2] however, the real situation of MDR-TB is not known. According to the 2017 WHO global report, the Republic of Angola is one of the three countries among the 30 high TB and MDR-TB burden countries in which a drug resistance survey has never been conducted.[2] Moreover, access to rapid diagnosis of TB and rifampicin (RMP) resistance was absent throughout the country when the study was conducted, while treatment for MDR-TB was available only in a single clinic in Luanda, Angola, and in Hospital Nossa Senhora da Paz (HNSP), Cubal, in South-East Angola, since May 2013.

HNSP is a reference centre for the diagnosis and treatment of TB.[4] Due to the absence of data on MDR-TB, we implemented the first Xpert® MTB/RIF testing (Cepheid, Sunnyvale, CA, USA) in Angola at the HNSP.

The objectives of the present study were to assess the prevalence of and risk factors for MDR-TB in a cohort of patients treated at the HSNP, to determine

MLA and ARS were co–principal investigators.

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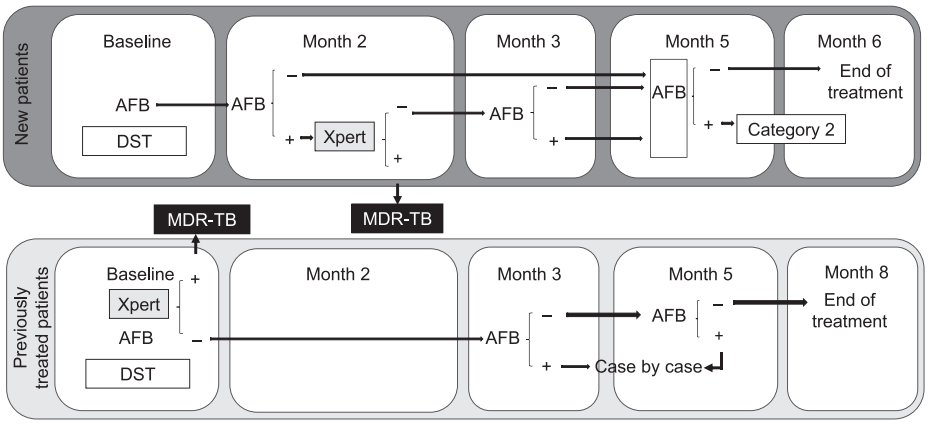


**Figure 1** Flow chart of new and previously treated patients. AFB = acid-fast bacilli; DST = drug susceptibility testing; − = negative; + = positive; MDR-TB = multidrug-resistant tuberculosis.

the usefulness of Xpert testing and to describe the outcomes of TB patients.

## METHODS

### *Study design*

This prospective cohort study was conducted at the HNSP from June 2014 to July 2015. The study protocol was approved by the Vall d'Hebron Research Institute Ethics Committee, Barcelona, Spain; Angolan National Tuberculosis Programme, Luanda; and the University of Katyavala Bwila Ethics Committee, Benguela, Angola. Participation was voluntary, and written informed consent was required for study inclusion. All patients aged ⩾16 years with a diagnosis of pulmonary TB based on smear-positive sputum were consecutively enrolled.

### *Data collection*

Sociodemographic characteristics, symptoms, illness duration and treatment history were recorded. The case definitions and classifications used in the present study are consistent with the 2013 WHO revised TB definitions and reporting framework.[5] All patients were offered HIV testing. Chest X-ray (CXR) was performed before starting treatment.

### *Sputum collection*

Standard volumes of sputum samples were collected from all patients in a plastic container at the time of diagnosis. The containers were stored at –80°C and periodically transported to the Microbiology Department of Vall d'Hebron University Hospital in Barcelona, Spain, for culture and drug susceptibility testing (DST). Sputum samples were collected for Xpert at the time of diagnosis in previously treated patients and after 2 months of treatment in new patients whose sputum remained acid-fast bacilli (AFB) positive. A detailed description of microbiological techniques has been previously described by our research team.[6] The patient flow chart is given in Figure 1.

### *Treatment and follow-up*

We followed national guidelines to treat patients diagnosed with TB.[7] New patients were started on first-line treatment consisting of 2 months of RMP, isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA), followed by 4 months of RMP and INH. Previously treated patients without RMP resistance detected on Xpert were started on WHO Category 2 treatment, i.e., 2 months of RMP, INH, ethionamide (ETH), PZA and streptomycin (SM) + 1 month of RMP, INH, ETH and PZA + 5 months of RMP, INH and ETH. If RMP resistance was detected on Xpert, an MDR-TB treatment regimen containing EMB, ETH, cycloserine (CS), ofloxacin (OFX) and a second-line injectable drug (kanamycin, capreomycin or amikacin, depending on availability from the national programme) for 8 months was initiated, followed by 12 months of EMB, ETH, CS and OFX. Directly observed treatment (DOT) was performed in all patients undergoing MDR-TB treatment during the first 8 months and during the first 2 months in patients receiving first-line and Category 2 treatment. Drugs were subsequently provided every month for all patients, and a relative was made responsible for providing community DOT. Sputum samples were collected from patients receiving first-line and Category 2 treatment at 2–3 months, 5 months and at the end of the treatment, and monthly in patients on MDR-TB treatment. If follow-up appointments were missed, a nurse attempted to contact the patient twice by telephone and/or a community health worker tried to locate the patient. If these efforts were unsuccessful, patient outcome was defined as lost to follow-up (LTFU). Treatment outcomes were based on 2013 WHO recommendations.[5] Due to the limited budget, we could not perform follow-up culture, and treatment outcomes were based on smear results. A successful outcome included patients who met the definition of cure or treatment complete. Treatment outcomes were evaluated in September 2017.

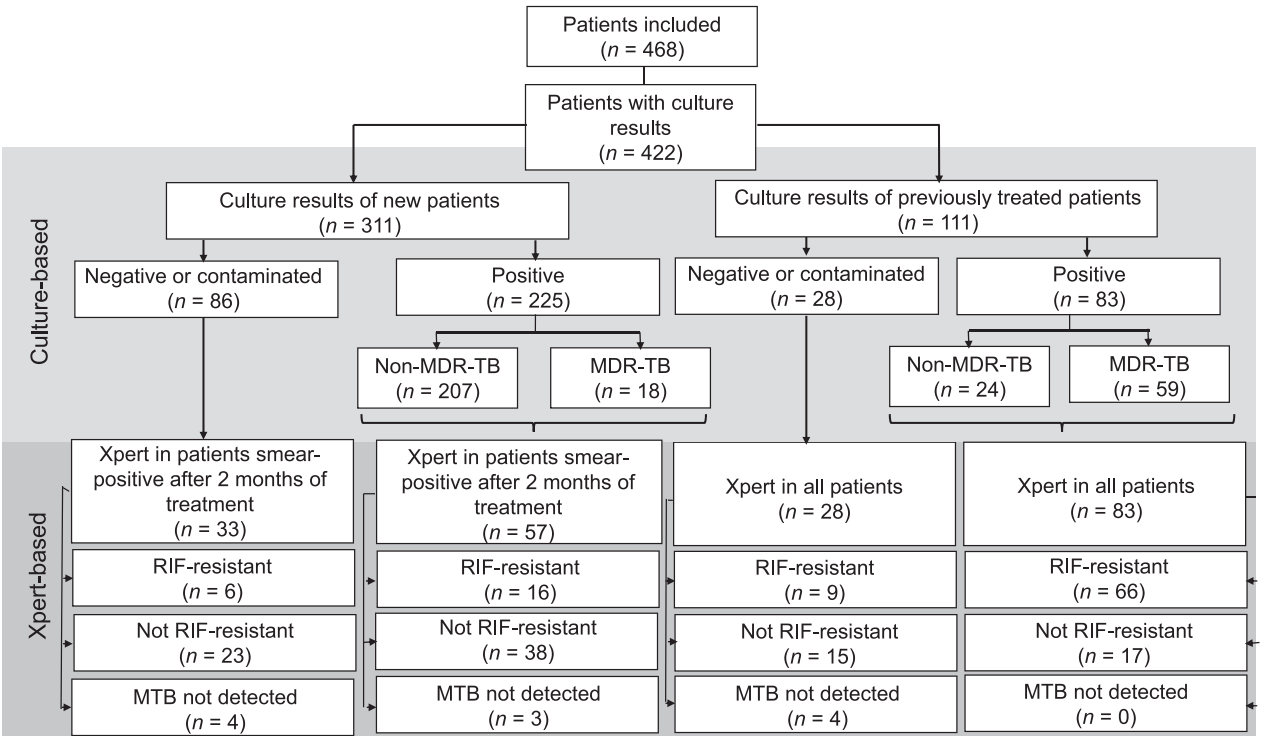


**Figure 2** Culture and Xpert® MTB/RIF results in new and previously treated patients. MDR-TB = multidrug-resistant tuberculosis; RIF = rifampicin; MTB = *M. tuberculosis*.

*Data analysis*

Data analysis was only performed in patients with a sputum culture result. Descriptive statistics are presented as number (percentage) and median (interquartile range [IQR]) or mean (standard deviation [SD]), depending on variable normality. Univariate logistic regression models were used to calculate unadjusted odds ratios (ORs) to determine the risk of MDR-TB and treatment outcomes. Variables with a significance of $P < 0.05$ on univariate analysis and variables considered to be clinically important were included in the multivariate logistic regression analysis. Treatment outcomes and risk factors for MDR-TB were only analysed in patients with *M. tuberculosis* complex (MTC) isolated in their sputum. For treatment outcomes, we performed both a per-protocol (PP) analysis (excluding patients who did not complete treatment) and an intention-to-treat (ITT) analysis (including patients who did not complete treatment as unsuccessful outcome). Two-sided $P < 0.05$ was considered statistically significant for all analyses. Analyses were performed using SPSS v23 (IBM, Armonk, NY, USA).

## RESULTS

Of the 468 patients included in the study, culture results were available for 422. Two hundred and sixty (61.6%) were male, and the mean age was 32.3 years (SD 12.2). HIV co-infection was detected in 28 (6.6%) patients. There were 311 (73.7%) new patients. A median of two TB treatments had been received before the current episode (IQR 1–2). Two hundred and twenty-five new cases and 83 previously treated cases were sputum culture-positive. The demographics and clinical characteristics of culture-positive patients are shown in Appendix Table A.1.

*Prevalence of multidrug-resistant tuberculosis*

MDR-TB was diagnosed in respectively 59/83 (71.1%) and 18/225 (8.0%) sputum samples from previously treated and new patients. Using Xpert, 75/111 (67.6%) sputum samples from previously treated patients and 22/90 (24.4%) new patients with a positive smear after 2 months of anti-tuberculosis treatment were RMP-resistant (Figure 2).

*Correlation between Xpert and drug susceptibility testing*

Xpert detected *M. tuberculosis* in 33/38 (86.8%) sputum samples for which culture results were negative. Of 11 sputum samples, 3 (27.3%) were culture-positive for *M. tuberculosis*; however, *M. tuberculosis* was not detected using Xpert. All three samples were from new patients after 2 months of treatment (Table 1). The correlation between Xpert and DST is shown in Tables 2 and 3.

*Risk factors for multidrug-resistant tuberculosis*

In the multivariate analysis, male sex (OR 2.95,

**Table 1** Xpert® MTB/RIF assay and conventional DST results among mycobacterial culture-positive sputum samples

| | Culture- and DST-based results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | New cases who were smear-positive at 2 months of treatment ($n = 90$) | | | | Retreatment cases ($n = 111$) | | | |
| Xpert | $RMP^S$ | $RMP^R$ | Negative | Contaminated | $RMP^S$ | $RMP^R$ | Negative | Contaminated |
| $RMP^S$ | 38 | 0 | 15 | 8 | 16 | 1 | 8 | 7 |
| $RMP^R$ | 1 | 15 | 5 | 1 | 6 | 60 | 5 | 4 |
| No *M. tuberculosis* | 3 | 0 | 2 | 2 | 0 | 0 | 3 | 1 |

DST = drug susceptibility testing; RMP = rifampicin; $RMP^R$ = RMP-resistant; $RMP^S$ = RMP-susceptible.

95%CI 1.35–6.44, $P = 0.007$), previous treatment (OR 20.86, 95%CI 9.53–45.67, $P < 0.001$), pleural thickening (OR 7.68, 95%CI 1.57–37.43, $P = 0.012$) and duration of illness >4 months (OR 3.34, 95%CI 1.45–7.69, $P = 0.005$) were independent risk factors for MDR-TB (Appendix Table A.2).

### *Clinical and microbiological outcomes*

At the end of treatment, 159/231 (68.8%) patients with non-MDR-TB had treatment success, 49/231 (21.2%) were LTFU, 7/231 (3.0%) experienced treatment failure, 14/231 (6.1%) died and 2/231 (0.9%) were transferred to other institutions. Of 77 patients with MDR-TB, 35 (45.5%) experienced treatment success, 27 (35.1%) were LTFU, 1 (1.3%) experienced failure and 14 (18.2%) died. The demographic and clinical characteristics related to successful and unsuccessful treatment outcomes are given in Appendix Tables A.3 and A.4. In ITT and PP multivariate analysis, patients infected with non-MDR-TB who did not achieve a successful treatment outcome were more likely to be sputum AFB-positive after 2 months of treatment (respectively OR 2.87, 95%CI 1.34–6.14, $P = 0.007$ and OR 10.58, 95%CI 2.54–44.11, $P = 0.001$).

## DISCUSSION

To our knowledge, this is the first prospective cohort study reporting data on the prevalence of and risk factors for MDR-TB in Angola. It is also the first study to use Xpert testing for TB diagnosis in this setting. The proportion of MDR-TB was 71.1% in previously treated patients and 8% in new patients. This prevalence is much higher than estimated by the WHO,[8] and it would rank Angola first in terms of MDR-TB among previously treated patients.[9]

MDR-TB prevalence in high TB burden sub-Saharan countries varies from 2% to 6.6% in new patients and 4.6% to 15% in previously treated patients.[10–12] The high MDR-TB prevalence found in our study may have been due to the availability of MDR-TB treatment at the HNSP during the study period, which may have led to more referrals of patients with previous treatment failure. However, if only patients from Cubal are taken into account, 5.2% of new and 42.2% of previously treated patients had MDR-TB. It is also possible that the long civil war that devastated the country for 27 years and which hindered the development of health programmes[13] was related to the high prevalence.

The usefulness of the Xpert test in the field is well-known.[14–16] In our study, the accuracy of Xpert in predicting RMP resistance was comparable to that reported previously. One sample was found to be RMP-susceptible on Xpert but RMP-resistant on culture + DST. Although 95–97% of RMP-resistant *M. tuberculosis* samples harbour mutations in the RMP resistance-determining region of *rpo*B as detected using Xpert, other mechanisms conferring RMP resistance have been reported.[17] Moreover, samples with mixed populations of RMP-susceptible and RMP-resistant bacilli may also cause false-negative results on Xpert.[18] In contrast, silent mutations or mutations conferring low resistance to RMP detected on Xpert but missed by conventional DST have also been reported.[19] This phenomenon could explain the six cases classified as RMP-resistant on Xpert but RMP-susceptible on culture + DST. *M. tuberculosis* was detected using Xpert in 33/38 sputum samples that were culture-negative. False-positive results on Xpert have been related to previous TB, low

**Table 2** Test characteristics of Xpert for the detection of *M. tuberculosis* compared with culture, the gold standard

| | Sensitivity % (95%CI) | Specificity % (95%CI) | PPV % (95%CI) | NPV % (95%CI) |
|---|---|---|---|---|
| Overall | 97.9 (95.4–100) | 13.2 (3.5–27.2) | 80.7 (74.3–86.7) | 62.5 (28.2–100) |
| New cases who were smear-positive after 2 months of treatment | 94.7 (88.8–100) | 9.1 (0–22.1) | 73.0 (62.6–83.3) | 40.0 (0–100) |
| Retreatment cases | 100 | 18.7 (0–40.2) | 86.5 (79.5–93.4) | 100 |

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

**Table 3** Test characteristics of Xpert for detection of rifampicin resistance compared with culture, the gold standard

| | Sensitivity % (95%CI) | Specificity % (95%CI) | PPV % (95%CI) | NPV % (95%CI) |
|---|---|---|---|---|
| Overall | 98.7 (96.8–100) | 88.7 (83.4–94.0) | 91.5 (86.8–96.1) | 98.2 (96–100) |
| New cases who were smear-positive after 2 months of treatment | 100 | 97.5 (93.4–100) | 93.8 (87.4–100) | 100 |
| Retreatment cases | 98.4 (91.3–99.7) | 72.7 (63.1–82.3) | 90.9 (84.7–97.1) | 94.1 (89.1–99.2) |

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

mycobacterial DNA load and a CXR not compatible with active TB.[20] However, as all patients who were Xpert-positive, culture-negative in our study had symptoms suggestive of TB, we strongly believe that these patients were true TB cases. Because mycobacterial culture viability declines with time,[21] the considerable distance to the reference laboratory may have affected our culture results. Conversely, Xpert failed to detect TB in samples collected after 2 months of treatment in three new patients whose sputum were initially culture-positive for TB. Although it has been reported that sputum samples evaluated using Xpert may remain positive for several months during treatment,[22] it is also well known that a low bacillary load may reduce Xpert sensitivity,[23] and this may explain the Xpert-negative result in these three cases.

We observed that male sex, previous anti-tuberculosis treatment, presence of pleural thickening and duration of illness were independent risk factors for MDR-TB. Previous treatment has been consistently identified as a risk factor for MDR-TB.[24,25] Being male appears to be associated with a higher risk of MDR-TB;[26] however, studies are not consistent, and the WHO suggests that the overall risk of MDR-TB is not influenced by sex.[9] Duration of illness >60 days, sputum AFB smear score >3+ and the presence of cavities on CXR have also been recently associated with MDR-TB.[27] Although we observed a relationship between sputum AFB smear >3+ and presence of cavities on CXR and MDR-TB in the univariate analysis, no association was observed in the multivariate model. High rates of sputum smear positivity are associated with chest cavities,[28] and this association may overestimate the relationship between these two variables and MDR-TB if they are analysed together. In contrast, we observed that pleural thickening was related to MDR-TB. One possible explanation is that pleural thickening was related to a remote history of TB, and the patient may not have remembered being treated for it. HIV co-infection has also been reported to be a risk factor for MDR-TB; however, this association is not consistent in the literature.[29,30] We did not find a relationship between HIV infection and MDR-TB.

With regard to treatment outcomes, we observed that respectively 68.8% and 45.5% of patients infected with non-MDR-TB and MDR-TB achieved a successful outcome. These outcome results fall below WHO targets,[31] but are similar to those for other sub-Saharan African countries.[2] A positive AFB smear after 2 months of anti-tuberculosis treatment was found to be a risk factor for an unfavourable outcome in patients with non-MDR-TB. This fact has been related to lung cavities,[32] bilateral involvement of the lungs[33] and high pre-treatment smear grade.[34] We also observed that people aged <20 years were more likely to achieve a successful outcome, a fact that has been reported previously.[35] In patients with MDR-TB, we did not observe a relationship between the variables analysed and unsuccessful outcomes. This was probably due to the small number of patients included in the analysis.

Our study had four main limitations. First, cure criteria were based on smear microscopy rather than culture. This limitation reflects the reality of TB diagnosis and management in many resource-poor settings. Second, we performed Xpert exclusively in previously treated patients and in new patients who were smear-positive after 2 months of treatment, and not in all patients. The rationale for this strategy was to be able to reach the largest population with limited resources, thereby prioritising the population at greater risk of MDR-TB. Third, some study culture samples were negative or contaminated. Although this is a frequent problem when shipping samples over long distances, we need to reinforce storage and sample transportation in further studies. Fourth, as we only included smear-positive patients aged ⩾16 years, our study may not be representative of the entire population. Furthermore, as HNSP is a specialised referral centre for TB, it may not represent the reality in other settings in Angola.

In conclusion, we observed that MDR-TB prevalence in Cubal, a rural setting in South-West Angola, was higher than estimated by the WHO and one of the highest worldwide. Facilities to diagnose and treat MDR-TB are therefore urgently needed in Angola.

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Conflicts of interest: none declared.

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## APPENDIX

**Table A.1** Demographics and clinical characteristics of patients culture-positive for *M. tuberculosis*

| | New patients ($n = 225$) *n/N* (%) | Previously treated patients ($n = 83$) *n/N* (%) | *P* value |
|---|---|---|---|
| Male sex | 145 (64.4) | 47 (56.6) | 0.209 |
| Age, years, median [IQR] | 28 [23–38] | 30 [24–35] | 0.477 |
| Place of residence | | | |
| Cubal | 154 (71.0) | 32 (38.6) | <0.001 |
| <50 km from Cubal* | 35 (16.1) | 12 (14.5) | |
| >50 km from Cubal† | 28 (12.9) | 39 (47) | |
| HIV infection | 12/222 (5.4) | 4/83 (4.8) | 1.000 |
| Clinical signs | | | |
| Cough | 215/215 (100) | 77/77 (100) | |
| Fever | 197/215 (91.6) | 68/78 (87.2) | 0.252 |
| Haemoptysis | 25/204 (12.3) | 14/77 (18.2) | 0.200 |
| BMI, kg/m$^2$, median [IQR] | 16.9 [15.6–18.7] | 16.1 [14.9–18.4] | 0.030 |
| Duration of illness, months, median [IQR] | 3 [2–5.7] | 12 [6–24] | <0.001 |
| Radiological findings, cm | | | |
| Cavitation | | | |
| Any size | 29/215 (13.5) | 22/78 (28.2) | 0.005 |
| ⩾5 cm | 18/215 (8.4) | 16/78 (20.5) | 0.004 |
| <5 cm | 11/215 (5.1) | 6/78 (7.7) | 0.404 |
| Lung infiltrates | 120/215 (55.8) | 47/78 (60.3) | 0.497 |
| Pleural thickening | 5/215 (2.3) | 8/78 (10.3) | 0.004 |
| Miliary TB | 9/215 (4.2) | 0/78 (0) | 0.119 |
| Pleural effusion | 4/215 (1.9) | 5/78 (6.4) | 0.060 |
| Drug susceptibility | | | |
| Susceptible to all first-line drugs | 167/225 (74.2) | 14/83 (16.9) | <0.001 |
| Resistance to one drug | 31/225 (13.8) | 7/83 (8.4) | 0.206 |
| RMP only | 1 (3.2) | 2 (28.6) | |
| INH only | 21 (67.7) | 4 (57.1) | |
| SM only | 8 (25.8) | 1 (14.3) | |
| PZA only | 1 (3.2) | 0 (0) | |
| Total polydrug resistance | 9/225 (4.0) | 3/83 (3.6) | 1.000 |
| INH+SM | 5 (55.5) | 0 (0) | |
| INH+PZA | 2 (22.2) | 0 (0) | |
| INH+EMB | 1 (11.1) | 0 (0) | |
| INH+SM+PZA | 0 | 2 (66.6) | |
| INH+SM+EMB | 0 | 1 (33.3) | |
| RMP+SM+PZA | 1 (11.1) | 0 | |
| MDR-TB | 18/225 (8.0) | 59/83 (71.1) | <0.001 |

* Includes the cities of Caimbambo and Ganda.
† Includes the cities of Benguela, Lobito, Bahia Farta, Chongoroi and Catumbela.
IQR = interquartile range; HIV = human immunodeficiency virus; BMI = body mass index; TB = tuberculosis; RMP = rifampicin; INH = isoniazid; SM = streptomycin; PZA = pyrazinamide; EMB = ethambutol; MDR-TB = multidrug-resistant TB.

**Table A.2** Risk factors associated with MDR-TB

| | No MDR-TB ($n = 231$) *n* (%) | MDR-TB ($n = 77$) *n* (%) | *P* value | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Male sex | 77 (33.3) | 39 (50.6) | 0.007 | 2.05 (1.22–3.47) | 0.007 | 2.95 (1.35–6.44) | 0.007 |
| Previous anti-tuberculosis treatment | 24 (10.3) | 59 (76.6) | <0.001 | 28.41 (14.45–55.85) | <0.001 | 20.86 (9.53–45.67) | <0.001 |
| Age, years | | | | | | | |
| <20 | 34 (14.8) | 7 (9.1) | 0.241 | 0.58 (0.24–1.36) | 0.208 | | |
| 20–40 | 147 (63.9) | 57 (74) | | 1.61 (0.90–2.86) | 0.106 | | |
| >40 | 49 (21.3) | 13 (16.9) | | 0.75 (0.38–1.47) | 0.404 | | |
| Chest X-ray | | | | | | | |
| Cavity >5 cm | 18 (8.2) | 16 (21.9) | 0.001 | 3.15 (1.51–6.57) | 0.002 | 1.38 (0.46–4.15) | 0.565 |
| Pleural thickening | 3 (1.4) | 10 (13.7) | <0.001 | 11.48 (3.07–42.99) | <0.001 | 7.68 (1.57–37.43) | 0.012 |
| Pleural effusion | 6 (2.7) | 3 (4.1) | 0.695 | 1.53 (0.37–6.27) | 0.556 | | |
| AFB >3+ | 117 (50.9) | 28 (36.4) | 0.027 | 0.55 (0.32–0.93) | 0.028 | 1.29 (0.61–2.73) | 0.500 |
| HIV-infected | 14 (6.1) | 2 (2.6) | 0.374 | 0.41 (0.09–1.84) | 0.242 | | |
| Duration of illness >4 months | 88 (38.1) | 62 (80.5) | <0.001 | 6.72 (3.60–12.53) | <0.001 | 3.34 (1.45–7.69) | 0.005 |
| BMI <18.5 | 133 (57.6) | 50 (64.9) | 0.255 | 1.36 (0.80–2.33) | 0.256 | | |

MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; AFB = acid-fast bacilli; HIV = human immunodeficiency virus; BMI = body mass index.

**Table A.3** Demographic and clinical characteristics related with successful and unsuccessful treatment outcome in patients with non-MDR-TB (intention-to-treat and per-protocol analysis)

| | Successful outcome ($n = 159$) | Unsuccessful outcome (per-protocol analysis) ($n = 21$) | Unsuccessful outcome (intention-to-treat) ($n = 72$) | Per-protocol | | | | Intention-to-treat | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Male sex | 103 (64.8) | 16 (76.2) | 51 (70.8) | 1.74 (0.60–5.00) | 0.304 | | | 1.32 (0.72–2.41) | 0.367 | | |
| Age, years | | | | | | | | | | | |
| <20 | 29 (18.2) | 1 (4.8) | 5 (7) | 0.22 (0.03–1.74) | 0.152 | | | 0.34 (0.13–0.92) | 0.033 | 0.27 (0.07–0.97) | 0.046 |
| 20–40 | 95 (59.7) | 16 (76.2) | 52 (73.2) | 2.16 (0.75–6.18) | 0.153 | | | 1.84 (0.99–3.41) | 0.051 | | |
| >40 | 35 (22.0) | 4 (19.0) | 14 (19.7) | 0.76 (0.26–2.64) | 0.757 | | | 0.87 (0.43–1.74) | 0.695 | | |
| Place of residence | | | | | | | | | | | |
| Cubal | 112 (72.3) | 16 (76.2) | 44 (62) | 1.22 (042–3.56) | 0.705 | | | 0.63 (0.34–1.13) | 0.122 | 1.43 (0.68–3.01) | 0.339 |
| <50 km from Cubal* | 24 (15.5) | 3 (14.3) | 13 (18.3) | 0.91 (0.25–3.33) | 0.886 | | | 1.22 (0.58–2.57) | 0.594 | | |
| >50 km from Cubal† | 19 (12.3) | 2 (9.5) | 14 (19.7) | 0.75 (0.16–3.49) | 0.718 | | | 1.76 (0.82–3.75) | 0.144 | | |
| AFB >3+ | 76 (47.8) | 10 (47.6) | 41 (57.7) | 0.99 (0.40–2.47) | 0.993 | | | 1.49 (0.85–2.62) | 0.164 | | |
| HIV-infected | 9 (5.7) | 3 (14.3) | 5 (7.1) | 2.76 (0.68–11.13 | 0.154 | | | 1.27 (0.41–3.95) | 0.675 | | |
| BMI <18.5 kg/m$^2$ | 88 (55.3) | 15 (71.4) | 45 (62.5) | 2.01 (0.74–5.47) | 0.168 | | | 1.34 (0.76–2.38) | 0.309 | 0.97 (0.48–1.94) | 0.925 |
| Duration of illness >4 months | 57 (35.8) | 9 (42.9) | 31 (43.1) | 1.34 (0.53–3.38) | 0.532 | | | 1.35 (0.77–2.39) | 0.297 | | |
| Cavities >5 cm | 12 (7.8) | 2 (9.5) | 6 (9) | 1.24 (0.26–5.95) | 0.791 | | | 1.16 (0.41–3.22) | 0.782 | | |
| Previous anti-tuberculosis treatment | 13 (8.2) | 7 (33.3) | 11 (15.3) | 5.61 (1.93–16.37) | 0.002 | | | 2.02 (0.86–4.77) | 0.106 | | |
| AFB-positive at month 2 or 3‡ | 26 (17.1) | 7 (70.0) | 19 (36.5) | 10.33 (2.51–42.46) | 0.001 | 10.58 (2.54–44.11) | 0.001 | 2.88 (1.42–5.84) | 0.003 | 2.87 (1.34–6.14) | 0.007 |
| INH resistance | 22 (13.8) | 5 (23.8) | 14 (19.4) | 1.95 (0.65–5.85) | 0.236 | | | 1.50 (0.72–3.14) | 0.278 | 1.56 (0.61–3.98) | 0.354 |
| TB treatment | | | | | | | | | | | |
| Category 1 | 145 (91.2) | 14 (66.7) | 61 (84.7) | 0.19 (0.07–0.56) | 0.002 | 0.35 (0.05–2.21) | 0.263 | 0.53 (0.23–1.25) | 0.147 | 0.54 (0.13–2.29) | 0.407 |
| Category 2 | 9 (5.7) | 4 (19.0) | 7 (9.7) | 3.92 (1.09–14.12) | 0.036 | | | 1.79 (0.64–5.03) | 0.266 | | |
| Second-line | 5 (3.1) | 3 (14.3) | 4 (5.6) | 5.13 (1.13–23.29) | 0.034 | | | 1.81 (0.47–6.96) | 0.387 | | |

* Includes the cities of Caimbambo and Ganda.
† Includes the cities of Benguela, Lobito, Bahia Farta, Chongoroi and Catumbela.
‡ AFB performed at month 2 in patients who received first-line treatment and at month 3 in those who received Category 2 treatment.
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; AFB = acid-fast bacilli; HIV = human immunodeficiency virus; BMI = body mass index.

**Table A.4** Demographic and clinical characteristics related with successful and unsuccessful treatment outcome in patients with MDR-TB (intention-to-treat and per-protocol analysis)

| | Successful outcome ($n = 35$) *n* (%) | Unsuccessful outcome (per-protocol analysis) ($n = 15$) *n* (%) | Unsuccessful outcome (intention-to-treat) ($n = 42$) *n* (%) | Per-protocol | | | | Intention-to-treat | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Sex, male | 17 (48.6) | 10 (66.7) | 22 (52.4) | 2.12 (0.60–7.48) | 0.244 | | | 1.16 (0.47–2.86) | 0.739 | | |
| Age, years | | | | | | | | | | | |
| <20 | 5 (14.3) | 2 (13.3) | 2 (4.8) | 0.92 (0.16–5.39) | 0.929 | | | 0.30 (0.05–1.65) | 0.167 | | |
| 20–40 | 22 (62.9) | 12 (80) | 35 (83.3) | 2.36 (0.56–9.96) | 0.241 | | | 2.95 (1.02–8.55) | 0.046 | 2.57 (0.76–8.69) | 0.130 |
| >40 | 8 (22.9) | 1 (6.7) | 5 (11.9) | 0.24 (0.03–2.13) | 0.200 | | | 0.46 (0.13–1.55) | 0.208 | | |
| Place of residence | | | | | | | | | | | |
| Cubal | 12 (34.3) | 4 (28.6) | 18 (46.2) | 0.77 (0.20–2.97) | 0.700 | | | 1.64 (0.64–4.20) | 0.301 | 1.49 (0.50–4.43) | 0.468 |
| <50 km from Cubal* | 6 (17.1) | 2 (14.3) | 4 (10.3) | 0.81 (0.14–4.57) | 0.807 | | | 0.55 (0.14–2.15) | 0.391 | | |
| >50 km from Cubal† | 17 (48.6) | 8 (57.1) | 17 (43.6) | 1.41 (0.40–4.92) | 0.588 | | | 0.82 (0.33–2.05) | 0.668 | | |
| AFB >3+ | 13 (37.1) | 8 (53.3) | 15 (35.7) | 1.93 (0.57–6.58) | 0.291 | | | 0.94 (0.37–2.39) | 0.897 | | |
| HIV | 1 (2.9) | 0 | 1 (2.4) | | | | | 0.83 (0.05–13.76) | 0.896 | | |
| BMI <18.5 kg/m$^2$ | 21 (60) | 12 (80) | 29 (69) | 2.67 (0.63–11.19) | 0.180 | | | 1.49 (0.58–3.81) | 0.408 | | |
| Duration of illness > 4 months | 27 (77.1) | 13 (86.7) | 35 (83.3) | 1.93 (0.36–10.38) | 0.446 | | | 1.48 (0.48–4.59) | 0.496 | | |
| Cavities >5 cm | 6 (17.6) | 5 (35.7) | 10 (25.6) | 2.59 (0.64–10.56) | 0.184 | | | 1.61 (0.52–5.02) | 0.412 | | |
| AFB-positive at months 2 to 3‡ | 11 (33.3) | 4 (66.7) | 14 (46.7) | 4.00 (0.63–25.32) | 0.141 | | | 1.75 (0.63–4.85) | 0.282 | 1.37 (0.46–4.13) | 0.575 |

* Includes the cities of Caimbambo and Ganda.
† Includes the cities of Benguela, Lobito, Bahia Farta, Chongoroi and Catumbela.
‡ AFB performed at month 2 in patients who received first-line treatment and at month 3 in those who received Category 2 treatment.
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; AFB = acid-fast bacilli; HIV = human immunodeficiency virus; BMI = body mass index.

## RÉSUMÉ

**CONTEXTE : La république d'Angola est l'un des 14 pays figurant dans les trois listes de l'Organisation Mondiale de la Santé [OMS] de pays durement frappés par la tuberculose (TB). La situation réelle de la TB multirésistante (TB-MDR) y est cependant inconnue.**

**MATERIEL ET MÉTHODES : Des patients âgés de ⩾16 ans ayant eu un diagnostic de TB pulmonaire ont été prospectivement enrôlés entre juin 2014 et juillet 2015. Des échantillons de crachat ont été recueillis pour une culture et un test de pharmacosensibilité chez tous les patients, et pour le test de l'Xpert® MTB/RIF chez tous les patients déjà traités et chez les nouveaux patients dont les crachats sont restés positifs après 2 mois de traitement.**

**RÉSULTATS : Un total de 422 patients ont été inclus et *Mycobacterium tuberculosis* a été isolé dans 308 échantillons de crachat. La prévalence de la TB-MDR a été de 8,0% (18/225) des nouveaux patients et de 71,1% (59/83) des patients déjà traités. Le sexe masculin (OR 2,95 ; IC95% 1,35–6,44 ; $P = 0,007$), un traitement de TB préalable (OR 20,86 ; IC95% 9,53–45,67 ; $P < 0,001$), la présence d'un épaississement pleural (OR 7,68 ; IC95% 1,57–37,43 ; $P = 0,012$) et une durée de la maladie de >4 mois (OR 3,34 ; IC95% 1,45–7,69 ; $P = 0,005$) ont été des facteurs de risque indépendants de TB-MDR.**

**CONCLUSION : La prévalence de la TB-MDR à Cubal est plus élevée que ne l'a estimé l'OMS pour l'Angola et est l'une des plus élevées dans le monde. Il est urgent que l'Angola dispose des structures de diagnostic et de traitement de la TB-MDR en Angola.**

## RESUMEN

**MARCO DE REFERENCIA: La República de Angola es uno de los 14 países que aparecen en las tres listas de la Organización Mundial de la Salud de países con mayor carga de enfermedad tuberculosa. Sin embargo, la situación real de la tuberculosis multirresistente (TB-MDR) se desconoce.**

**MATERIAL Y MÉTODOS: Todos los pacientes de edad ⩾16 años con un diagnóstico de TB pulmonar fueron incluidos desde junio de 2014 a julio de 2015 de manera prospectiva. En todas las muestras de esputo se realizó cultivo y sensibilidad a fármacos antituberculosos. Las muestras de esputo de todos los pacientes previamente tratados y de los pacientes nuevos con baciloscopia positiva al segundo mes de tratamiento se analizaron también mediante Xpert® MTB/RIF.**

**RESULTADOS: Se incluyeron un total de 422 pacientes, aislándose *Mycobacterium tuberculosis* en 308 muestras de esputo. La prevalencia de TB-MDR fue del 8,0% (18/225) en pacientes nuevos y del 71,1% (59/83) en pacientes previamente tratados. El sexo masculino (OR 2,95; 95%CI 1,35–6,44; $P = 0,007$), el tratamiento antituberculoso previo (OR 20,86; 95%CI 9,53–45,67; $P < 0,001$), la presencia de engrosamiento pleural (OR 7,68; 95%CI 1,57–37,43; $P = 0,012$), y la duración de enfermedad mayor a 4 meses (OR 3,34; 95%CI 1,45–7,69; $P = 0,005$) fueron factores de riesgo independientes asociados a TB-MDR.**

**CONCLUSIONES: La prevalencia de TB-MDR en Cubal es más alta que la estimada por la OMS para Angola, y una de las más altas a nivel mundial. Se necesitan de manera urgente facilidades para diagnosticar y tratar la TB-MDR en Angola.**