

Multidrug-resistant tuberculosis: patients in KwaZulu-Natal have better cure rates than patients in the Eastern Cape (PETTS Cohort).

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South Africa has the third highest tuberculosis (TB) and the fifth highest drug-resistant tuberculosis (DR-TB) burden in the world. The number of new multidrug-resistant tuberculosis (MDR-TB) cases, defined as TB resistant to the two most important anti-TB drugs (isoniazid and rifampicin) as well as the number of extensively drug-resistant tuberculosis (XDR-TB) cases, defined as MDR-TB with additional resistance to any fluoroquinolone and injectable second-line TB drug, is rapidly increasing in South Africa. The increase of DR-TB is largely due to the HIV epidemic and the challenges that are faced with the management of the disease (1).

KwaZulu-Natal (KZN) and the Eastern Cape (EC) have the highest burden of DR-TB cases in South Africa. For example, the number of MDR-TB cases diagnosed in KZN and EC in 2010 was 2032 and 1782 respectively and the number of XDR-TB cases 201 and 320 respectively (1).

PETTS cohort

During 2005-2008 the TB Epidemiology and Intervention Research Unit at the Medical Research Council (MRC) in Pretoria conducted a study in collaboration with the Centre for Disease Control, Atlanta, USA (CDC). The objectives of the “Preserving the Effective TB Treatment Study” (PETTS) were to determine the rate of, risk factors for and consequences of acquired resistance to second-line drugs (SLD) in MDR-TB patients in South Africa. This study was a prospective observational study in which new MDR-TB cases (that had given informed consent) were enrolled in EC from 2005-2008 and KZN during 2006.



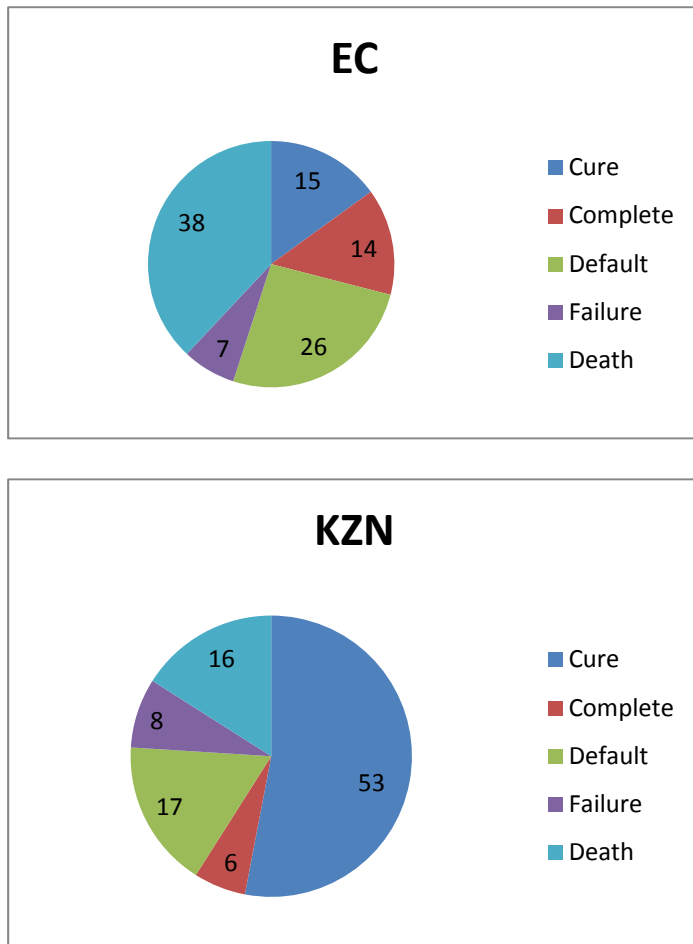
Sputum specimens were collected from the patients at the specialised MDR-TB hospitals and sent to the MRC in Pretoria where the specimens were cultured for mycobacteria at the start of MDR-TB treatment and thereafter on a monthly basis until the end of their MDR-TB treatment episode. *Mycobacterium tuberculosis* isolates were then shipped to CDC for drug susceptibility testing (DST) against 12 first- and second-line drugs (using the proportional method on Middlebrook 7H10 agar).

Patient information on demographics, previous TB history, treatment used during the MDR-TB episode, duration of hospitalisation and laboratory results from the National Health Laboratory Services (NHLS) were collected from the patient case records at the specialised MDR-TB hospitals during the hospitalisation period. Follow-up information on treatment, laboratory results and treatment outcomes was collected at the clinics to which the patients were discharged to.

During the enrolment period the standardised regimen for EC for the first 6 month intensive phase was kanamycin, ofloxacin, ethionamide, ethambutol (if susceptible), terizidone or cycloserine (if resistant to ethambutol) and pyrazinamide (if susceptible) and an additional 18 months continuation phase on the same regimen without kanamycin. KZN had the same regimen except that kanamycin was replaced with amikacin and ofloxacin was replaced with ciprofloxacin. Kanamycin and amikacin are both from the aminoglycoside (injectable) group of drugs, as ofloxacin and ciprofloxacin are both fluoroquinolones. A third injectable drug, capreomycin, is not used for MDR-TB, but cross-resistance between these 3 drugs is known.

Preliminary findings from the study revealed differences in treatment outcomes between EC and KZN. Patients in KZN had significant higher cure rates, lower default rates, and lower mortality than EC (Figure 1). This was unexpected, as these are neighbouring provinces, and they have a similar TB burden. We investigated patient-related, health system-related and treatment-related factors to provide more insight into these findings.

Figure 1. Treatment outcomes (%) of MDR-TB patients in KZN and EC



Some of the patient-related factors that were investigated were age, weight, gender, unemployment, prior TB episodes and HIV-status. Treatment-related factors that were investigated were, the number of drugs included in the treatment of the MDR-TB episode and the number of those drugs that were considered to be effective in the treatment. Baseline drug-resistance to the first-line and second-line DSTs was also considered a treatment-related factor. Turn-around time from specimen collection to TB confirmation, specimen collection to MDR-TB confirmation and MDR-TB confirmation to MDR-TB treatment initiation were considered as health system-related factors.

Descriptive results from the study

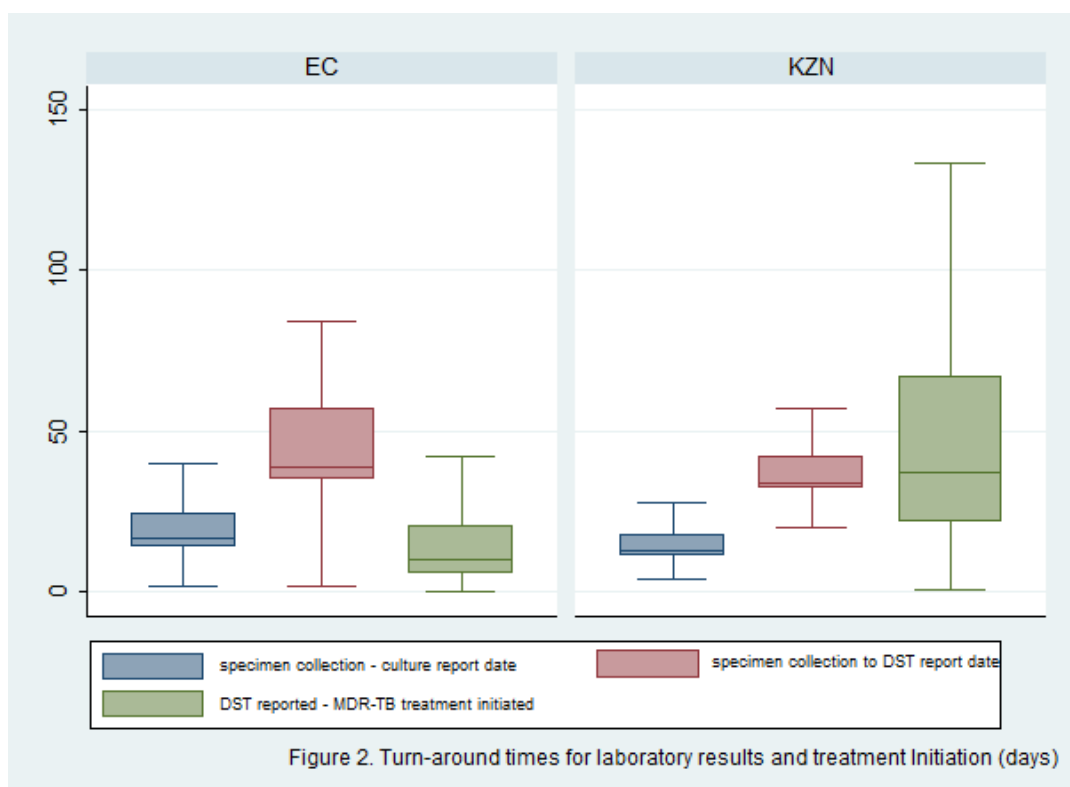
A total of 225 MDR-TB cases from EC and 197 from KZN were enrolled. All patients had a known treatment outcome except one patient from EC. Baseline DSTs done by CDC were available for 132 (59%) from EC and 99 (50%) from KZN.

The mean age at MDR-TB treatment initiation in EC was 37.3 years and in KZN, 34 years ($p=0.004$) and the mean weight was 50.3 kg and 52.8 kg respectively ($p=0.017$). Hundred and ten (49%) of patients in EC and 103 (52%) in KZN ($p=0.515$) were male. Unemployment in the EC and KZN patients was 150 (67%) and 130 (66%) respectively ($p=0.965$). The majority of patients had a prior TB episode before their MDR-TB episode started (EC: 206 (92%); KZN: 187 (95%); $p=0.224$) and only 8 patients were previously treated with second-line TB treatment. More than half of the patients in both provinces were HIV positive (EC: 120 (54%); KZN: 110 (56%); $p=0.352$) and the majority of them were smear positive at MDR-TB initiation (EC: 189 (84%); KZN: 174 (88%); $p=0.329$).

The mean number of drugs used in the MDR-TB treatment episode in both provinces was 8 drugs and the mean number of drugs that was effective during the treatment episode was 4. A drug was considered effective for treatment if it was recognized for the treatment of TB; if the patient never received the drug during a prior TB episode or received it for less than 3 months during a prior TB episode and if the patient was not resistant to the particular drug. Group 5 drugs were not considered to be effective since the efficacy of those drugs has not been determined yet.

From the baseline first-line and second-line DSTs performed by CDC, it was found that 85 (64%) of patients from EC and 34 (34%) in KZN were resistant to all four first-line drugs (rifampicin; isoniazid; streptomycin; ethambutol). Twenty six (20%) from EC were resistant to one fluoroquinolone (ciprofloxacin or ofloxacin) and 6 (6%) in KZN. Sixty seven (51%) of patients in EC were resistant to one injectable drug (kanamycin; amikacin; capreomycin) compared to 11 (11%) in KZN. 65 (49%) of patients in EC were found to be resistant to all 3 injectable drugs compared to only 8 (8%) in KZN. Twenty two (17%) of the patients in EC were found to have XDR-TB and 6 patients in KZN.

The turnaround time from specimen collection to culture reported and specimen collection to MDR-TB confirmation was more or less the same for both provinces. There was however a significant difference between the time MDR-TB was confirmed to MDR-TB treatment was initiated. In KZN the majority of patients were only started on treatment 22-67 days after MDR-TB was confirmed (Figure 2, Table 1).



Time Analysis (median [IQR];days)	EC n=224	KZN n=197	p-value (¹)
Time from specimen collected to culture reported	17 [14-25]	13 [11-18]	<0.001
Time from specimen collected to DST reported	39[35 - 57]	34 [32-43]	<0.001
Time from DST reported to MDR TB treatment started	10 [6-21]	37 [22-67]	<0.001

(¹) Mann-Whitney test statistic

Factors related to unfavourable treatment results in EC

KZN had a 53% cure rate compared to 15% in EC. The high drug resistance in EC, particularly to the injectable drugs could be a reason for the unfavourable treatment outcomes seen in the province. Also contributing to the better outcomes in KZN is the use of amikacin, which is considered to be a better drug than kanamycin. However, the time from DST report date to treatment initiation in KZN is a concern. A previous study conducted in KZN showed a high primary default rate that is linked to mortality before MDR-TB treatment initiation (2). In this same study it was concluded that mortality prior to treatment initiation is a source of bias towards improved treatment outcomes. Improved TB case detection and earlier and appropriate DR-TB treatment initiation should be considered as important indicators for health system effectiveness, not just favourable treatment outcomes. These two indicators of the health systems are important precursors for reducing mortality from TB.

The rapid time to treatment initiation in EC had no significant effect on the treatment outcomes, which emphasise the fact that early treatment initiation is just one side of the coin. The other obstacle that is faced is high baseline drug-resistance which leads to ineffective treatment and poor treatment outcomes. Already 49% of the EC patients in this study indicated baseline resistance to all three injectable drugs used in second-line DR-TB treatment. This means that for these particular patients, capreomycin cannot be used as a replacement drug. This calls for infection control measures to be strengthened to prevent the transmission of these strains.

The different treatment regimens in the two provinces could have had an impact on the treatment outcomes. The limited drugs need to be managed effectively to optimise their use. This can be done by testing for resistance at baseline and incorporating the better drug (for instance amikacin rather than kanamycin) in the regimen.

Note that the views expressed in this article are those of the author(s) and do not necessarily represent the views of PHASA.

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