PUBLIC HEALTH ACTION TO REDUCE THE BURDEN OF RIFAMPICIN RESISTANT TUBERCULOSIS

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Introduction

The global burden of multidrug-resistant tuberculosis (MDR-TB) – specifically *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid - remains high and was estimated at 450 000 incident cases in 2012 of which 170 000 cases were fatal.[1] In 2012, South Africa reported a total of 15 419 laboratory confirmed MDR-TB cases of which a treatment regimen was initiated in 6 494 (42%) cases.[1] This "gap" between diagnosis and treatment has subsequently increased with the expanded rollout of the Xpert MTB/Rif assay (GXP) and the increase in absolute numbers of rifampicin resistant cases detected.[2]

In an attempt to address this gap, the National Department of Health (NDoH) plans to appoint one linkage officer per district to enhance the tracing of patients diagnosed with rifampicin resistant tuberculosis (RR-TB) or MDR-TB and to ensure initiation of appropriate treatment. Although this process is still being rolled out, pre-existing tracer teams are already in place in some districts. In addition, the National Institute for Communicable Diseases (NICD) initiated the release of weekly alerts in January 2014. The primary objective of these alerts is to facilitate patient tracing and to improve the link between diagnosis and treatment. These alerts contain line listings of cases newly reported as RR-TB from those laboratories in South Africa using the Xpert MTB/Rif assay (GXP).[3] Alerts are sent to selected individuals in each provincial DoH and the line lists are broken down by province and district. However, this surveillance system is a one way process with a push of data and requires a feedback loop to assess effectiveness.

In order to strengthen this surveillance system, the introduction of community surveillance assistants (CSAs) has been proposed. The function of the CSAs will be to work with the existing tracer teams and follow up cases through patient tracing and interview. In addition, they will facilitate the collection of additional sputum specimens for genotyping and drug susceptibility testing at the NICD. These data will inform cluster monitoring and provide reasons for failure to initiate treatment, using a case record form (CRF). CRF forms are regularly submitted to the NICD and this information can be fed back to the NDoH in a bid to close the diagnosis – treatment gap.

A pilot study was initiated to evaluate how effectively these public health strategies improve linkage between diagnosis and care, and reduce initial loss to follow up among RR-TB cases diagnosed with GXP. Overall, it is envisaged that these strategies will decrease the burden of drug resistant tuberculosis in the selected districts.

Methods

Four districts were selected across South Africa: Francis Baard (FB - Northern Cape province), Dr Kenneth Kaunda (KK - North West Province), Nelson Mandela Metro (NMM- Eastern Cape Province) and Ehlanzeni (EZ-Mpumalanga Province). The target population included all patients diagnosed with RR-TB by GXP between 1 January and 31 March 2015. The study was nested into the existing GERMS-SA surveillance programme at the NICD. University ethics clearance as well as provincial and district approvals were obtained prior to initiation.

Community surveillance assistants (CSAs) were recruited in each district. Weekly case alerts as well as any new cases reported from the primary pathology laboratory in each district were used to regularly monitor and initiate early action. Cases in which the patient was known were followed-up at the primary diagnostic site to obtain their current treatment status. Known patients were contacted and a CRF for each patient was created. Subsequent sputum collections were taken following written informed consent from affected patients. If a patient was not known, a CSA would gather contact details from the relevant facility and either find the patient through the current tracing system or, if that failed, make an attempt to locate the patient directly and complete the process. All CRFs were sent to the NICD for data capture and further analysis. In addition, two field coordinators liaised with the field teams and performed an audit of their case tracing activities as part of the quality control process.

Results

Case numbers

A total of 286 RR-TB cases was identified via the notification system during the 3-month study period. Sixteen line listings representing exact duplicates from 8 patients were excluded. The specific reasons for exclusion were: repeated testing of patients at the same facility during the same week (N=2), repeated testing of patients at the same facility during different weeks (N=2) and repeated testing of patients at the different facilities during different weeks (N=4). One additional duplicate was identified (different 2nd name) and removed, bringing the unique line listing total to 276 cases.

Project sites

One CSA was appointed to each of the three selected sites and two CSAs were appointed to NMM-Eastern Cape based on an expected higher case burden.

The Francis Baard district revealed lower case numbers which could easily be managed by the CSA. However, patients were often scattered such that additional time and resources were required for follow-ups. Coordination with the MDR facility and the existing tracer team was very helpful for accessing patients located remotely from Kimberly.

The Dr Kenneth Kaunda district utilizes a centralized approach in which all RR-TB patients are referred to the MDR-TB unit at Tshepong hospital in Klerksdorp. This simplified the tracer requirements and thus the combined activities of the GERMS surveillance officer and the CSA were sufficient. Particular challenges for case finding in this district included referral of cases from neighbouring areas not relevant to the study and the presence of migrant workers at mines located within the district.

The Ehlanzeni district experienced a very high case load coupled to a wide geographic distribution with some cases more than 200km away. A total of 53 cases was excluded due to insufficient capacity to cover the large Bushbuckridge area using a single CSA.

The Nelson Mandela Metro has a well established and coordinated tracing system in place. In addition, the local MDR facility dedicates specific days for new MDR-TB case enrollments. Thus, coordination involving these mechanisms was used to achieve the tracing objectives. Challenges included cases being admitted outside of allocated days as well as delayed enrollment of cases into the MDR program pending confirmation of diagnosis and identification of a potentially high risk strain. These delays negatively affected the study objectives.

A total of 223 cases was thus available for inclusion in the study. The Nelson Mandela Metro experienced the highest case load compared to Francis Baard district which recorded the lowest (table 1).

Table 1: Distribution of rifampicin resistant tuberculosis (RR-TB) cases diagnosed by the Xpert MTB/RIF assay (GXP) and alerted by district during the period 1 January to 31 March, 2015.

District	Number GXP RR alerted cases	%
Dr Kenneth Kaunda	45	20
Ehlanzeni*	43	19
Francis Baard	16	7
Nelson Mandela Metro	119	52
All districts	223	100

*53 cases from the Bushbuckridge area were excluded – see text for details

Description of identified cases

The 223 cases identified were diagnosed at 103 different facilities of which of 20% of primary diagnoses came from a hospital as opposed to a clinic. The performance of each district, based on percentage of RR-TB patients diagnosed by GXP and subsequently placed on treatment, varied over the three months analyzed (figure 1). A general monthly increase in the proportion of cases placed on treatment was observed in Dr Kenneth Kaunda district while the reverse trend was evident in the other three districts. It should however be noted that the numbers for Francis Baard district are small, and that 2 of the 3 cases not placed on treatment were diagnosed on the last day of the study and were scheduled for follow up. On average, 69% of cases traced across the 4 districts were recorded as having started treatment (figure 1). Reasons for not having started treatment despite patient tracing efforts are presented in table 2.

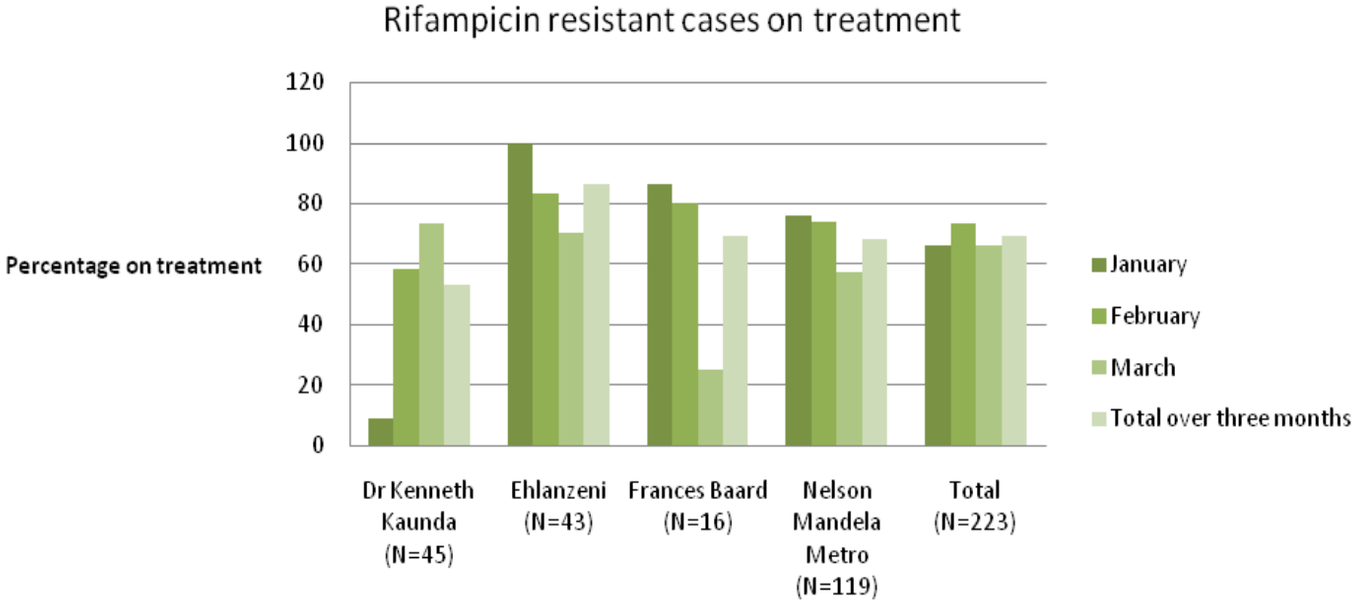

Figure 1: Percentages of rifampicin resistant tuberculosis (RR-TB) cases by district by month identified and subsequently started on treatment during the period 1 January to 31 March, 2015. Actual numbers are given in parentheses.

Table 2: Frequencies and proportions of common reasons for not initiating TB treatment despite patient tracing efforts across all districts in the study during the period 1 January to 31 March, 2015.

Reason	Number	%
Patient died	**3**	**4**
Patient refused treatment	**2**	**3**
Patient not found at address	**1**	**1**
Patient never returned	2	3
Patient moved	**1**	**1**
Patient from different district	**1**	**1**
Incorrect patient information	4	6
No tracing information	43	61
Migrant worker	3	4
Prisoner	**1**	**1**
Not done	8	11
Ongoing	**1**	**1**
Total	**70**	**100**

Numbers and percentages in bold indicate successful tracing but unsuccessful outcome (11%)

Discussion

This study provided important insights into the gap between the diagnosis of RR-TB and subsequent initiation of treatment and the issues that underlie the problem were highlighted.

Using rifampicin alerts, the majority of true RR-TB cases could be identified within a reasonable timeframe. The identification of duplicates assisted in understanding the extent and nature of the problem and improved tracing performance. An additional 29 cases that did not appear through the alerts were detected across the 4 districts. The reason(s) for this is/are unknown and should be investigated as this poses a potential problem in estimating the true case burden.

Operational challenges restricted a complete assessment of the Ehlanzeni district system and thus performance may be poorer in difficult-to-reach areas. Each district had a slightly different approach with a varying capability for patient tracing. Cases located further away from central sites required more resources to achieve follow-up. Similarly, differences in caseloads affected human resource distribution and logistical support.

The overall rate of 69% of cases notified and documented as having initiated treatment is low. This is because the GXP provides a rapid diagnosis and it therefore follows that a high rate of diagnosis should lead to a high rate of treatment initiation. No overall increase in cases on treatment by month was however observed in this study, but additional work is required to compare this data to a period preceding this project.

Other studies are being conducted to assess the impact of the GXP. Importantly, a recent report from the XTEND study showed that despite the increase in detection rate for TB (not specifically drug resistant TB), as well as rapid turnaround time of the test when

compared to smear microscopy, the GXP did not reduce initial loss to follow-up, did not increase the proportion of patients initiating treatment and did not reduce overall mortality.[4] Another feasibility study - TB-NEAT- showed that the GXP can produce rapid results in a clinic based setting with rapid initiation of treatment. However, these findings also did not translate into reduced TB-related morbidity.[5] Although the present findings were generated from a pilot study, the need to strengthen the current follow-up system is clearly evident. A feedback loop is required to close the gap between diagnosis and treatment which will enhance the impact of the GXP intervention.

Introducing the CSAs has provided a useful approach to monitoring the diagnosis-treatment gap by supporting existing follow-up structures through a supervised and a standardized reporting system that enables comparisons between sites. Of the cases that could not be traced and were not on treatment, 61% had no tracing information and 6% had incorrect tracing information. This is a major hindrance to the follow-up system and highlights several instances where documentation relating to patient contact details was lacking at the diagnosing facility or unreliable information was provided for subsequent patient tracing. These constitute areas requiring urgent attention. Of the remaining patients, 10 were successfully traced and found to have valid reasons for not being on treatment, implying that the overall rate of successful tracing was could be adjusted to 73%.

Conclusion

Diagnosing RR-TB rapidly and closing the gap between diagnosis and treatment initiation are essential tools for the reduction of TB induced morbidity and mortality. Various approaches including electronic notification systems and tracer teams are essential components of a TB control programme and resources should be allocated accordingly.

Acknowledgements

We thank the provincial and district Departments of Health for their assistance and their diligent work in tracing and managing patients in the program. We also thank the NHLS and Corporate Data Warehouse staff for their efforts in diagnosing patients, storing information and providing data for this study. Thanks are also also due to the alerts who are required to improve TB related health services. We are furthermore indebted to the community surveillance assistants (CSAs) who were employed through funding received from Clinton Health Access Initiative (CHAI).

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