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Surveillance for multi-drug and rifampicin resistant tuberculosis and treatment outcomes among previously treated persons with tuberculosis in the era of GeneXpert in rural eastern Uganda

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ABSTRACT

Rationale: Previously treated persons with bacteriologically confirmed pulmonary tuberculosis (BC-PTB) have increased risk of developing multi-drug resistant or rifampicin resistant tuberculosis (MDR/RR-TB). Surveillance for resistance is critical to identify and treat MDR/RR-TB to ensure cure and prevent transmission. There are limited studies conducted on this subject.

Objectives: We examined the frequency and factors associated with MDR/RR-TB surveillance among previously treated persons with BC-PTB, and described their treatment outcomes in rural eastern Uganda.

Methods: We reviewed treatment records for BC-PTB between January 2015 and June 2018 at 10 clinics in eastern Uganda. We collected data on demographics, surveillance for MDR/RR, use of GeneXpert and treatment outcomes. We performed bivariate and multivariate analyses. For multivariate analysis, we used the modified Poisson regression analysis with robust standard errors and stated the results as adjusted risk ratio (aRR) with 95% confidence intervals (CI). All analyses were conducted in R version 3.5.2.

Measurements and main results: We obtained records for 135 previously treated persons with BC-PTB and of these, 41 (30.4%) had undergone surveillance for MDR/RR-TB. Treatment failures were less likely to have surveillance compared to relapses (aRR, 0.28; 95% CI, 0.08–0.95), and there was an increasing trend in the likelihood for surveillance between 2015 and 2018 (aRR, 1.77; 95% CI, 1.39–2.25). There was no difference in MDR/RR-TB surveillance rate between health facilities with and without GeneXpert on-site (aRR, 1.52; 95% CI, 0.81–2.86) and between male and female patients (aRR, 0.54; 95% CI, 0.21–1.37). Overall, 92 (68.1%) previously treated persons with BC-PTB were successfully treated for tuberculosis.

Conclusions: MDR/RR-TB surveillance and treatment success rates among previously treated persons with BC-PTB in rural eastern Uganda are low. Tuberculosis programs should strengthen MDR/RR-TB surveillance and especially target those with treatment failure.

1. Introduction

Drug resistant tuberculosis is a growing global public health threat. In 2018, almost half a million cases of tuberculosis were newly diagnosed as resistant to rifampicin, the most effective first-line drug [1]. Of these cases, 78% had multidrug-resistant tuberculosis (MDR-TB) [2], a form of tuberculosis which is resistant to both isoniazid and rifampicin, the two most effective first-line anti-tuberculosis drugs [3]. Globally, 30 countries are classified by the World Health Organization (WHO) as having high MDR-TB burden [4]. The 2019 global tuberculosis report indicates that 3.4% of persons with new bacteriologically confirmed pulmonary tuberculosis (BC-PTB) diagnosis and 18% of previously treated persons with BC-PTB were either multi-drug resistant or rifampicin resistant tuberculosis (MDR/RR-TB) cases [1]. Persons with new BC-PTB diagnosis are those who have never been treated for tuberculosis or had been on treatment for less than 4 weeks. Previously treated persons with BC-PTB are those who have relapsed after, defaulted during, or failed on first line tuberculosis treatment [5]. Among persons with new BC-PTB diagnosis, MDR-TB results from the transmission of multidrug resistant *Mycobacterium tuberculosis* (MTB) strains while in previously treated persons with BC-PTB, it results from the selection of single drug resistant strains [6].

Previously treated persons with BC-PTB are more likely to have MDR/RR-TB compared to persons with new BC-PTB diagnosis [7, 8]. The latest Uganda National Drug Resistance Survey indicates that 1.4% of persons with new BC-PTB diagnosis and 12.1% of previously treated

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persons with BC-PTB have MDR/RR tuberculosis, mostly associated with urban residence and age greater than 35 years [5]. A systematic review and meta-analysis indicates that the pooled risk of MDR-TB is at least 10-fold higher in previously treated persons with BC-PTB compared to persons with new BC-PTB diagnosis, and three times higher among people living with Human Immunodeficiency Virus (PLHIV) [6]. There is a need for MDR-TB surveillance among previously treated persons with BC-PTB and persons with tuberculosis co-infected with HIV given the high risk of MDR/RR-TB. This will help to close the gap between the onset of MDR/RR-TB and its detection thus accelerating early detection of drug resistant tuberculosis. Xpert® *Mycobacterium Tuberculosis* and Rifampicin resistance (Xpert® MTB/Rif) test commonly known as GeneXpert is an effective tool for the diagnosis of pulmonary tuberculosis and MDR/RR-TB surveillance in all persons with symptoms of tuberculosis [5].

In Uganda, GeneXpert has been available on a large scale for all persons with symptoms of tuberculosis since 2017. Prior to this, GeneXpert was mainly used for MDR/RR-TB surveillance among previously treated persons with BC-PTB and PLHIV who have symptoms of tuberculosis. Presently, there is large scale expansion of GeneXpert to both urban and rural health facilities in Uganda but data are limited on the success of routine MDR/RR-TB surveillance among previously treated persons with BC-PTB. In addition, the few studies have not described treatment outcomes of previously treated persons with BC-PTB in these settings. Therefore, the primary objective of this study was to determine the level of MDR/RR-TB surveillance among previously treated persons with BC-PTB, the associated factors and treatment outcomes in rural eastern Uganda. This evidence is useful in evaluating the performance of district tuberculosis control programs and in designing context-based strategies for tackling operational and implementation challenges.

2. Methods and materials

2.1. Study design and setting

We collected data from routine records in the laboratory and tuberculosis treatment clinics at 10 health facilities in four districts in rural eastern Uganda between January 2015 and June 2018. Data were collected using an abstraction form in which the sequence of variables followed that recorded in the tuberculosis treatment register (Supplementary material I). The districts included were Soroti, Kumi, Ngora, and Serere which make up the larger Teso region of eastern Uganda, located 250 km from Kampala, the capital city. The four districts are predominantly rural and majority of residents are subsistence mixed farmers, keeping goats and cattle and tending crops for a livelihood. Data collection took place at the 10 largest tuberculosis diagnostic and treatment units in the region between April and May 2019. The study setting and dataset are fully described elsewhere [9].

Of the 10 study sites, seven had GeneXpert onsite while the remaining three had access to GeneXpert offsite but within five kilometer radius. GeneXpert for the diagnosis of pulmonary tuberculosis and MDR/RR-TB in Uganda was launched by the Ministry of Health in July 2017, at selected health facilities [10].

Peripheral health facilities without GeneXpert collect samples and transport them to sites with the service through a hub system [10]. A hub system represents the flow of samples from peripheral health facilities to health facilities with GeneXpert. In most cases, each hub system has two hub riders who collects and transports samples, and deliver the sample results between peripheral health facilities and GeneXpert sites on specific days and times of the week through a designated route. In cases of urgency for sample transportation, a back-up hub rider is available. In each district, there is a District Hub Coordinator who plans, organizes, coordinates, and manages the hub system and reports to the Regional Hub Coordinator who in turn reports to the National Hub Coordinator in the Ministry of Health.

We reviewed records at these health facilities for patient attendances that took place between January 2015 and June 2018. We retrieved data for all persons with BC-PTB but we restricted the present analysis to previously treated persons with BC-PTB.

2.2. Eligibility criteria

Patients were eligible to participate in this analysis if they had attended tuberculosis treatment clinics at the 10 health facilities between January 2015 and June 2018, and were presenting as previously treated persons with BC-PTB. Persons with new BC-PTB diagnosis were not considered for this analysis, and we also excluded patients whose previous tuberculosis treatment status could not be ascertained.

2.3. Study variables and measurements

The independent variables that we extracted included district where previously treated persons with BC-PTB received treatment, level and type of health facility ownership, whether the health facility was a GeneXpert site or not, year patient started tuberculosis treatment, age category, sex, type of previously treated persons with BC-PTB namely: relapse, treatment failure or lost to follow-up; and the HIV sero-status. Our primary outcome variable was MDR/RR-TB surveillance which was measured as the proportion of previously treated adults with BC-PTB registered in care with a GeneXpert result at the beginning of tuberculosis treatment, documented either in the tuberculosis or laboratory unit registers. In the registers, data are coded as “1″ and “0″ to indicate participants with and without MDR/RR-TB surveillance, respectively, [11].

The secondary outcome, tuberculosis treatment outcomes at the end of eight months of treatment, were defined in accordance to the WHO criteria [12] as described in Supplementary material II.

2.4. Data analysis

We computed frequencies and percentages for categorical variables such as the study outcomes, and calculated means with standard deviations for numerical data. In bivariate analysis, we present contingency tables for categorical variables and compared participants with and without MDR/RR-TB surveillance. We used the Chi-square test to determine whether there was a statistically significant difference in the distribution of these variables, by MDR/RR-TB surveillance status, and used the Fisher's exact test in these analyses, if the expected cell counts were less than five. We used the Student's *t*-test to compare means of numerical variables between the two groups. In multivariate analysis, we conducted a generalized linear model with a log-link function and Poisson regression for all variables that were statistically significant at bivariate analysis, to determine factors independently associated with the outcome variable. We reported the results as risk ratio (RR), both unadjusted and adjusted with corresponding 95% confidence intervals (CI). We used the RR as a preferred measure of effect over odds ratio (OR) because the outcome variable was very frequent and therefore the OR would overestimate the strength of the association [13]. All the data analyses were conducted in R statistical and programming language version 3.5.2 [14] at the 5% level of significance.

2.5. Human subjects' issues and ethics approval

We received ethical approval from Mbarara University of Science and Technology Research Ethics Committee, MUST-REC (reference number 03/11-18). The study also received clearance from the Uganda National Council for Science and Technology (HS 2531). We requested for a waiver of patient consent from MUST-REC because it was impractical to obtain informed consent from the study participants as this was a retrospective study. Participant records were handled

Table 1
Baseline characteristics of participants with respect to MDR/RR-TB surveillance.

Characteristics		Patient had MDR/RR-TB surveillance			*P* value
		No (n = 94)	Yes (n = 41)	Total (n = 135)	
District	Soroti	58 (61.7)	17 (41.5)	75 (55.6)	0.131
	Kumi	25 (26.6)	14 (34.1)	39 (28.9)	
	Ngora	9 (9.6)	8 (19.5)	17 (12.6)	
	Serere	2 (2.1)	2 (4.9)	4 (3.0)	
Type of health facility	Public/or government	86 (91.5)	41 (100.0)	127 (94.1)	0.126
	Private not for profit	8 (8.5)	0 (0.0)	8 (5.9)	
Level of health facility	Health Center IV	33 (35.1)	16 (39.0)	49 (36.3)	0.190
	District Hospital	17 (18.1)	12 (29.3)	29 (21.5)	
	Referral Hospital	44 (46.8)	13 (31.7)	57 (42.2)	
GeneXpert site	No	32 (34.0)	6 (14.6)	38 (28.1)	0.036
	Yes	62 (66.0)	35 (85.4)	97 (71.9)	
Year of tuberculosis treatment	2015	47 (50.0)	6 (14.6)	53 (39.3)	< 0.001
	2016	20 (21.3)	6 (14.6)	26 (19.3)	
	2017	23 (24.5)	8 (19.5)	31 (23.0)	
	2018	4 (4.3)	21 (51.2)	25 (18.5)	
Age category (years)	15–34	43 (45.7)	17 (41.5)	60 (44.4)	0.869
	35–50	26 (27.7)	13 (31.7)	39 (28.9)	
	> 50	25 (26.6)	11 (26.8)	36 (26.7)	
	Mean (SD))	40.36 (15.20)	41.54 (15.54)	40.72 (15.26)	0.682
Sex	Male	67 (71.3)	37 (90.2)	104 (77.0)	0.029
	Female	27 (28.7)	4 (9.8)	31 (23.0)	
Type of previously treated person with bacteriologically confirmed pulmonary tuberculosis	Relapse	53 (56.4)	33 (80.5)	86 (63.7)	0.016
	Failure	19 (20.2)	2 (4.9)	21 (15.6)	
	Lost to follow-up	22 (22.4)	6 (14.6)	28 (20.7)	
HIV test result	Negative	66 (70.2)	26 (65.0)	92 (68.7)	0.695
	Positive	28 (29.8)	14 (35.0)	42 (31.3)	

confidentially and data were abstracted only at clinic premises, and names were not collected in the dataset for analysis.

2.6. Reporting of study results

We adhered to the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15,16], a tool that guides the design, conduct, analysis, and reporting of cross-sectional, case-control, and cohort studies. All the tables were auto-generated in R version 3.5.2 program using the *"tableone"* package.

3. Results

3.1. Study profile, participant baseline characteristics and magnitude of MDR-TB surveillance

We retrieved 135 records of previously treated persons with BC-PTB and of these, 41 (30.4%) had surveillance for MD/RR-TB. We present the details of participants' characteristics with respect to surveillance for MD/RR-TB in Table 1. Participants who had surveillance for MDR-TB were mostly from Soroti district, government health facilities, at Health Center IV level of care, and from health facilities with GeneXpert onsite. Participants who had undergone MDR/RR-TB surveillance were similar in the distribution of their age (p = 0.682). There were statistically significant differences between the two MDR/RR-TB surveillance categories with respect to having GeneXpert site (p = 0.036), year of tuberculosis treatment (p < 0.001), sex (p = 0.029), and type of previously treated persons with BC-PTB (p = 0.038).

3.2. Treatment outcomes among previously treated persons with BC-PTB

In Table 2, we present the summary of the treatment outcomes among previously treated persons with BC-PTB. Our results showed that 59(43.7%) were cured while 33(24.4%) completed treatment, which are favorable treatment outcomes. The unfavorable treatment outcomes were distributed as follows: 11(8.1%) died; 19(14.1%) were lost to follow-up, and 10(7.4%) had missing treatment outcome. In general, 92(68.1%) of the participants were successfully treated for tuberculosis.

Table 2
Treatment outcomes among previously treated persons with BC-PTB.

Characteristics	Level	Frequency (%)
Treatment outcomes	Cured	59 (43.7)
	Completed treatment	33 (24.4)
	Failed treatment	3 (2.2)
	Died	11 (8.1)
	Lost to follow up	19 (14.1)
	Missing treatment outcome	10 (7.4)
Successful treatment	No	43 (31.9)
	Yes	92 (68.1)
	Total	135 (100.0)

3.3. Results of multivariate analysis of factors associated with MDR/RR-TB surveillance

The results of the regression analysis are presented in Table 3. In unadjusted analysis, we found MDR/RR-TB surveillance among previously treated persons with BC-PTB was high at sites that had a GeneXpert compared to those without (RR, 2.29; 95% CI, 1.04–5.00) and a temporal trend with increase in likelihood of surveillance between 2015 and 2018 (RR, 1.95; 95% CI, 1.53–2.50). However, females were less likely to undergo MDR/RR-TB surveillance compared to the males (RR, 0.36; 95% CI, 0.14–0.94), while those with treatment failure (RR, 0.25; 95% CI, 0.06–0.96) and lost to follow-up (RR, 0.56; 95% CI, 0.26–1.20) were less likely to undergo surveillance for MDR/RR-TB relative to relapse cases. In adjusted analysis, there was an increasing trend in the likelihood for MDR/RR-TB surveillance between 2015 and 2018 (aRR, 1.77; 95% CI, 1.39–2.25), while patients with treatment failure were significantly less likely to undergo MDR/RR-TB surveillance compared to relapse cases (aRR, 0.28; 95% CI, 0.08–0.95).

Although the unadjusted analysis (RR, 2.29; 95% CI, 1.00–5.00) was borderline significant, there was no significant difference in MDR/RR-

Table 3
Regression analysis results of factors associated with MDR/RR-TB surveillance.

Variable	Level	Modified Poisson regression analysis			
		Unadjusted analysis (RR, 95% CI)		Adjusted analysis (aRR, 95% CI)	
GeneXpert at site	No	Ref		Ref	
	Yes	2.29*	(1.04,5.00)	1.52	(0.81,2.86)
Year of treatment	2015	Ref		Ref	
	1 year increase	1.95***	(1.53,2.50)	1.77***	(1.39,2.25)
Sex	Male	Ref			
	Female	0.36*	(0.14,0.94)	0.54	(0.21,1.37)
Type of previously treated persons with bacteriologically confirmed pulmonary tuberculosis	Relapse	Ref		Ref	
	Failure	0.25*	(0.06,0.96)	0.28*	(0.08,0.95)
	Lost to follow-up	0.56	(0.26,1.20)	0.66	(0.32,1.39)

Note: (1) *$p < 0.05$;
*** $p < 0.001$ at 5% significance level; (2) All risk ratios (RR) and 95% confidence intervals (CI) in brackets (3) aRR: Adjusted RR; (4) RR: Unadjusted RR.

TB surveillance between health facilities with and without GeneXpert (aRR, 1.52; 95% CI, 0.81–2.86) at the adjusted analysis. There was also no significant difference in MDR/RR-TB surveillance for male and female participants (aRR, 0.54; 95% CI, 0.21–1.37).

4. Discussion

Our study among previously treated persons with BC-PTB in rural Uganda shows that only about three in 10 received surveillance for MDR-RR TB. This is far below the national target of 80% [5] and the global rate of 51%, estimated in 2018 [1]. The suboptimal MDR/RR-TB surveillance is an indication that a considerably large number of previously treated persons with BC-PTB who have MD/RR-TB miss the opportunity for early diagnosis and treatment. This increases the risk of transmission of MDR-TB at both household and community levels thus worsening tuberculosis morbidity and mortality. Our findings signal lapses in the delivery of services in accordance to national tuberculosis control guidelines at district level and implies that increased efforts are needed to address the low MDR/RR-TB surveillance. A previous study found that scaling up GeneXpert should be combined with health system interventions, namely daily transporting of sputum to GeneXpert sites, text message communication of GeneXpert results to peripheral health facilities, performance feedback through quality improvement frameworks, and single sample led fluorescence microscopy to facilitate effective implementation and ensure high quality care to persons with tuberculosis [17].

MDR/RR-TB surveillance showed a trend towards a path of improvement over the three year period that the data were collected. We interpret this with caution because this analysis was not designed to explain the improvements. Although they were only modest improvements, the reasons should be intriguing given the low level of surveillance. The likely explanation may lie with improvements in the strength of the district health system. In a qualitative study in this region [18], a high rate of treatment success was attributed to improvement in staffing levels, enhanced technical expertise of healthcare workers in tuberculosis care through mentorships and coaching, and the introduction of novel interventions such as continuous quality improvement to address gaps in tuberculosis outcome. These activities are consistent with the WHO guidelines on a good health system. According to the WHO [19], a strong health system is one that has a well-performing health workforce which is available, competent, responsive, and productive in achieving the best possible health outcomes in addition to a functional health information system.

Our study indicates that previously treated persons with BC-PTB who had earlier failed treatment were less likely to have MDR/RR-TB surveillance compared to the relapse cases. To the best of our knowledge, there are no prior studies to corroborate this finding and the explanation is not obvious. It is not clear whether this is a decision based on clinical judgment by the healthcare workers. Further studies are needed to explore this finding in detail.

We found no statistically significant differences in MDR/RR-TB surveillance between health facilities with and without GeneXpert onsite. We anticipated that health facilities with testing services on site would be more likely to have MDR/RR-TB surveillance done, but this was not the case. In our setting, seven of the 10 study sites had a GeneXpert onsite and those without were able to access GeneXpert within five kilometer radius. This finding is limiting since only three of the 10 study sites had no GeneXpert and only few sputum samples were not examined. There is a possibility that this analysis lacks sufficient power to detect a statistically significant difference. Despite this concern, the findings indicate that in the midst of limited resources, GeneXpert need not be placed at all health facilities, but can be located at geographically convenient health facilities, within easy reach of the contiguous health facilities [20]. Further research may need to be done to examine additional strategies and considerations to ensure health facilities are within easy reach of GeneXpert.

Our data shows a treatment success rate of 68%, which is much lower than the WHO desired target of at least 90% treatment success rate [21]. However, the present treatment success rate is comparable to the global treatment success rate among retreatment tuberculosis cases [2]. The low treatment success rate among previously treated persons with BC-PTB is consistent with several other studies in Uganda [22–24], all of which paint a picture of doom and gloom regarding treatment success for previously treated persons with BC-PTB. Our result shows that a significant proportion of previously treated persons with BC-PTB have unfavorable treatment outcomes due to treatment failure, mortality, relapse, and lost to follow up. In a recent meta-analysis [25], lower treatment success rate among previously treated persons with BC-PTB was linked to drug fatigue resulting from high pill burden and long treatment duration that compromised treatment adherence [26,27]. Overall, tuberculosis treatment programs need to figure out mechanisms to improve outcomes for previously treated persons with BC-PTB.

We found a mortality rate of 8.1% which is much lower than that reported in several cohorts of previously treated persons with BC-PTB in sub Saharan Africa. For instance in Ghana [28], one study reported mortality of 20%. A study at the tuberculosis treatment unit of Mulago National Referral Hospital [29] reported mortality of 62% in their cohort of previously treated persons with BC-PTB. There are fundamental differences between the Ghana and Mulago studies. In the Ghana cohort, the study included persons with extrapulmonary tuberculosis which is a poor prognostic factor. In the Mulago study, the study participants were urban and majority referral, and the follow-up period to determine mortality was also long term. The observed differences in mortality could have resulted from variations in the proportions of HIV infection in the two cohorts. Although HIV infection is a known risk factor for tuberculosis disease and increased risk for mortality, as was demonstrated in a Ghanaian cohort, this was not the case in our cohort. It is not clear what the long term mortality is like in our treatment

cohort but is likely to rise from what we have reported in our results.

Although the sample size is small, our study has generated novel information on MDR/RR-TB surveillance that has potential to inform tuberculosis programs in decision making regarding where to place GeneXpert. Accordingly, more data are required to support the design of mechanisms to increase MDR/RR-TB surveillance using GeneXpert. Our study has other limitations as well. As expected with record reviews, there were cases of some missing data. Some previously treated persons with BC-PTB were lost to follow up and it is not clear whether those lost might have had worse or better outcomes than those who remained in treatment. We might have underestimated our mortality rate if those lost to follow-up were more likely to die compared to those who stayed in the program. Secondary data does not permit the investigation of certain factors that potentially influence MDR/RR-TB surveillance such as health systems-related factors. We conducted this study in a rural setting and the results may have limited external validity for urban health facilities. Our study should not be considered as an assessment of the impact of MDR/RR-TB surveillance due to study design limitations. The analysis of secondary data could not permit the investigation of other reasons for poor use of GeneXpert in previously treated persons with BC-PTB such as challenges in specimen transportation, delays in specimen processing, physician knowledge, and patient factors such as refusal among others. Lastly, our sample size was small because many study sites have low numbers of participants.

To obtain a sufficiently large sample size, one would require to recruit from many sites, which we attempted. Despite this measure, there is a possibility that this analysis lacks sufficient power to detect a statistically significant difference.

5. Conclusion

In conclusion, our study found very low levels of MDR/RR-TB surveillance and treatment success rate among previously treated persons with BC-PTB in rural eastern Uganda, although the surveillance has increased between 2015 and 2018. Previously treated persons with BC-PTB who had in the past failed treatment were less likely to have MDR/RR-TB surveillance compared to relapse cases. We recommend the implementation of interventions that can improve surveillance for MDR/RR-TB at these sites. More research should be done to examine how GeneXpert can be made accessible at health facilities in rural areas.

Declaration of Competing Interest

None declared.

Ethical statement

We received ethical approval from Mbarara University of Science and Technology Research Ethics Committee, MUST-REC (reference number 03/11-18). The study also received clearance from the Uganda National Council for Science and Technology (HS 2531).

We requested for a waiver of patient consent from MUST-REC because it was not practical to obtain informed consent from the study participants as there was no means to reach them, and second, the number of participants retrieved in the dataset was very large. Participant records were handled confidentially and data were abstracted only at clinic premises, and names were not collected in the dataset for analysis.

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CRediT authorship contribution statement

Jonathan Izudi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Visualization, Writing - original draft, Writing - review & editing. **Imelda K Tamwesigire:** Methodology, Supervision, Writing - review & editing. **Francis Bajunirwe:** Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2020.100153.

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