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SHORT COMMUNICATION

Increase in rifampicin resistance among people previously treated for TB

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People previously treated for TB are at a higher risk of rifampicin-resistant or multidrug-resistant TB (RR/MDR-TB). Uganda's recent RR-TB estimates were not updated, including during the COVID-19 pandemic. Using programmatic data (2012–2021), we report on the distribution and trends in RR-TB among people previously treated for bacteriologically confirmed pulmonary TB (BC-PTB) across six TB clinics in Kampala, Uganda. The RR-TB prevalence between 2012 and 2015 was 0% (95% CI 0–2.3). The prevalence rose significantly in recent years to 7.0% (95% CI 4.4–10.8) between 2016 and 2021 ($P < 0.001$). RR-TB is increasing among people previously treated for BC-PTB in Kampala; surveillance for RR-TB should be enhanced.

Drug-susceptible pulmonary TB is treated with a 6-month regimen comprising first-line drugs: isoniazid (H), rifampicin (RIF, R), ethambutol (E) and pyrazinamide (Z) (2RHZE/4RH)*.[1] However, resistance to either RIF or isoniazid or both (defined as multidrug-resistant TB [MDR-TB]) continues to undermine effective TB control globally.[1] People with RIF-resistant tuberculosis (RR-TB) or MDR-TB are treated with second-line anti-TB drugs, an expensive (US$1,000/person) and lengthy (9–12 months) regimen, with serious side effects and suboptimal treatment success rates of 50–75%. People previously treated for TB are at a higher risk of RR/MDR-TB than people with a new diagnosis of TB.[2,3] About 18–21% of people previously treated for TB develop either RR-TB or MDR-TB.[1]

Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), a rapid molecular test, offers a quick turnaround time for diagnosing drug-susceptible and RR-TB. In Uganda, Xpert testing is not available in lower-level health facilities but is deployed in hospital and county-level health facilities. Peripheral health facilities access Xpert testing through a hub system. However, Xpert testing faces implementation challenges such as a lack of local capacity to provide timely troubleshooting and maintenance services, and the need for backup batteries to ensure continued testing or charging in places with frequent power outages.[4]

Past national surveillance data show that the prevalence of RR-TB in Uganda increased between 2014 and 2018.[5] However, these estimates have not been updated recently, including during the COVID-19 pandemic. We describe here the distribution and trends in RR-TB among people aged ⩾15 years previously treated for bacteriologically confirmed pulmonary TB (BC-PTB) across six large TB clinics in Kampala, Uganda, based on retrospectively abstracted data between January 2012 and December 2021. People with BC-PTB were excluded if RIF resistance status was unknown. The full dataset is described elsewhere.[6] The variables abstracted included health facility-level data and demographic and clinical data of people with BC-PTB, including age, sex, prior TB treatment status, year of TB diagnosis and treatment, HIV status, baseline mid-upper arm circumference (MUAC), baseline weight, baseline RIF resistance status, and baseline sputum smear grade.

People with RIF resistance detected or those with indeterminate results were deemed to have RR-TB, while those with undetected RIF resistance were considered not RR. Sputum smear grade ⩾2+ was considered high, while 1+ and scanty were regarded as low. MUAC was measured using the WHO colour-coded tape marked green, yellow and red to signify no, moderate and severe malnutrition, respectively.

We summarised numerical data as means and standard deviations, and categorical data as frequencies and percentages. χ^2 or Fisher's exact test was used to compare differences in the prevalence of RR-TB with categorical variables. The Student's *t*-test was used to compare mean differences in RR-TB with numerical data. Time trends in RR-TB were analysed using a plot of RR-TB prevalence against the year of TB diagnosis, compared with the average yearly increase in RR-TB. However, as the relationship between time and RR-TB prevalence was non-linear, we used a generalised additive model, a flexible modelling approach, to account for the non-linearity by fitting a spline term for time in the trend analysis.

Of 675 people (age: ⩾15 years) previously treated for TB, 196 (29.0%) were excluded: 195 did not have BC-PTB and one person had BC-PTB but unknown RR-TB status. We therefore analysed data on 479 participants, and found that 19 (4.0%) had RR-TB. RR-TB was more common among those who sought care at Health Centre IV level, were males, aged 35–44 years and diagnosed with TB in 2020. Statistically significant differences in RR-TB were observed concerning the year of RR-TB diagnosis and baseline body weight (Table 1). RR-TB prevalence between 2012 and 2015 was 0% (95% confidence interval [CI] 0–2.3; Figure).

*H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; numbers before the letters indicate the duration in months of the phase of treatment.

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TABLE Distribution of participant characteristics according to RR-TB status

Variables	Level	Overall (*n* = 479) *n* (%)	RR-TB		*P* value
			No (*n* = 460) *n* (%)	Yes (*n* = 19) *n* (%)	
Level of health centre	III	237 (49.5)	231 (50.2)	6 (31.6)	0.174
	IV	242 (50.5)	229 (49.8)	13 (68.4)	
Sex	Female	135 (28.2)	128 (27.8)	7 (36.8)	0.551
	Male	344 (71.8)	332 (72.2)	12 (63.2)	
Age group, years	15–24	70 (14.6)	69 (15.0)	1 (5.3)	0.358
	25–34	179 (37.4)	174 (37.8)	5 (26.3)	
	35–44	139 (29.0)	132 (28.7)	7 (36.8)	
	45–54	69 (14.4)	65 (14.1)	4 (21.1)	
	⩾55	22 (4.6)	20 (4.3)	2 (10.5)	
	Mean ± SD	34.9 ± 10.8	34.7 ± 10.7	39.5 ± 12.0	0.053
Year of TB treatment	2012	87 (18.2)	87 (18.9)	0 (0.0)	0.002
	2013	94 (19.6)	94 (20.4)	0 (0.0)	
	2014	15 (3.1)	15 (3.3)	0 (0.0)	
	2015	10 (2.1)	10 (2.2)	0 (0.0)	
	2016	28 (5.8)	27 (5.9)	1 (5.3)	
	2017	25 (5.2)	21 (4.6)	4 (21.1)	
	2018	38 (7.9)	36 (7.8)	2 (10.5)	
	2019	62 (12.9)	57 (12.4)	5 (26.3)	
	2020	64 (13.4)	58 (12.6)	6 (31.6)	
	2021	56 (11.7)	55 (12.0)	1 (5.3)	
Type of patient with retreatment BC-PTB	Relapse	477 (99.6)	458 (99.6)	19 (100.0)	1.000
	Treatment after failure	2 (0.4)	2 (0.4)	0 (0.0)	
MTB load	1+	214 (44.7)	201 (43.7)	13 (68.4)	0.059
	⩾2+	265 (55.3)	259 (56.3)	6 (31.6)	
Baseline weight, kg	Mean ± SD	50.8 ± 17.0	51.4 ± 16.2	35.6 ± 26.0	<0.001
MUAC	Green	389 (81.2)	372 (80.9)	17 (89.5)	0.583
	Yellow	28 (5.8)	27 (5.9)	1 (5.3)	
	Red	62 (12.9)	61 (13.3)	1 (5.3)	
HIV status	Negative	181 (37.8)	173 (37.6)	8 (42.1)	0.043
	Positive	158 (33.0)	148 (32.2)	10 (52.6)	
	Unknown	140 (29.2)	139 (30.2)	1 (5.3)	

RR-TB = rifampicin-resistant TB; SD = standard deviation; BC-PTB = bacteriologically confirmed pulmonary TB; MTB = *M. tuberculosis*; MUAC = mid-upper arm circumference.

The prevalence rose significantly in recent years (2016–2021) to 7.0% (95% CI 4.4–10.8; $P < 0.001$).

We observed an increase in RR-TB prevalence between 2012 and 2022 that peaked at approximately 32% in 2020, which is higher than the previous estimates of 23.5% in southwestern Uganda[7] and 16.7% per national data in Uganda.[8] These data highlight the need for enhanced surveillance of RR-TB, including universal testing for RIF resistance. Between 2011 and 2015, Uganda restricted Xpert testing to people with a previous history of TB treatment. From 2019 onwards, testing was expanded to include all people with TB regardless of treatment history.[5] However, nearly 30% (196/475) of people previously treated for TB were excluded as their RR-TB status was unknown. Thus, RR-TB prevalence may be higher than what is reported here, further underscoring the critical importance of scaling up and ensuring access to molecular testing for RIF resistance at the time of TB diagnosis.

The increase in RR-TB prevalence is consistent with a previous Ugandan study that reported an increasing trend between 2014 and 2018.[5] The absence of RR-TB between 2012 and 2015 may be attributable to limited access to Xpert testing in the country at the time. The increase in RR-TB between 2015 and 2020 likely reflects the scale-up of Xpert testing across health facilities. RR-TB prevalence declined in 2021, potentially reflecting interruptions in the delivery of TB care due to the COVID-19 pandemic.[1] The strengths of our study include being the first study to report trends in RR-TB among previously treated people with BC-PTB in Uganda and the large sample size compared to previous studies. Limitations include a lack of data on factors that influence development of RR-TB, including the type of anti-TB regimen, duration of TB treatment, adherence to TB treatment and quality of anti-TB drugs, among others. As the RR-TB data concern only those who had accessed the study sites, the estimate may not accurately reflect the full burden of RR-TB in the community.

In summary, RR-TB prevalence has increased between 2012 and 2021 among previously treated people with BC-PTB. Improving surveillance for RR/MDR-TB through universal access to Xpert testing across TB clinics in Kampala and beyond is needed.

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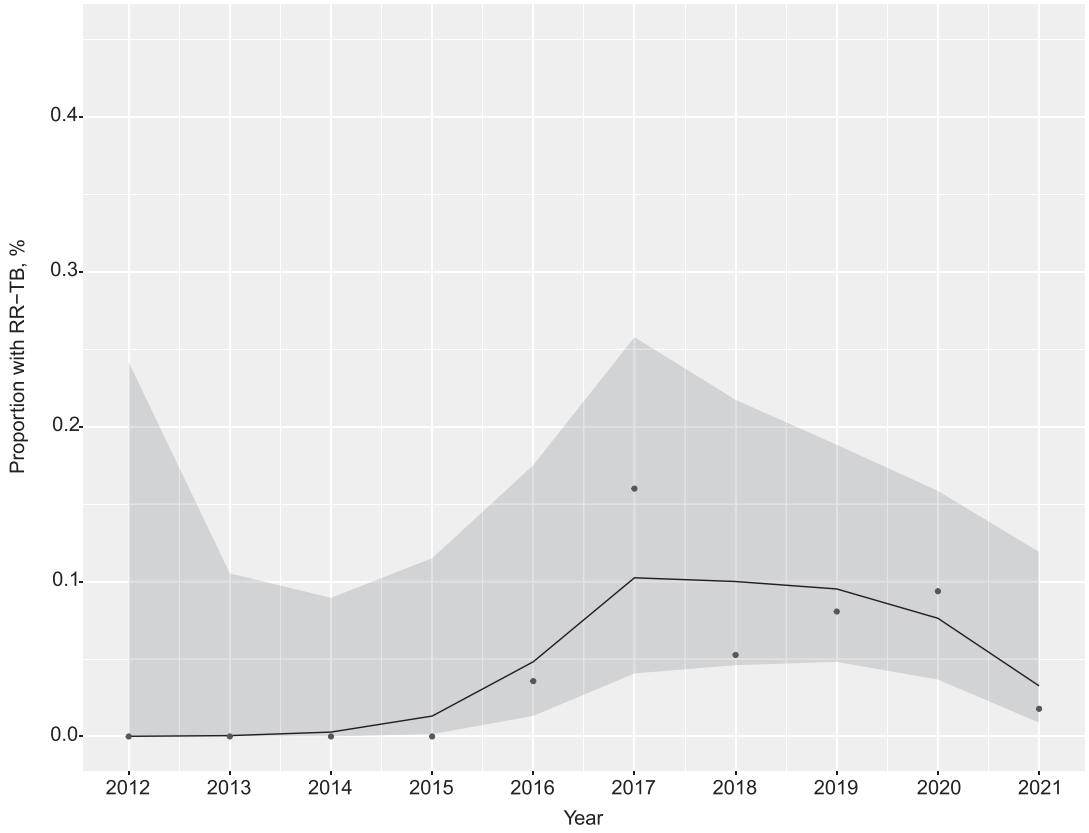

FIGURE Trend of RR-TB between 2012 and 2021. RR-TB = rifampicin-resistant TB.

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Les personnes précédemment traitées pour TB sont à plus haut risque de TB résistante à la rifampicine ou de TB multirésistante (RR/MDR-TB). Les estimations récentes de l'Ouganda sur la RR-TB n'ont pas été mises à jour, y compris pendant la pandémie de COVID-19. À l'aide de données programmatiques (2012–2021), nous présentons un rapport sur la distribution et les tendances de la RR-TB chez les personnes précédemment traitées pour une TB pulmonaire confirmée bactériologiquement (BC-PTB) dans six cliniques antituberculeuses de Kampala, Ouganda. La prévalence de la RR-TB entre 2012 et 2015 était de 0% (IC 95% 0–2,3). Une augmentation significative de sa prévalence a toutefois été observée au cours des dernières années, atteignant 7,0% (IC 95% 4,4–10,8) entre 2016 et 2021 ($P < 0{,}001$). La RR-TB est en augmentation chez les personnes précédemment traitées pour BC-PTB à Kampala ; la surveillance de la RR-TB doit donc être renforcée.

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