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Tuberculosis transmission in Households of Pulmonary Tuberculosis Patients with Alcohol use in the Puducherry Region

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ABSTRACT

Introduction: Tuberculosis control remains an ongoing challenge for low and middle-income countries with lack of understanding of the factors determining transmission of infection. This study aimed to investigate the impact of alcohol use among pulmonary tuberculosis patients on transmission to their household contacts in Puducherry and adjoining districts of Tamil Nadu, India.

Methodology: Data from a large-scale cohort comprising TB patients and their household contacts were analyzed. Alcohol consumption was assessed using the Alcohol Use Disorders Identification Test (AUDIT) questionnaire, while the infection was evaluated via the Mantoux test using an approved Tuberculin/PPD product. Mediation analysis explored the relationship between alcohol consumption, TB infection, and potential mediators.

Results: A substantial proportion of TB patients reported alcohol use (59.9%), and a significant association was found between smear positivity and LTBI infection among household contacts. Its reported prolonged exposure to tuberculosis was reported, with a majority (76.1%) spending >6 hours/day in proximity. However, lower LTBI positivity of 43.1% (95% CI 37.4%, 48.6%) was observed among the HHCs of TB patients with high-risk of alcohol use as compared to 53.9% (95% CI 51.2%, 56.5%) in the HHCs of ICs with low risk of alcohol. Alcohol use was associated with decreased time spent with household contacts, partially mediating the relationship between alcohol use and LTBI.

Conclusion: The study underscores the complex interplay between alcohol use, transmission dynamics, and household interactions. Strategies targeting alcohol reduction alongside TB control efforts are crucial for mitigating the transmission. Addressing alcoholism is imperative in TB control interventions. Further research is needed to elucidate transmission dynamics and develop targeted interventions.

Keywords: tuberculosis, alcohol use, household contacts, transmission, smear positivity, LTBI

Introduction

Tuberculosis (TB) remains a critical health issue as it affects numerous individuals across the world even today, continuing to be one of the leading causes of morbidity and mortality worldwide. Ongoing advancements in preventative procedures and treatment seem to witness limited progress when battling this disease in low and middle-income countries. According to the World Health Organization (WHO) report 2023, every year approximately 10 million people fall ill with TB and it resulted in 1.3 million deaths worldwide in 2022[1]. India, with its large population and high burden of TB, bears a substantial share of the global TB epidemic. In 2020, an estimated 2.42 million people developed TB in India[2].

In order to effectively control TB burden in India, targeted research needs to be conducted to identify different factors that contribute to tuberculosis transmission. Alcohol consumption has been identified as one of the possible risk factors. Alcohol consumption is high in India and especially high in the Puducherry region[3,4]. Alcoholism can have a significant impact on tuberculosis patients, both in terms of transmission and disease severity. Studies show that alcohol use increases the bacterial load in respiratory secretions, thereby making alcoholic TB patients more likely to transmit the disease to others. In addition, alcohol abuse also weakens the immune system, making them more susceptible to TB infection as well as increasing the likelihood of progression from latent TB infection to active TB disease[5]. This amplifying effect makes tuberculosis treatment more difficult, leading to higher sputum-positive rates. Patients with alcohol use have also been found to have lower adherence to treatment. Therefore, people who consume alcohol are at increased risk of contracting tuberculosis and are at increased risk of transmitting tuberculosis. With 60% of TB patients in Puducherry having a history of alcohol use, transmission associated with alcohol use in TB patients, therefore, needs to be understood.

Transmission of TB within households has been the focus of most TB transmission studies. Household transmission accounts for a significant proportion of all tuberculosis cases spread across India. We have previously reported the prevalence of latent tuberculosis infection (LTBI) among household contacts (HHC) in Pondicherry as 52.6%[6]. Close and prolonged contact with an infectious TB patient significantly increases the risk of transmission within households. Household members, especially those living in crowded and poorly ventilated spaces, are particularly vulnerable to contracting TB from an infected individual[7]. However, TB can spread among the extra-household contacts who spend time with TB patients, which is less well studied. Lack of knowledge on the settings where transmission is probably happening and an oversight of the extra-household contacts, especially those with higher susceptibility due to alcohol use, may lead to less than desired effects of the programmatic interventions targeted only on household contacts[8].

We are investigating the association of alcohol use among pulmonary TB patients and TB infection in their household contacts in Puducherry region, with the aim of deducing the settings where the transmission is happening from the TB patients with alcohol use.

Methodology

A cross-sectional analysis of data was done from a large-scale ongoing cohort study conducted under the Regional Prospective Observational Research for Tuberculosis (RePORT)-India Consortium[9]. The study included two cohorts: the first cohort (cohort A) comprised new sputum smear positive pulmonary TB patients (PTB) from tuberculosis units (TUs) in three districts in South India (one TU from Pondicherry and two TUs each from Cuddalore and Villupuram) recruited between 2014 and 2018. The second cohort consisted of household contacts (HHCs) - adults and children of TB patients in Cohort A who did not have active TB but had recent exposure (within the past three months) to the index case (IC) from Cohort A. Households with a minimum of three members, including the index case, were enrolled in the second cohort. HHCs were recruited within seven days of the IC starting anti-tuberculosis therapy. A total of 1523 HHCs of 538 ICs were enrolled in the parent study. The parent study excluded participants with psychiatric conditions that could potentially interfere with giving informed consent. The study included basic sociodemographic details, clinical characteristics, the exposure of household contacts to index cases, smear positivity and the time spent with households. Alcohol Use Discorder Identification Test (AUDIT) questionnaire was used to categorize the ICs to high and low risk of hazardous use of alcohol. A cut off score ≥ 8 was considered to have high risk of hazardous use of alcohol or alcohol addiction. For assessment of LTBI in the HHCs, TST by Mantoux method was performed using an approved Tuberculin/PPD product (Tuberculin RT 23 SSI). Participants having an induration of ≥ 5 mm are being considered as positive for LTBI in our analysis.

Ethical approval for the study protocol was granted by the JIPMER Scientific Advisory Committee and the Institutional Ethics Committee of JIPMER. Additionally, the study also obtained approval

from the institutional review boards at Boston Medical Center and Rutgers New Jersey Medical School. Informed consent was obtained from adults (≥18 years), while for participants under 18 years, parental consent was obtained in addition to the assent form.

Data was entered into a Microsoft Access database, and analysis was conducted using Stata version 14.2 software. The characteristics of participants were summarized as mean and standard deviation, frequency and percentages. A chi-square test was performed to find the association between the smear positivity of the index case and the LTBI infection among household contacts with a low and high risk of hazardous use of alcohol. Factors with P-values less than 0.05 were considered statistically significant.

Furthermore, a mediation analysis was conducted to investigate the relationship between alcohol use of the IC and LTBI, with the smear status of ICs and time spent by the IC at the house as potential mediators. The mediation analysis was conducted using a bootstrapping method to estimate the indirect effects and their 95% confidence intervals.

Results

We analysed data of 538 IC and 1523 of their HHCs included in the study. The majority of active TB cases were in the age group of 40-60 years (55.9%) and were predominantly male (78.6%). Among the active PTB patients, a significant proportion were married (75.3%) and had a high school level of education (51.1%). Additionally, 65.1% of active TB patients were underweight (<18.5), current smokers (26.2%), and reported alcohol use (59.9%). Majority of the TB patients were employed (75.7%), and a substantial proportion had a family income in the range of INR 5000-10000 (40.1%). (Table 1)

The largest proportion of the HHCs belonged to the age group of 20-40 years (48.3%). Females constituted the majority among HHCs (60.2%), and nearly half of them were unmarried (49.5%). The highest proportion of HHCs (38.1%) had education up to the high school. A considerable proportion (32%) of HHCs were underweight (BMI <18.5) and reported never smoking (92.1%). However, a relatively low percentage reported alcohol use (10.4%) (Table1).

Table 1: Epidemiological and socio demographic characteristics of the patients with active Pulmonary Tuberculosis (N=538) and their Household Contacts (N=1523)

Characteristics	Group	Active TB case N (%)	Household Contacts N (%)
Age	<20	13 (2.4)	337(22.1)
	20-40	157 (29.2)	735 (48.3)
	40-60	301 (55.9)	366 (24)
	>60	67 (12.5)	85(5.6)
Gender	Male	423(78.6)	606 (39.8)
	Female	115(21.4)	917 (60.2)
Marital status	Unmarried	97 (18)	754 (49.5)
	Married	405 (75.3)	698 (45.8)
	Separated/Widow	36 (6.7)	71 (4.7)
Educational status	No education	84 (15.6)	196 (12.9)
	Primary	77 (14.3)	152 (10)
	High	275 (51.1)	759 (49.8)
	Higher Secondary	50 (9.3)	195 (12.8)
	Graduate	52 (9.7)	221 (14.5)
BMI	Underweight	350 (65.1)	487 (32)
	Normal	149 (27.7)	648 (42.5)
	Overweight	21 (3.9)	286 (18.8)
	Obese	18 (3.3)	102 (6.7)
Smoking	Never smoker	277 (51.5)	1403 (92.1)
	Current	141 (26.2)	108 (7.1)
	Ex-Smoker	120 (22.3)	12 (0.8)
Alcohol use	Yes	322 (59.9)	159 (10.4)
	No	216 (40.1)	1364 (89.6)
Average number of Household per TB patients is 3			

Among all ICs, 50% had a higher smear grading; a significantly higher proportion of 83% with high-risk of alcohol use had higher sputum smear grades as compared to 44% of the others. Time to detection in MGIT was <8 days in 44% of the ICs with low-risk of alcohol use and 49% in those with high-risk alcohol use. We found that 73% of active TB patients reported being unable to perform normal activities, scoring below 80 on the Karnofsky's performance scale. Out of the ICs with high-risk alcohol use, 84% were in this category when compared to 72% of those having low-risk alcohol use, which was statistically significant. The duration from symptoms to diagnosis was $\geq$ 4 weeks in 70% among index cases without much difference between those with high or low risk of alcohol use (Table 2).

Table 2: Clinical characteristics of the active TB patients

Characteristics	Group	Active TB case N (%)	Active cases with low risk of alcohol use (475)	Active cases with high risk of alcohol use* (63)	P value
Smear grading	Low	277 (51)	266 (56)	11 (17)	**P<0.001**
	High	261 (49)	209 (44)	52 (83)	
Time to Detection	<8 days	238 (44)	207 (44)	31 (49)	0.152
	8-15 days	264 (49)	239 (50)	25 (40)	
	>15 days	36 (7)	29 (6)	7 (11)	
Severity of Disease (KS score)	Able to do Normal activity (≥80)	144 (27)	134 (28)	10 (16)	**0.036**
	Not able to do Normal activity (<80)	394 (73)	341 (72)	53 (84)	
Duration from symptoms to diagnosis	< 4 weeks	146 (27)	128 (27)	18 (29)	0.785
	≥4 weeks	392 (73)	347 (73)	45 (71)	

* *High-risk of alcohol use is defined as AUDIT score of $\geq$ 8*

About 11.2% of household contacts reported sharing meals at least two times in a day with the ICs without any difference between the HHCs of ICs with high or low risk of alcohol use. However, we found that a major proportion of household contacts (76.1%) reported spending more than 6 hours per day in close proximity to the active TB patients, this being much lesser in the HHCs of ICs with high-risk of alcohol use (52.5%) and statistically significant. On assessing the sleeping habits of the HHCs in relation to the ICs we observed that a significantly higher proportion of HHCs shared the same bed with the ICs with low-risk alcohol use as compared to the HHCs of ICs with high-risk alcohol use (28.3% vs 14.5%). (Table 3).

Table 3: Details of exposure of household contacts to their index cases

Characteristics	Group	Total Household contacts (1523)	HHC of active TB patients with low risk of alcohol use (1344)	HHC of active TB patients with high risk of alcohol use (179)	P Value
Meal sharing	None	274	248 (18)	26 (14)	0.403
	≤2	1081	947 (71)	134 (75)	
	>2	168	149 (11)	19 (11)	
Time spent each other	<6 hours	364	279 (21)	85 (48)	**P<0.001**
	≥ 6 hours	1159	1065 (79)	94(52)	
Sleeping habit	Same room, same bed	407	381 (28)	26(14)	**0.001**
	Same room different bed	616	532(40)	84(47)	
	Same building, different room	465	403(30)	62(35)	
	Different building	35	28(2)	7(4)	

The overall LTBI positivity in the HHCs in our study being 52.5%, we observed a lower LTBI positivity of 43.1% (95% CI 37.4%, 48.6%) among the HHCs of TB patients with high-risk of alcohol use as compared to 53.9% (95% CI 51.2%, 56.5%) in the HHCs of ICs with low risk of alcohol with non-overlapping confidence intervals, whereas the proportion with higher smear grades was nearly

double in ICs with high-risk of alcohol use as compared to low-risk alcohol use (83% vs 44%). (Figure 1)
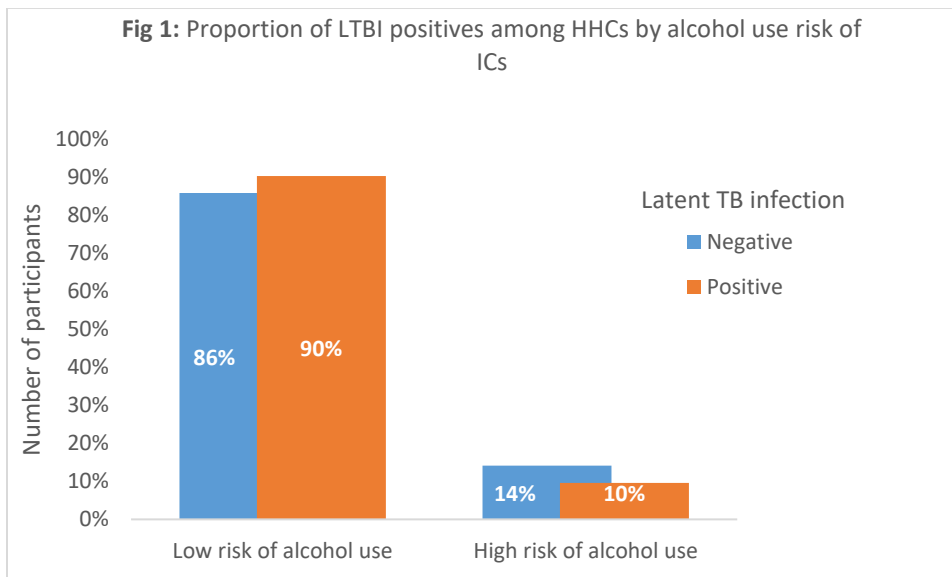
Overall, high sputum smear positivity of the TB patients was not associated with higher LTBI positivity in HHCs (*p =0.77*). We stratified the analysis based on the level of alcohol use of the IC. In the ICs with low risk alcohol use, we observed 2% points lower LTBI positivity among the HHCs of ICs with high smear grades as compared to 9% points higher LTBI positivity in HHCs of ICs with high risk alcohol use, neither of the differences being statistically significant.
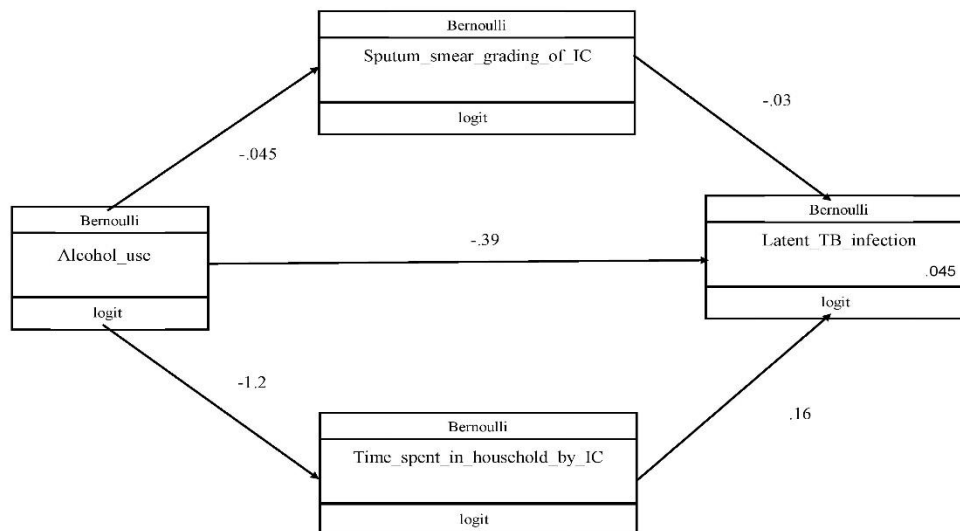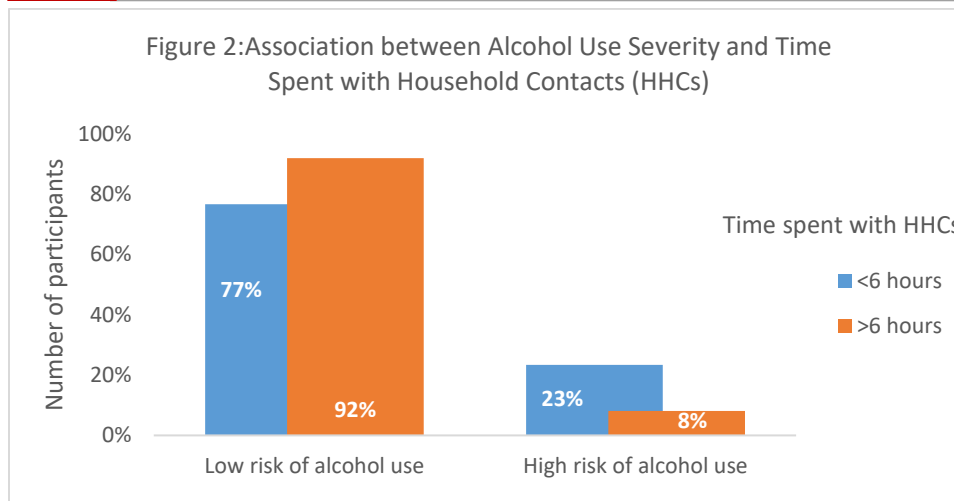
We performed a mediation analysis to investigate the relationship between alcohol use of the IC and latent tuberculosis infection (LTBI), with the smear of

ICs and time spent by the IC at the house as potential mediators. Alcohol use (independent variable) is significantly associated with a decreased likelihood of LTBI (p = 0.016). The association between alcohol use and the smear result of IC (mediator) is not statistically significant (p = 0.789), whereas alcohol use of IC is significantly associated with decreased time spent with household contacts (mediator) (p < 0.001). The proportion of the indirect effect mediated by smear positivity is negligible. Approximately 34.07% of the indirect effect of alcohol use on LTBI is mediated by the time spent by index case patients at the house. The total indirect effect is approximately 51.17% of the direct effect. Approximately 33.85% of the total indirect effect of alcohol use on LTBI is mediated (Figure 3).

Table 4: Association of infectiousness of index cases with LTBI positivity in HHC stratified by risk of hazardous use of alcohol in index case

Smear Grading	Low risk for hazardous use of alcohol among Index Case (N=1344)			P value	High risk for hazardous use of alcohol among Index Case (N=179)			P value
	LTBI -ve	LTBI +ve	Total		LTBI -ve	LTBI +ve	Total	
Low	202 (45%)	250 (55%)	452	0.45	39(63%)	23(37%)	62	0.24
High	418 (47%)	474 (53%)	892		63(54%)	54(46%)	117	
Total	620	724	1344		102	77	179	

Fig 1: Proportion of LTBI positives among HHCs by alcohol use risk of ICs

Figure 2: Association between Alcohol Use Severity and Time Spent with Household Contacts (HHCs)

Discussion

Household contacts are known to be high-risk group for developing TB. In a systematic review and meta-analysis of 20 papers from 14 Sub-Saharan African countries, the prevalence of active TB in the HHC of TB patients was found to range from 0.6% to 7.04%, the pooled prevalence being 3.29 % (95 %CI; 2.35 %-4.23 %, I[2]; 98.48 %). Pulmonary TB being more infectious, their HHC are a greater risk[10]. From a follow-up study of the HHC in the 100 million Brazilian Cohort (100MCohort) from 2004 to 2018, the incidence of TB in the HHC was nearly three times higher (adjusted RR 2·84 [95% CI 2·55–3·17]) in cohabitants of pulmonary TB patients as compared to the extra-pulmonary TB. A modelling study was conducted to estimate the number of people in this high-risk category, which included 20 countries with >80% of incident TB globally in 2019[11]. India was found to have the largest number of HHC exposed to incident pulmonary TB, with an estimated 114 million people (95% UI 97-134), the overall estimate of HHC with exposure globally being 38 million (95% UI 33 to 43 million)[12].

Households provide an ideal setting for transmission of TB from TB patients to their contacts. While sharing the airspace often in overcrowded poorly ventilated dwellings, they indulge in activities that increases release of the bacilli into the air, such as talking, eating and sleeping together increasing the probabilities of transmission[13]. Within the HHC in our study, 82% reported sharing meals with TB patients at least once or twice a day. Other studies too have reported a high proportion of the patients having food together with the family members[14,15]. Close contact during meal sharing provides an opportunity for the transmission of respiratory

droplets containing Mycobacterium tuberculosis, thereby increasing the risk of infection[16,17].

Duration of contact too is known to be prolonged within the households, therefore providing ample opportunity for TB transmission[18]. In our study, a considerable proportion of household contacts reported spending more than 6 hours per day in close proximity to active TB patients. Although a portion of household contacts reported sharing the same room but sleeping in different beds from active TB patients, it is important to note that the shared airspace still pose a potential risk of transmission even during sleep. Evidence from various studies has established the risk of LTBI among household contacts sharing same room[19,20]. This prolonged exposure increases the likelihood of inhaling infectious particles and acquiring TB infection. Studies conducted in India found that majority of symptomatic contacts had a longer duration of contacts with the index cases[21-23]. This highlights the importance of implementing effective preventive measures, such as proper ventilation, respiratory hygiene practices and reduced duration of contact with index cases, to minimize the spread of TB within households.

A striking finding of this study was the high percentage of active PTB patients who reported drinking alcohol as compared to other studies which have reported a lower alcohol use of 40% among pulmonary TB patients[24]. In addition to weakening the immune system, alcoholism impairs lung function, not only making individuals more susceptible to TB, but also increasing the severity of disease. This is supported by our finding of 83% of ICs with high-risk alcohol use having higher smear grades compared to 44% in those having low-risk. Additionally, alcohol use can contribute to behaviors that increase the risk of transmission, such as inadequate hygiene practices and close contact with infectious individuals.

We observed contradictory findings. In our study, we noted an overall latent TB infection (LTBI) positivity rate of 52.5% among HHCs. Interestingly, we observed a lower LTBI positivity rate of 43.1% among HHCs of TB patients with a high risk of alcohol use compared to 53.9% among HHCs of IC with low-risk alcohol consumption. This discrepancy, juxtaposed with the higher smear grading, indicative of higher infectiousness among TB patients with high-risk alcohol use, underscores the complexity of TB transmission dynamics in our setting[25,26].

Generally, studies exploring TB infection among the HHCs have focused on their characteristics and the details of contact with the TB patient such as relationship with the patient, duration of contact, sharing of meals and bed [27]. Patient attributes such as HIV status have also been scrutinized for their role in transmission[28,29]. Our previous report, as in other studies on assessment of risk factors for TB infection in the HHCs of TB patients, have not included the alcohol use status of the TB patients. We sought to address this gap and explain the finding of lower LTBI positivity among the HHCs of ICs with high-risk alcohol use.

Our findings unveiled a significant disparity in the time spent by the ICs with their HHCs based on their alcohol use. TB patients with more severe alcohol use were spending less time with their HHCs. This corroborates with the findings of sleeping habits of patients in our study. We found half the proportion of TB patients with high-risk alcohol use slept in the same room and/ or bed as that of the low-risk alcohol use participant. This observation elucidates the difference in infectiousness between ICs and the LTBI positivity of their HHCs when stratified by alcohol use risk.

Mediation analysis further explained the impact of alcohol use of the IC on TB transmission dynamics, revealing significant association of alcohol use of IC with decreased time spent with household contacts as a mediator (p < 0.001). The direct effect suggests that alcohol use is negatively associated with LTBI, indicating that higher levels of alcohol use are linked to a lower likelihood of LTBI. While smear grade did not mediate this relationship significantly, time spent by the ICs with the HHCs partially mediated it, with approximately 34.07% of the effect of alcohol use on LTBI. Therefore, we report an interesting observation on the behavior of the ICs with high-risk alcohol use, which disputes the existing assumptions and have the potential to change the understanding of settings of TB transmission in areas reporting high alcohol use such as ours. The ICs with high-risk alcohol use spent much less time within their households and this mediated the association of the alcohol use and lower LTBI positivity in their HHCs, which otherwise would have led to a scenario of higher LTBI positivity in their HHCs as these are the patients having higher infectiousness[30]. This leads to the understanding that these patients are spending more time outside of their households, which probably is associated with their alcohol use. The close contacts therefore are possibly also the people outside of their households. Further research is needed to explore other potential contacts and hotspots in the transmission of TB. These findings highlight the importance of considering contextual factors in tuberculosis transmission dynamics and suggest potential implications for interventions

targeting alcohol risk reduction to mitigate LTBI prevalence as has been suggested by others[31,32].

Interestingly, our study suggests that highly infectious TB patients with high-risk alcohol use may not primarily transmit the infection within the household, hinting at community-level transmission avenues. Alcohol use being common among pulmonary TB patients in Puducherry region, almost two-thirds of those having alcohol use have been found to visit the local-made alcohol shops (arrack shops) every day with most spending up to one hour there every day[33]. These can be one of the major hotspots of transmission as well as others still unexplored. This study underscores the importance of broadening transmission investigations beyond household settings, which would help implementation of early diagnosis and treatment measures to curb transmission.

Conclusion

Pulmonary TB patients with high-risk alcohol use expectorate more number of bacilli in their sputum, which makes them highly infectious. Contrary to the expectation, we found lower LTBI positivity among their HHCs, which we were able to explain was being mediated through the less time spent by them in their households. Therefore, it is understood that they were spending more time in other places in the community and there are contacts outside of their households who might be getting infected but still not under the radar of the national TB programmes. Further research is warranted to elucidate the intricacies of TB transmission dynamics among alcohol-consuming TB patients, guiding targeted interventions and control measures. In conclusion, addressing alcoholism as a driver of TB transmission is imperative. Integrated approaches targeting both conditions are crucial for effective prevention and control strategies.

Conflict of interest
The authors declare that there are no conflicts of interest associated with this study.

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