

## REVIEW ARTICLE

# Betel Quid Use and Tuberculosis Transmission: A neglected focus area for Tuberculosis Control in LMIC's.

Priyanka Manghani<sup>1</sup>, Narayana Prasad<sup>2</sup>, Nishtha Khatri<sup>3</sup>, Robert Paulino Ramirez<sup>4\*</sup>, Shishir Gokhale<sup>5\*\*</sup>, KM Monirul Islam<sup>6</sup>, Piyusha Majumdar<sup>7</sup>, Tran Hoang<sup>8</sup>, Hanifa Denny<sup>9</sup>

<sup>1</sup>Epidemiologist, California Rural Indian Health Board and former research volunteer- Public Health Literacy. Role: Worked on study design, data synthesis and manuscript preparation, along with revisions, final approval of the manuscript; <sup>2</sup>Technical Director, Cardiovascular Imaging and Core Lab, Brigham and Women's Hospital & Director, Public Health Literacy. Role: Worked on study design, data synthesis and manuscript preparation, along with revisions, final approval of the manuscript; <sup>3</sup>Lecturer, Division of Holistic Health, Mahati wellness, Mumbai, India. Role: Worked on study design, data synthesis and manuscript preparation, along with revisions, final approval of the manuscript; <sup>4</sup>Instituto de Medicina Tropical & Salud Global, Universidad Iberoamericana (UNIBE), UNIBE Research Hub, Santo Domingo, 22333, Dominican Republic. Role: Study design, manuscript preparation and revisions and final approval of the manuscript; <sup>5</sup>Professor and Head of Dept of Microbiology, Manipal College of Medical Sciences, Pokhara, Nepal. Role: Study design, manuscript preparation and revisions and final approval of the manuscript; <sup>6</sup>Regional Director, Public Health Literacy. Role: Study design, manuscript preparation and revisions and final approval of the manuscript; <sup>7</sup>Associate Professor, Indian Institute of Health Management and Research. Role: Manuscript preparation and revisions and final approval of the manuscript; <sup>8</sup>Technical Advisor, FHI 360. Role: Manuscript preparation and revisions and final approval of the manuscript; <sup>9</sup>Professor of Occupational Health, Diponegoro University, Indonesia. Role: Manuscript preparation and revisions and final approval of the manuscript.

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**\*Corresponding Author:** Robert Paulino Ramirez, Instituto de Medicina Tropical & Salud Global, Universidad Iberoamericana (UNIBE), UNIBE Research Hub, Santo Domingo, 22333, Dominican Republic. Email: r.paulino1@unibe.edu.do

**\*\*Alternate corresponding author:** Shishir Gokhale, Professor and Head of Dept of Microbiology, Manipal College of Medical Sciences, Pokhara, Nepal. Email : [shishirmanju@gmail.com](mailto:shishirmanju@gmail.com)

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Habitual betel quid consumption and spitting contributes to Tuberculosis (TB) transmission due to direct exposure to pathogens, immunosuppression, and social contact. Despite betel quid being classified as a Group 1 Human Carcinogen, and a high prevalence of betel quid consumption in TB patients, there exists a knowledge gap in the relationship between quid use and TB, which presents as neglected opportunity to address the global burden of Tuberculosis in Low- and Middle-Income Countries (LMIC's). Understanding such a knowledge gap is crucial when taking the measures at various levels including research prioritization, behavior change communication, legislation to address the availability and access of quid products coupled with community-based interventional strategies. This paper thus looks at empirical evidence on quid use and its effects on Tuberculosis spread and identifies feasible, applicable changes required at various levels to curtail the spread of Tuberculosis among betel quid users.

**Keywords:** Tuberculosis Transmission, Behavior Change Communication, Interventional Strategies.

## INTRODUCTION

Betel quid popularly known as paan, is a popular chewing product composed of the nut of the areca palm, the leaf of the betel pepper (*Piper betel*), and a tint of lime (calcium hydroxide).<sup>1</sup> It is the fourth most addictive substance after alcohol, nicotine, caffeine and it is a group 1 oral carcinogen, consumed by more than 600 million people globally.<sup>2,3</sup>

There is a large volume of scientific evidence linking betel and areca nut consumption with an increased risk of oral cancers. A meta-analysis of fifteen case control studies showed that betel quid without tobacco has an independent positive association with oral cancer due to the carcinogenic potential of areca nut, with an odds ratio (OR) of 2.82 (95% CI=2.35–3.40,  $P<0.001$ ).<sup>4</sup> The burden due to betel induced oral cancer is quite large, and a study conducted in Taiwan assessing risk of oral cancer in high risk individuals found that those consuming betel nuts were 2.12 times more likely to develop oral cancer, using smoking as a baseline for comparison (HR = 2.12), thus stating that chewing betel nut had a significantly higher oral cancer incidence risk than those who only had a habit of smoking.<sup>5</sup> It has been found that nearly 50% of oral cancers occurring in regions such as the Indian subcontinent and Taiwan are attributed to betel quid chewing (population attributable fraction, 53.7% for residents in Taiwan and 49.5% for the Indian population), which highlights the need to address this modifiable risk factor.<sup>6</sup>

Arecoline, one of the alkaloids found in the areca nut component of betel quid is parasympathetic in action and leads to salivary glandular secretion when one is chewing the quid producing large volumes of saliva, followed by spitting of excess saliva as well as quid.<sup>7,8</sup> Spitting the quid can lead to the potential spread of communicable diseases due to the possibility of person-to-person transmission of tuberculosis owing to the communal environment of quid chewers, spitting of saliva and exposure to pathogens through salivary droplets.<sup>8</sup> However, this potential association is

often ignored in the tuberculosis spread pathway as compared to traditional cigarette smoking and TB, which is known to increase the risk of TB while also contributing to poor treatment outcomes.<sup>9</sup> Thereby, the aim of this review article is to address the ignored association between betel quid consumption and the transmission of TB; especially since there has been a rising prevalence of betel quid consumption in Asia; with a high betel quid use disorder being reported across endemic South-east Asian regions such as India, Pakistan, Sri Lanka (8.4 - 40%) followed by Nepal, Malaysia, Indonesia (10.3-47.8%) and China, Taiwan (2.3-29%), Palau & Solomon Islands (72-83%).<sup>10,11</sup> This recent increase in betel quid consumption is contributed to easy availability of betel quid, and their low cost as compared to cigarettes along with social acceptance of quid chewing.<sup>10,12</sup> Considering this geographic region accounts for 45% of the global TB burden and 81% of the global TB deaths, the possibility of stronger association between betel quid and tuberculosis should be explored.<sup>13,14</sup>

A study in Cambodia found a strong association between betel quid use and tuberculosis (OR 4.43, 95% CI =1.66-11.86).<sup>8</sup> Another study in Indonesia found that amongst patients with active TB and betel chewing, there was a higher TB transmission owing to betel chewing culture.<sup>15</sup> Further, a study conducted in Northern India found a high prevalence of current tobacco consumption in incident TB cases, with 10.7% of 211 incident cases being active consumers of smokeless tobacco.<sup>16</sup> In lieu of these findings, our paper further explores the current empirical evidence available on betel quid use and its effects on Tuberculosis spread, and identifies feasible, applicable intervention strategies required at various levels so as to curtail the spread of Tuberculosis among betel quid users.

### **Pathologies Linked to Betel Consumption**

Betel nut consumption has been associated with an increased risk of a variety of malignant conditions, along with various other pathologies.

Betel nut has been classified as a group 1 carcinogen by the International Agency for Research on Cancer.<sup>10</sup> Given this, most evidence on the health effects of betel have been focused on oral and other cancers, its impact on cardiovascular health, cerebrovascular diseases.<sup>17,18</sup> The alkaloids of areca nut are its prime carcinogenic ingredient, and areca nut in any form contributes to oral cancer in addition to cancers of the esophagus, liver, pancreas, larynx, and lungs becoming fairly common in areca nut users as well.<sup>10,19,20</sup> Habitual betel quid chewing has also been found to contribute to adverse cardiovascular outcomes. It is known to be a risk factor for arrhythmias and premature ventricular contractions.<sup>21,22</sup>

A systematic review found that habitual betel quid chewing was associated with hypertension, atherosclerosis, inflammation, and ischaemic heart disease in addition to being an independent risk factor for cardiovascular disease in women.<sup>23</sup> Areca nut has also found to have an association with systemic health conditions including diabetes, metabolic syndrome, and hepatocellular carcinoma.<sup>24-27</sup>

There has also been evidence showing the impact of areca nut consumption on respiratory pathologies such as asthma. A case control study in Taiwan found a significant association between betel consumption and asthma (Adjusted OR 2.05, 95% CI = 1.12-3.76).<sup>28</sup>

It is important to recognize that excessive consumption of betel nut can lead to addiction. Furthermore, the habit of chewing betel nut can spread among individuals through social interactions, contributing to a wider prevalence of betel nut addiction.<sup>29</sup>

### **Betel Use and Tuberculosis: Gaps in epidemiological evidence**

Despite the evidence showing an association between betel consumption and the cardiovascular diseases, respiratory and oncology pathologies, there is limited evidence on the possible association of betel quid consumption and tuberculosis in specific. This evidence is also limited as compared to the empirical evidence available on smoking and tobacco, where smoking has been known to be a risk factor for TB and a contributor to poor treatment outcomes.<sup>9</sup> A study in Cambodia found a strong association between betel quid and tuberculosis (OR 4.43, 95% CI=1.66-11.86).<sup>8</sup> However, no causality could be determined and this association was based on small group of prevalent TB cases (N=8 TB cases amongst 63 betel quid users), which do not make the results generalizable.<sup>8</sup> However, the study highlighted the possibility of an increased risk of TB infection in quid users with several factors contributing to the pathophysiology of TB in these cases such as person to person transmission, spread through spitting of quid saliva and immunosuppression.<sup>8</sup> Similarly, a study conducted in Indonesia found that of 51.8% (N=57) patients who had active TB, the TB transmission was higher when there was active TB and betel chewing present.<sup>15</sup>

Areca nut chewers have been found to be predisposed to asthma owing to increased bronchoconstriction and a decreased forced expiratory volume in the first second (FEV1).<sup>17</sup> A case control study in India found that a history of asthma was associated with an increased risk of developing pulmonary tuberculosis, with 74.5% of positive TB cases having a history of asthma.<sup>30</sup> However, there is poor evidence linking the increased risk of TB in asthma patients. A case control study in the UK found a very slight amount of risk for tuberculosis in asthma patients; while three studies conducted in Western Africa found that history or treatment of asthma had no effect on the risk for tuberculosis.<sup>31,32</sup> In addition to asthma, areca nut has also been found to be positively correlated with COPD and lung function impairment.<sup>33</sup> This could be linked to eotaxin-1 activation and chronic inflammation and COPD is a known risk factor for pulmonary tuberculosis.<sup>34,35</sup>

Areca nut also leads to suppression of T-cell activity and decreased release of cytokines, thus impacting the immune system.<sup>17</sup> This could potentially contribute to the risk for TB, since TB is common in immunocompromised persons and the adaptive immune response mediated by T cells is critical for control of *Mycobacterium tuberculosis* (*M. tuberculosis*) infection in humans.<sup>36,37</sup> Furthermore, betel is also known to increase the risk of Type 2 Diabetes Mellitus which is a known risk factor for the development of TB.<sup>38,39</sup>

While the above evidences outline a possible linkage of betel quid consumption, immunosuppression and TB risk, there remain gaps in evidence regarding the direct impact of betel quid consumption on individual risk and susceptibility for pulmonary tuberculosis, with no robust scientifically researched data that offers insight into its effect. Fig.1 displays an epidemiological triad to explain this potential association, while Table 1 presents the empirical findings of epidemiological studies describing the association between betel quid use and tuberculosis.

### **Socio-cultural factors influencing Betel Use**

Betel quid is a form of smokeless tobacco, and its use has been an important part in various South-Asian cultures strongly influenced by social acceptability, traditional medicine as well as religious beliefs.<sup>40,41</sup> Betel has been used in South-Asian culture for functions such as weddings and reconciliation ceremonies as well as in traditional medicine as an anti-septic and breath freshener.<sup>41,42</sup> Areca nut is one of the major constituents of betel quid and is considered a vital ingredient in religious ceremonies and its consumption in betel quid is also related to its euphoric stimulation property owing to the high levels of psychoactive alkaloids present in it.<sup>19,43</sup>

Chewing of areca nut has been shown to increase work capacity, causing hot sensations and fuelling alertness.<sup>43</sup> Some of the common reasons why users claimed they chewed areca nut was the refreshing feeling it gave along with its good taste, or as a snack to relive stress and/or to strengthen gums.<sup>44</sup>

The high prevalence of consuming betel in South-East Asia is also influenced by factors such as age, gender, education, and socio-economic disparities in purchasing power. Since betel is a form of smokeless tobacco, many advertising campaigns do not outline the health risks of betel as compared to cigarette smoking.<sup>45</sup> A qualitative study looking at perceptions of adolescents towards areca nut found that adolescents view tobacco as higher risk substances due to the greater focus on tobacco harms through various media portals.<sup>46</sup> Additionally, since areca nut is marketed as a sweeter substance, many adolescents do not perceive it as a harmful substance to health and it is often consumed for a boost of energy.<sup>46</sup> In many regions, cigarette smoking is more prevalent in men and is not considered socially acceptable for women and hence areca nut consumption is more prevalent amongst women and adolescent girls owing to greater social acceptability.<sup>46,47</sup> Lastly, betel has easy availability coupled with an attractive price point and misleading advertisements as compared to cigarettes, which further influence its consumption in society.<sup>12</sup>

### **Possible suggestions to contain TB spread amongst betel users**

#### ***Focus on prevention, health education and integration into National Tuberculosis Control***

##### ***Programs:***

There is poor awareness and literacy regarding the health impacts of betel quid as compared to cigarettes. This can be attributed to factors such as misrepresentation and false perception that

betel has potentially less negative health impacts compared to cigarettes.<sup>47</sup> Addressing this false perception is crucial which highlights the need for health literacy programs. Health promotion programs should focus on increasing public literacy of the negative health impacts of smokeless tobacco products such as betel. Much like the measures incorporated to address negative health consequences in cigarette advertisements, similar regulations could be improvised to spread information regarding the health impacts of betel. This initiative requires multi-stakeholder engagement including policy makers and government agencies. Addressing the negative health impacts of betel quid would be particularly challenging in low socio-economic groups and rural areas, where a far more intensive effort would be required, with health promotion plans having to be culturally sensitive. Such initiatives should be designed with respect to a sociocultural context in a diverse society such as Southeast Asian countries. Integrating these initiatives into National TB control programs is an option, but the successful implementation remains a daunting task. Health literacy measures to educate patients, and their families about the harmful effects of betel quid and TB spread should be implemented at macro level agencies with necessary economic and human resources support at downstream agencies. Healthcare professionals could play a significant role in educating patients. Hence, there is a need to highlight how to effectively utilise physicians, nurses and public health specialists in this wave to spread awareness focused on preventing the spread of TB in betel nut users. Additionally, regular follow-ups should be conducted with betel users to map their progress and further motivate them to quit betel consumption. While there is lack of empirical evidence on how betel quid consumption can impact TB treatment outcomes, patients should be encouraged to quit betel quid use during the treatment and de-addiction programs, behaviour change communication campaigns can aid in this process. There is limited evidence on the role of capacity building of providers, community health workers and other stake holders to address this seriously impactful cultural habit. Strategic and time-tested interventions to support the role of capacity building, health literacy and social partnerships could help us understand what pillars of health systems can be leveraged upon to address this concern.

**Regulation of access and product availability:** Easy access and affordability are another attractive factor as to why people opt to chew smokeless tobacco such as betel.<sup>10,12</sup> To curtail this, there is a need to advocate for regulatory and legal measures to control the easy access and affordability of betel. A simulated analysis conducted in Taiwan to identify cross price elasticity of betel nut based on the tax increases found that betel nuts were price inelastic.<sup>48</sup> Conducting simulations of how heavier taxation, and legislative regulations could impact betel consumption trends, would help in appropriate planning and implementation of regulatory policies. The dimensions of the chemical components of Areca Nut in cigarettes that could be used in sports environments, such as baseball, in countries like the Dominican Republic and other LMIC's in the Americas are still unknown, however on multiple business websites they are offered at a very low cost, which suggests that it could be used on a low scale, and therefore, its right dimensions remains elusive.<sup>50</sup>

**Epidemiological, longitudinal and prospective research:** In addition to the above measures, it is crucial to advocate for further epidemiological research to better understand the relationship between betel quid consumption and tuberculosis transmission. Epidemiological studies can help to understand the mechanisms through which betel may contribute to TB risk as well treatment outcomes, which is crucial for developing strategies in LMIC's where there is a dual burden of TB and social factors such as betel quid consumption.

### **Limitations of the study**

There are extensive variations in cultural practices and geographical differences in betel quid use across various regions, hence it will be difficult to generalize any data, and the findings related to this topic. Moreover, there is a shortage of mechanistic studies that investigate the biological mechanisms through which betel quid use might influence TB transmission, hindering a thorough understanding of the underlying processes. Future research addressing these limitations will be essential for achieving a more precise and comprehensive understanding of the connection between betel quid use and TB transmission.

### **CONCLUSION**

LMICs face a dual disease burden of tuberculosis and betel quid consumption. They play role as social determinants and contributing to global health concern contributing to high mortality. Global health implications of betel quid consumption necessitate a multi-pronged approach, aimed at raising awareness about its health risks, regulations in accessibility, and conducting research to better understand its implications for TB transmission. Prospective research to determine the potential association of betel quid use and its association with tuberculosis transmission as well as impact on TB treatment outcomes can help build evidence to address the knowledge gap, while also addressing this missed opportunity in tuberculosis control.

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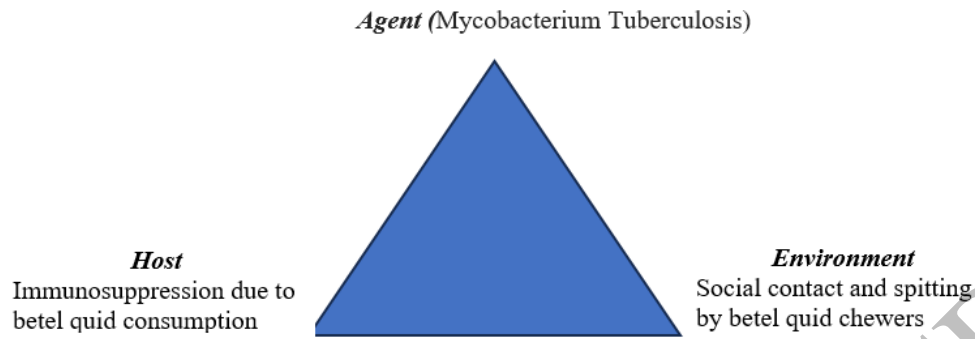
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**Table 1: Summary of current epidemiological evidence on the association between betel quid consumption and tuberculosis.**

Study	Country	Year	Design	Results	Limitations
Betel quid use in relation to infectious disease outcomes in Cambodia <sup>8</sup>	Cambodia	2012	Cross-sectional study	There was an association between the intensity of betel quid use and tuberculosis (OR 1.50, 95% CI =0.96–2.36) with a strong association between betel quid use and tuberculosis in men (OR 4.43, 95% CI= 1.66–11.86).	Prevalent cases, results cannot be generalized and no causality.
Factors Influencing Transmission of Tuberculosis in Ngeu Nata Culture among Ngada Community in Kupang, East Nusa Tenggara, Indonesia <sup>15</sup>	Indonesia	2021	Cross-sectional study	There was a high TB transmission behaviour in betel eating respondents (51.8%).	Results cannot be generalized and no causality.



**Fig. 1: Epidemiological Triad for the potential association between TB and betel quid use.**

**Fig. 1: Epidemiological Triad for the potential association between TB and betel quid use.**