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Prevalence of Latent Tuberculosis (LTB) among Household Contacts of Newly Diagnosed Omani Pulmonary Tuberculosis Patients

Jeffrey Singh[1], Lamiya Balushi[1], Nada Mahrazi[1], Esklid Peterson[2], Olivier Koole[3], Fatma Al Ajmi[1], Padmamohan Kurup[1]

[1]Directorate General of Health Services, Ministry of Health, Muscat, Oman
[2]Directorate General of Disease Surveillance and Control, Head Quarters, Ministry of Heath, Muscat, Oman
[3]London School of Hygiene and Tropical Medicine, London, UK
Email: jeffsinghs@gmail.com

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Abstract

Background: Oman is a high-income, low prevalent country for tuberculosis disease. Although the rates have remained static over the last decade, the country is aiming for Tuberculosis (TB) elimination. Household contacts of pulmonary TB (PTB) patients form a high-risk group of susceptible individuals who could remain reservoirs of active disease. **Objective:** A retrospective study was conducted to estimate the prevalence of latent TB infection by Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) screening tests among the household contacts of Omani patients with pulmonary tuberculosis. **Design:** A cross-sectional survey conducted between 2017 and 2018 of TB cases and their contacts in Muscat Governorate, Oman. **Results:** Out of the 278 contacts identified, 188 contacts fulfilled the inclusion criteria and were enrolled into the study. The prevalence of Latent Tuberculosis Infection (LTBI) was 22.8% (95% CI: 17.0 - 29.5) among household contacts. We found higher proportions of LTBI among females than males (28.7% vs. 15%, p = 0.027). Those who were exposed to Acid Fast Bacilli (AFB) smear positive cases were more likely to be LTBI (28.7% versus 15% in smear negative cases; p = 0.047). We also found an increasing trend of infection (32.3%) in the oldest age group (46 - 80 years). **Conclusion:** Besides children, female household contacts and older age contacts should be prioritized for screening as they are more likely to be infected and develop active disease.

Keywords

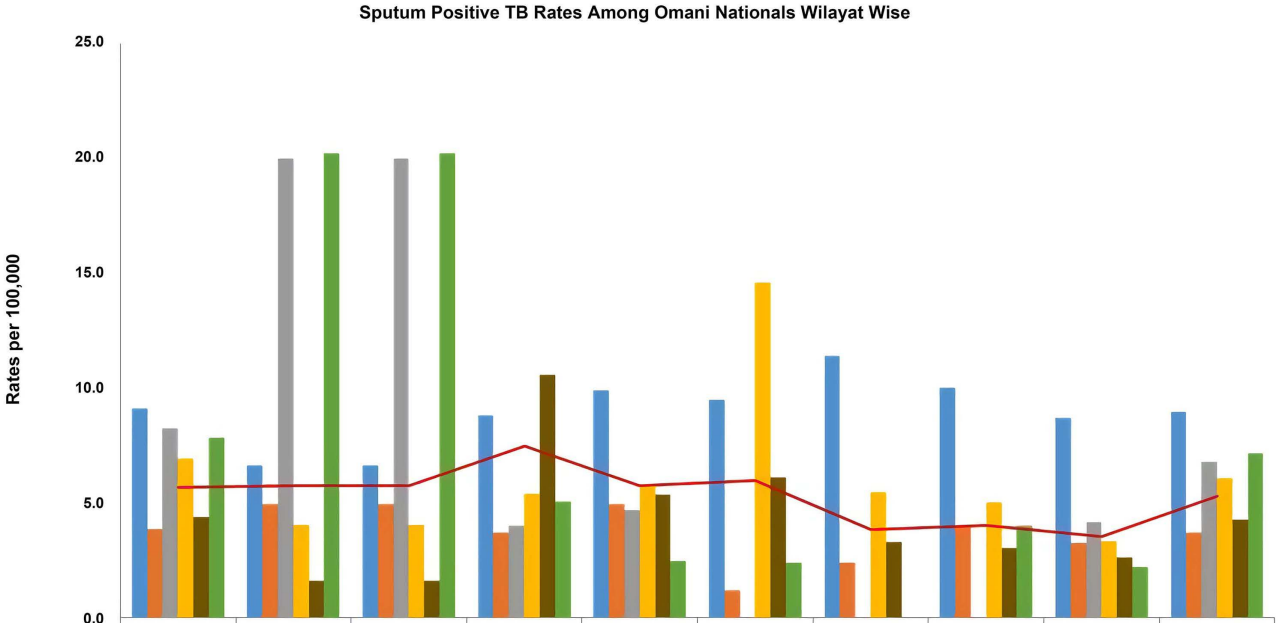
Latent TB Infection, Interferon Gamma Release Assay, Tuberculin Skin Test, Cavitary Lesions

1. Introduction

Oman is part of the Middle East and North African region (MENA) located in the south-eastern corner of the Arabian Peninsula. The 2018 mid-year population of the country was 4,601,706 with expatriates forming 40% of it. Muscat Governorate, the capital with an area of 370 km^2 is divided into 6 administrative districts and has the highest population density of 1.4 million with 64.5% of them being expatriates. 90% of these expatriates are from high TB burden countries [1].

The National TB program was established in 1981, it successfully managed to reduce the TB sputum positive incidence rates from 21 per 100,000 in 1981 to 6.4 per 100,000 in 2006 [2]. The average incidence of sputum positive pulmonary TB, however, has since remained stagnant (around 5.3 per 100,000) over the last decade (**Figure 1**).

The social and economic development in the past fifty years and universal health care access has also contributed to this reduction. Increased life expectancy of citizens, increasing prevalence of diabetes mellitus and migrant workers coming from TB high prevalent countries are factors that contribute not only to the increased risk of infection to a susceptible population but also continuous TB disease transmission [3] [4]. One of the key steps in reducing the incidence of TB



	2009	2010	2011	2012	2013	2014	2015	2016	2017	Average
Amerat	9.1	6.6	6.6	8.8	9.87	9.5	11.4	10.0	8.69	8.9
Bausher	3.8	4.9	4.9	3.7	4.94	1.2	2.4	4.0	3.25	3.7
Muscat	8.2	20.0	20.0	4.0	4.68	0.0	0.0	0.0	4.13	6.8
Muttrah	6.9	4.0	4.0	5.4	5.69	14.6	5.5	5.0	3.32	6.0
Seeb	4.4	1.6	1.6	10.6	5.36	6.1	3.3	3.0	2.59	4.3
Quriyat	7.8	20.2	20.2	5.1	2.45	2.4	0.0	4.0	2.18	7.1
Region	5.7	5.7	5.7	7.5	5.75	6.0	3.8	4.0	3.52	5.3

Figure 1. Trend of sputum positive TB cases per 100,000 (2009-2017, 6 Districts) Regional Annual Report, Muscat 2017 Courtesy: Regional TB program.

disease is to identify the proportion of latent TB infection (LTBI) especially in high risk populations such as contacts of active pulmonary TB.

Immunological tests like TST (Tuberculin skin test), and QFT (QuantiFERON) are used to detect LTBI. Both these tests are presently included in the national policy and include all residents (expatriates and nationals) for testing household contacts for infection. During their first visit all contacts undergo clinical examination, complete blood count, erythrocyte sedimentation rate, chest X-ray and QuantiFERON testing. Once these tests are done, the contact is subjected to TST testing. The TST result is read after 72 hrs. Once active disease is ruled out, contacts with LTBI are counselled and offered LTBI treatment which consists of either a 6-month of isoniazid (INH) or INH and Rifapentine combination, once daily dose for 12 weeks. Children who are less than five years of age are started with chemoprophylaxis irrespective of the result. However, if negative a repeat IGRA/TST is done after a period of three months to confirm an infection, and if negative the medications are stopped. Contacts are followed up every 6 months from the date of initial contact screening for two full years.

In Oman TB case notifications are mandatory and treatment is made available only through Ministry of Health institutions.

As we were interested to study the prevalence of infection among Omani household contacts only and as there is limited social interaction between Omani nationals and expatriates among household contacts, we focused on describing the prevalence of LTBI among household contacts of newly diagnosed Omani nationals with sputum culture positive pulmonary tuberculosis (PTB) in Muscat Governorate. We also aimed to identify associated risk factors for LTBI among these contacts.

2. Materials and Methods

2.1. Data Collection

This cross-sectional survey was conducted between 2017 and 2018 by reviewing the hospital electronic health records (EHR) of TB cases and their contacts in Muscat Governorate.

As per policy, contact listing of all notified TB cases are made by the tuberculosis focal point (TBFP) of the governorate and referred to the local health center for screening.

Information that was collected included demographic profile of index cases and their infectiousness based on sputum microscopy and chest X-ray. Information on contacts included age, gender, body mass index, history of smoking, alcohol, HIV, diabetes or any immunocompromised diseases, Chest X-ray, BCG scar and LTBI status based on IGRA and/or TST. The data was collected using a data sheet and the information was transferred to Microsoft access data base. Each row of data sheet represented data of one household contact.

Sample size was estimated, from previous annual regional TB reports, for an assumed prevalence of 16.3% with a precision of +/− 5%. The required sample was 219. Since we took all patients, the total contacts during the period was more

than this number as average household size was >5 in Oman.

Once active TB disease was ruled out among the contacts by evaluating each contact for signs and symptoms of disease, laboratory investigations that included complete blood count, erythrocyte sedimentation rate and a chest X-ray (three samples of AFB sputum was done, if any contact had clinical symptoms or signs or abnormalities noted in the chest X-ray), we used a cutoff of ≥10 mm Mantoux and or QFT positive result from the laboratory to define cases with LTBI.

2.2. Inclusion Criteria

Household contacts of Omani sputum culture positive pulmonary TB cases, who were screened for LTBI either through Mantoux or QuantiFERON testing.

2.3. Exclusion Criteria

Contacts that were positive for TB disease and contacts of relapse TB cases were excluded. Contacts of relapse cases were excluded due to the uncertainty of exposure. Expatriate cases and their contacts were not included in this analysis.

2.4. Data Management and Data Analysis

Microsoft Access 2010 data management software was used for data entry and SPSS software version seventeen was used for data analysis. All information regarding cases were coded with unique ID's, without any personal identity. Information from electronic case records were cross checked with our secondary data source, the regional TB registers for consistency and validity.

Prevalence estimates were presented with 95% confidence interval (CI) limits. We used Chi-square tests to compare proportions, a p-value of <0.05 was considered statistically significant for the study.

2.5. Ethic statement

Ethic clearance was obtained from the institutional ethical committee under the Center of Studies & Research, Directorate General of Planning & Studies, Ministry of Health, Oman (Ref: MH_DGPS_MG_5/2018) and the London School of Hygiene and Tropical Medicine (Ref: 14692).

3. Results

3.1. Demographic and Social Characteristics

278 household contacts of twenty-seven PTB cases, were selected from contact screening records. 2 cases and their twenty contacts were excluded. In addition, seventy contacts (male:female, 3:4), were also discarded because they did not have either a TST or IGRA test done. 188 contacts were included in the final analysis (**Figure 2**).

None of the contacts were diagnosed with active TB disease during the study period. All the contacts who had LTBI were counselled and offered chemoprophylaxis according to the national policy.

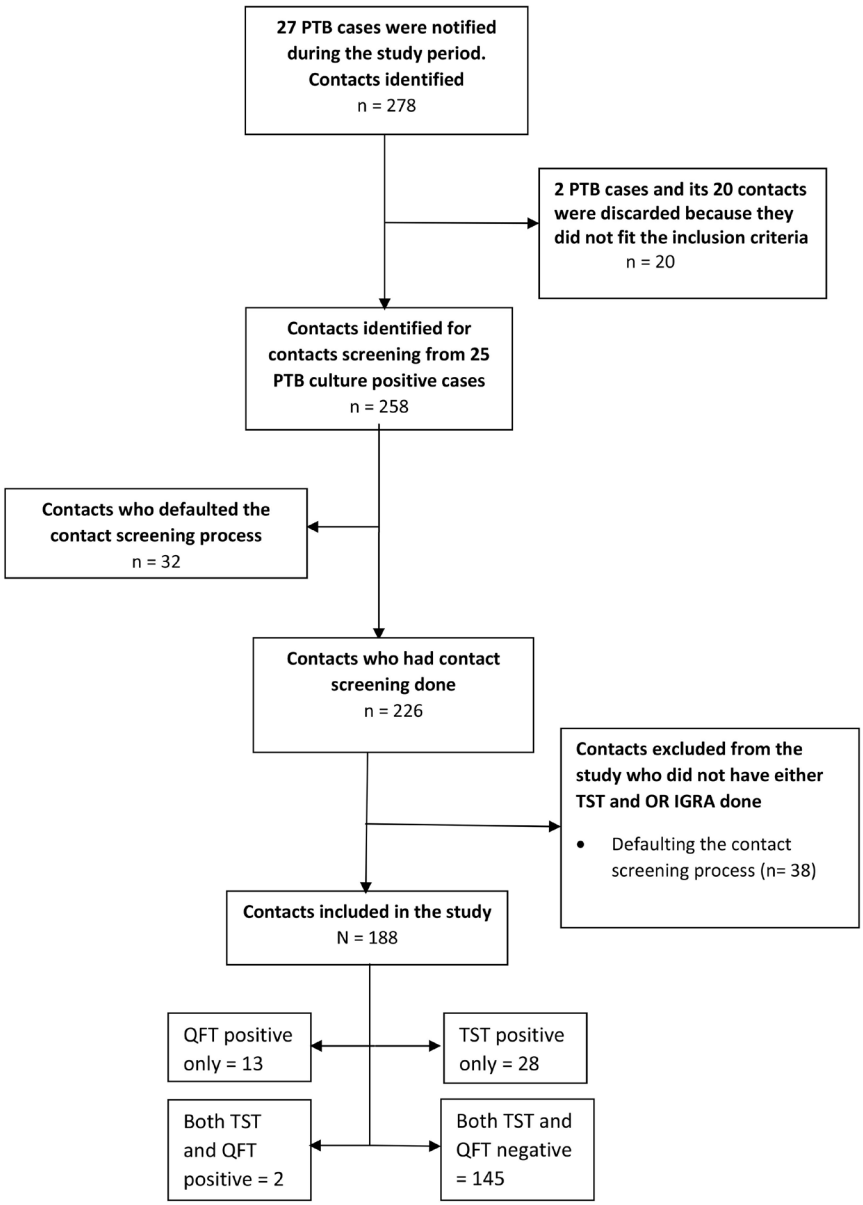


Figure 2. Flow Chart of the study participants.

3.2. Characteristics of PTB Patients

The twenty-five PTB cases had a mean age of 55 years (IQR 45 - 59) with male: female ratio of 3:2. One of the TB cases was co-infected with HIV. 12 (48%) of the index cases gave history of diabetes, 5 (20%) consumed alcohol regularly, and 6 (24%) were current and 2 (8%) previous smokers. 7 (28%) of them gave history of previous contacts to TB patients. Household Contact Characteristics are summarized in Table 1.

3.3. LTBI Prevalence among Household Contacts in the Study

The overall prevalence of LTBI in our study measured by a positive TST or IGRA positivity was 22.8% (95% CI: 17.0 - 29.5). LTBI positivity rate was 31/108

Table 1. Characteristics of participants.

	Screened with TST/IGRA N = 188	Both tests positive	Both tests negative	Only QFT positive	Only TST positive
Gender, n (%)					
Female	108 (57.4)	2 (1.9)	77 (71.3)	10 (9.3)	19 (17.6)
Male	80 (42.6)		68 (100)	3 (3.8)	9 (11.3)
Age Group, n (%)					
0 - 5	10 (5.3)		10 (100)		
6 - 13	32 (17)		27 (84.4)	3 (9.4)	2 (6.3)
14 - 45	115 (61.2)	2 (1.7)	87 (75.7)	4 (3.5)	22 (19.1)
46 - 80	31 (16.5)		21 (67.8)	6 (19.4)	4 (12.9)
BCG scar n (%)					
Present	117 (62.2)	2 (1.7)	89 (76.1)	10 (8.5)	16 (13.7)
Absent	18 (9.6)		15 (83.3)	1 (5.6)	2 (11.1)
Missing	53 (28.2)	2 (1.9)	41 (77.4)	2 (3.8)	10 (18.9)

(28.7%, 95% CI: 21.02 - 37.8) for females and 12/80 (15.0%, 95% CI: 8.79 - 24.4) for males.

Among the age groups there was an increasing trend of infection seen from none in the youngest age group 0 - 5 years to 32.3% in the oldest age group (46 - 80 years).

63 (33.5%) of the contacts were exposed to sputum smear negative but culture positive PTB, and 125 (66.5%) were exposed to sputum positive TB. 34 (27.2%, 95% CI: 19.67 - 35.9) contacts exposed to sputum positive TB cases were positive for LTBI, whereas 9 (14.3%, 95% CI: 6.7 - 25.4) were positive among 63 contacts of AFB sputum negative cases (Table 2).

3.4. Association between Exposure and LTBI Testing

LTBI rates were compared based on exposure characteristics (gender, age-group, family size, chest X-ray findings and AFB direct smear results).

Significant associations were noted in the gender, female versus male (28.7% vs 15%, p = 0.027) and exposure to AFB sputum smear positive versus smear negative (27.2% vs 14.3%, p = 0.047). Other parameters measured did not show statistical significance in this study (Table 2).

4. Discussion

We found that 22.8% of the persons exposed to active TB cases were positive for LTBI. This estimate was low compared to the findings in a systematic review done by Fox and colleagues [5]. However, we expected this finding in our study, since the incidence of active PTB disease has remained quite low over the last decade (Figure 1).

Table 2. Risk factors for LTBI.

Exposure characteristics	Category	Total Contacts (%)	LTBI + (n%) 43 (22.8)	p value
Gender	Female	108 (57.4)	31 (28.7)	0.027
	Male	80 (42.6)	12 (15.0)	
Age Group	0 - 5	10 (5.3)	0 (0)	0.132
	6 - 13	32 (17)	5 (15.6)	
	14 - 45	115 (61.2)	28 (24.3)	
	46 - 80	31(16.5)	10 (32.3)	
Family size	8 member and less	37 (19.7)	9 (22.5)	0.814
	more than 8 members	151 (80.3)	34 (79.1)	
Chest X-ray	cavity	48 (25.5)	14 (29.2)	0.229
	no cavity	140 (74.5)	29 (20.7)	
AFB Sputum Smear*	0	63 (33.5)	9 (14.3)	0.047
	1+/2+/3+	125 (66.5)	34 (27.2)	
BCG scar	Present	117 (86.7)	28 (23.9)	0.49
	Absent	18 (13.3)	3 (16.6)	

In low incidence countries the TB epidemiology is characterized by a low rate of transmission in the local population, with occasional outbreaks and most of the cases arising from progression of LTBI rather than recent transmission [6].

This estimate indicates that targeting household contacts with LTBI can substantially contribute to the reduction in the incidence of TB in the country and move towards achieving TB elimination targets. WHO recommends either IGRA or TST to be done for contact screening in high and upper middle-class income countries that has an annual incidence of less than 100 per 100,000 [7].

We found a significantly different proportion in LTBI between male and female contacts ($p = 0.027$). A higher proportion of female contacts (28.7 %) tested positive for latent tuberculosis infection compared to male contacts (15%). Infectious diseases, especially TB have shown to have a predilection to male persons, contrary to what we found for LTBI in this study [8]. However, we did find a significantly higher proportion of males among contacts who defaulted from TST/IGRA testing which could have possibly contributed to this higher proportion of LTBI in females. A prevalence study done in the Northern part of Iran, though revealed no difference among genders [9]. While a population-based survey done in Saudi Arabia did show a higher prevalence of positive TST among male contacts while IGRA results showed no difference [10]. Factors that contribute to this difference have been suggested to be the risk-taking characteristics of males, genetic predisposition and immunological attributes [11] [12].

The highest prevalence of LTBI was seen in the 46 - 80 age group, with about 32.3% prevalence. LTBI testing of contacts not only detects recent infection but also the cumulative exposure prior to the recent TB diagnosis. Older individuals

have a higher baseline of prevalence [13] [14]. Children below the age of 5 who were exposed to infectious TB, were not found to be LTBI positive. In contrast, a study done by Khan and her colleagues in Malawi, showed that 1% childhood infection to TB bacilli, occurred either from an unknown casual contact in the community or a known household case [13]. Childhood infection to TB bacilli points out a recent transmission and serves as a sentinel for infectious TB, mostly adults in the community [15] [16].

We did not find any statistical difference in LTBI among those with BCG scar. Bacillie Calmette Guerin (BCG) vaccination protection has shown to be effective up till 15 years [17]. BCG vaccination was introduced during the early 70's as part of the immunization schedule in Oman and is given soon after birth [18]. Though various studies show variable effects of BCG efficacy, a systematic review of Randomized Controlled Trials have concluded that in the absence of M. *tuberculosis* infection or sensitization with environmental mycobacteria, the BCG vaccine efficacy is quite high against PTB and possibly disseminated TB and TB meningitis [19].

Oman is situated near to the equator and the prevalence of Non Tuberculosis Mycobacterium (NTM) is on the rise with Mycobacterium avium complex (MC) organism frequently isolated [20]. In Oman, TST is part of the screening test for LTBI and the likelihood of false positives is conceivable due to the high BCG vaccine coverage and prevalence of NTMs. Nevertheless, the benefits of INH treatment have been shown in TST positive contacts [21]. Therefore, serious consideration must be given to revisit this policy of TST testing among household contacts. IGRA testing is most suitable in a BCG vaccinated population and in a community with an increased prevalence of NTM but operational issues arising from conducting a phlebotomy process in children less than 5 years of age poses a challenge.

Sputum positive cases with cavitary lesions are highly infectious and may be "super-spreaders" [22]. Cavitary lung lesions permit the replication of the bacilli extracellular thus intensifying the bacilli load [22]. In this study higher LTBI positivity was noted among contacts of patients with cavitary lesions, without statistical significance.

48% of the index cases in this study were having diabetes. Consideration must be given to the growing diabetic epidemic in the Middle East, since it can significantly increase the annual risk of infection (ARI) among contacts exposed to infectious TB and increase their chance of developing active disease.

5. Limitations

Data for the study was collected retrospectively. This resulted in scanty data about risk factors such as smoking, alcohol consumption, BCG scar, and diabetes. Details of contacts that included height and weight were missing.

Patient characteristics such as AFB sputum smear positivity, cavity on chest X-ray were common for many of the contacts since many of them were exposed

to the same patient. Influence of patient characteristics must thus, be interpreted with caution.

We limited the statistical analysis to single risk factor analysis because of the limited number of cases.

6. Conclusions

LTBI treatment options should be provided to high risk contacts. In our setting, besides children, female household contacts and older age contacts should be prioritized for ensuring screening as they are more likely to be infected, default and develop active disease.

The use of TST and IGRA for the diagnosis of LTBI in our setup also needs to be further reviewed to recommend the best suitable testing tool in Oman.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] National Center for Statistics and Information (2019).

[2] National TB Control Program C, Ministry of Health, Oman (2012) Tuberculosis Control Program.

[3] Al-Lawati, J.A., Panduranga, P., Al-Shaikh, H.A., Morsi, M., Mohsin, N., Khandekar, R.B., *et al.* (2015) Epidemiology of Diabetes Mellitus in Oman: Results from Two Decades of Research. *Sultan Qaboos University Medical Journal*, **15**, e226-e233.

[4] Al-Maniri, A., Fochsen, G., Al-Rawas, O. and De Costa, A. (2010) Immigrants and Health System Challenges to TB Control in Oman. *BMC Health Services Research*, **10**, Article No. 210. https://doi.org/10.1186/1472-6963-10-210

[5] Fox, G.J., Barry, S.E., Britton, W.J. and Marks, G.B. (2015) Contact Investigation for Tuberculosis: A Systematic Review and Meta-Analysis. *European Respiratory Journal*, **41**, 140-156. https://doi.org/10.1183/13993003.50708-2012

[6] Dye, C., Glaziou, P., Floyd, K. and Raviglione, M. (2013) Prospects for Tuberculosis Elimination. *Annual Review of Public Health*, **34**, 271-286. https://doi.org/10.1146/annurev-publhealth-031912-114431

[7] WHO (2015) Guidelines on the Management of Latent Tuberculosis Infection.

[8] Nhamoyebonde, S. and Leslie, A. (2014) Biological Differences between the Sexes and Susceptibility to Tuberculosis. *The Journal of Infectious Diseases*, **209**, S100-S106. https://doi.org/10.1093/infdis/jiu147

[9] Moosazadeh, M., Khanjani, N. and Parsaee, M. (2015) The Prevalence of Latent Tuberculosis Infection and Smear Positive Pulmonary Tuberculosis in People with Household Close Contact with Tuberculosis in North of Iran. *Iranian Journal of Medical Sciences*, **40**, 161-165.

[10] Balkhy, H.H., El Beltagy, K., El-Saed, A., Aljasir, B., Althaqafi, A., Alothman, A.F., *et al.* (2017) Prevalence of Latent Mycobacterium Tuberculosis Infection (LTBI) in Saudi Arabia; Population Based Survey. *International Journal of Infectious Diseases*, **60**, 11-16. https://doi.org/10.1016/j.ijid.2017.03.024

[11] Aabye, M.G., Ravn, P., PrayGod, G., Jeremiah, K., Mugomela, A., Jepsen, M., *et al.* (2009) The Impact of HIV Infection and CD4 Cell Count on the Performance of an Interferon Gamma Release Assay in Patients with Pulmonary Tuberculosis. *PLoS ONE*, **4**, e4220. https://doi.org/10.1371/journal.pone.0004220

[12] Getahun, H., Matteelli, A., Abubakar, I., Aziz, M.A., Baddeley, A., Barreira, D., *et al.* (2015) Management of Latent *Mycobacterium tuberculosis* Infection: WHO Guidelines for Low Tuberculosis Burden Countries. *European Respiratory Journal*, **46**, 1563. https://doi.org/10.1183/13993003.01245-2015

[13] Houben, R.M. and Dodd, P.J. (2016) The Global Burden of Latent Tuberculosis Infection: A Re-Estimation Using Mathematical Modelling. *PLOS Medicine*, **13**, e1002152. https://doi.org/10.1371/journal.pmed.1002152

[14] Negin, J., Abimbola, S. and Marais, B.J. (2015) Tuberculosis among Older Adults 2013: Time to Take Notice. *International Journal of Infectious Diseases*, **32**, 135-137. https://doi.org/10.1016/j.ijid.2014.11.018

[15] Khan, P.Y., Glynn, J.R., Fielding, K.L., Mzembe, T., Mulawa, D., Chiumya, R., *et al.* (2016) Risk Factors for *Mycobacterium tuberculosis* Infection in 2-4 Year Olds in a Rural HIV-Prevalent Setting. *The International Journal of Tuberculosis and Lung Disease*: *The Official Journal of the International Union against Tuberculosis and Lung Disease*, **20**, 342-349. https://doi.org/10.5588/ijtld.15.0672

[16] Middelkoop, K., Bekker, L.-G., Morrow, C., Zwane, E. and Wood, R. (2009) Childhood Tuberculosis Infection and Disease: A Spatial and Temporal Transmission Analysis in a South African Township. *South African Medical Journal*, **99**, 738-743.

[17] Abubakar, I., Pimpin, L., Ariti, C., Beynon, R., Mangtani, P., Sterne, J.A., *et al.* (2013) Systematic Review and Meta-Analysis of the Current Evidence on the Duration of Protection by Bacillus Calmette-Guerin Vaccination against Tuberculosis. *Health Technology Assessment*, **17**, 1-372. https://doi.org/10.3310/hta17370

[18] Ministry of Health O. (2002) Manual on Expanded Program on Immunization.

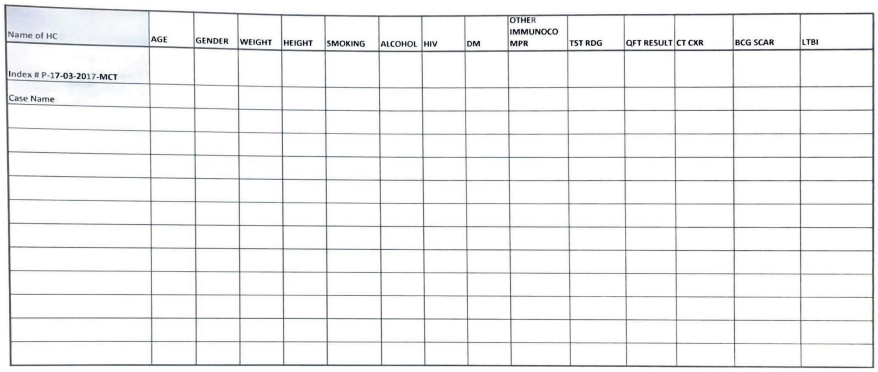
[19] Mangtani, P., Abubakar, I., Ariti, C., Beynon, R., Pimpin, L., Fine, P.E.M., *et al.* (2014) Protection by BCG Vaccine against Tuberculosis: A Systematic Review of Randomized Controlled Trials. *Clinical Infectious Diseases*, **58**, 470-480. https://doi.org/10.1093/cid/cit790

[20] Al-Mahruqi, S.H., van-Ingen, J., Al-Busaidy, S., Boeree, M.J., Al-Zadjali, S., Patel, A., *et al.* (2009) Clinical Relevance of *Nontuberculous mycobacteria*, Oman. *Emerging Infectious Diseases*, **15**, 292-294. https://doi.org/10.3201/eid1502.080977

[21] Jensen, A.V., Jensen, L., Faurholt-Jepsen, D., Aabye, M.G., Praygod, G., Kidola, J., *et al.* (2013) The Prevalence of Latent *Mycobacterium tuberculosis* Infection Based on an Interferon-Gamma Release Assay: A Cross-Sectional Survey among Urban Adults in Mwanza, Tanzania. *PLoS ONE*, **8**, e64008. https://doi.org/10.1371/journal.pone.0064008

[22] Salgame, P., Geadas, C., Collins, L., Jones-Lopez, E. and Ellner, J.J. (2015) Latent Tuberculosis Infection: Revisiting and Revising Concepts. *Tuberculosis*, **95**, 373-384. https://doi.org/10.1016/j.tube.2015.04.003

Appendix



Name of HC	AGE	GENDER	WEIGHT	HEIGHT	SMOKING	ALCOHOL	HIV	DM	OTHER IMMUNOCOMPR	TST RDG	QFT RESULT	CT CXR	BCG SCAR	LTBI
Index # P-17-03-2017-MCT														
Case Name														

Figure S1. Data sheet (template).