2018-09-18

Chronic respiratory symptoms and lung abnormalities among people with a history of tuberculosis in Uganda: a national survey.

van Kampen, SC

10.1093/cid/ciy795
Clinical Infectious Diseases
Oxford University Press (OUP)

Journal: Clinical Infectious Diseases

DOI: 10.1093/cid/ciy795

Article: Chronic respiratory symptoms and lung abnormalities among people with a history of tuberculosis in Uganda: a national survey

Acceptance date: 2018-09-10

AUTHOR'S ORIGINAL VERSION (before acceptance)

Title

Chronic respiratory symptoms and lung abnormalities among people with a history of tuberculosis in Uganda: a national survey

Authors

Sanne C van Kampen, Clinical Trials and Population Studies Department, University of Plymouth, 1 Davy Road, PL6 8BX, Plymouth, UK

Rupert Jones, Clinical Trials and Population Studies Department, University of Plymouth, 1 Davy Road, PL6 8BX, Plymouth, UK

Harriet Kisembo, Department of Radiology, Mulago Hospital, Upper Mulago Hill, 256 Kampala, Uganda

Rein MGJ Houben, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel St, WC1E 7HT, London, UK

Yinghui Wei, Centre for Mathematical Sciences, School of Computing, Electronics and Mathematics, University of Plymouth, Plymouth, PL4 8AA, UK

Frank R Mugabe, National Tuberculosis and Leprosy Programme, Ministry of Health, Plot 6, Lourdel Road, Nakasero, P.O Box 7272, Kampala, Uganda

Elizeus Rutebemberwa, Lung Institute, Makerere University, Upper Mulago Hill, 256 Kampala, Uganda

Bruce Kirenga, Lung Institute, Makerere University, Upper Mulago Hill, 256 Kampala, Uganda

Keywords: tuberculosis; chronic respiratory disorders; epidemiology; prevalence survey; Uganda

Running title: Post-TB respiratory problems in Uganda

Corresponding author:

Dr Sanne Christine van Kampen

Clinical Trials and Population Studies Department, University of Plymouth

Plymouth Science Park, 1 Davy Road,

PL6 8BX, Plymouth, UK

Email: sanne.vankampen@plymouth.ac.uk

Tel.nr: +44 1752 764267; +44 7972 703087

Alternative corresponding author:

Dr Rupert Jones

Clinical Trials and Population Studies Department, University of Plymouth

Plymouth Science Park, 1 Davy Road,

PL6 8BX, Plymouth, UK

Email: rupert.jones@plymouth.ac.uk

Tel.nr: +44 1752 764258

Key points

Among the general population of Uganda, ex-TB patients are at high risk of chronic cough, phlegm, chest pain, haemoptysis and chest x-ray abnormalities. A history of TB was a greater predictor of chronic respiratory problems than old age or smoking.

Word counts: Abstract: 198. Text:2,986

ABSTRACT

Background

People with pulmonary tuberculosis (TB) are at risk of developing chronic respiratory disorders due to residual lung damage. So far, the scope of the problem in high burden TB countries is relatively unknown.

Methods

Chronic respiratory symptoms (cough and phlegm lasting >2 weeks) and radiological lung abnormalities were compared between adults with and without a history of TB among the general population of Uganda. Multivariable regression models were used to estimate odds ratios with adjustment for age, gender, smoking, education, setting and region. Random effects models accounted for village clustering effect.

Results

Of 45,293 invited people from 70 villages, 41,154 (90.9%) participated in the survey. 798 had a history of TB and among them, 16% had respiratory symptoms and 41% x-ray abnormalities. Adjusted odds ratios showed strong evidence for individuals with a history of TB having increased risk of respiratory symptoms (OR=4·02, 95%CI: 3·25-4·96) and x-ray abnormalities (OR=17·52, 95%CI: 14·76-20·79); attributing 6% and 24% of the respective population risks.

Conclusions

In Uganda, a history of TB was a strong predictor of respiratory symptoms and lung abnormalities, before older age and smoking. Eliminating TB disease could reduce the prevalence of chronic respiratory symptoms as much as eliminating smoking.

BACKGROUND

Tuberculosis (TB) is the biggest cause of death from a single infectious disease resulting in an estimated 10·4 million new patients and 1·3 million deaths globally in 2016.[1] Uganda has a high burden of TB with an estimated incidence of 201 new TB cases and 26 TB-related deaths per 100,000 population per year.[2] Yet, TB-associated mortality and morbidity are usually only captured during treatment, while post-treatment sequelae are less well documented and recognized. TB disease can lead to chronic lung damage including scarring, fibrosis and cavitation, with associated radiological abnormalities.[3, 4] These lung abnormalities are the main risk factor for cured TB patients to develop airflow limitations, chronic respiratory symptoms and diseases including chronic obstructive pulmonary disease (COPD), bronchiectasis and aspergillosis.[4-8] People with post-TB chronic respiratory disorders can be prone to breathlessness, fatigue, physical inactivity and psychosocial isolation which have negative consequences for quality of life and earnings.[9, 10]

Simultaneously, chronic respiratory diseases show an increasing global trend with COPD now being the third leading cause of death. An estimated 3·2 million people died of COPD in 2015, disproportionately affecting people in low- and middle-income countries where diagnosis and treatment are often poor.[11, 12] In Uganda, a recent survey in a rural district found a COPD prevalence as high as 16%.[13] Recent international surveys have confirmed that TB is an important risk factor of COPD, besides smoking and air pollution.[11, 12] A history of TB is estimated to triple the risk of COPD (OR 3·05, 95%CI: 2·42-3·85) and even more in countries with a higher TB incidence.[14-17] Despite the emerging evidence on the relationship between TB and chronic lung disorders, there is a lack of programmatic recommendations and interventions to identify and manage patients beyond their cure of TB.[18, 19] A systematic scoping review conducted by the authors found that no international TB guidelines addressed the issue.[20] There is a limited number

of studies on the prevalence of post-TB lung disorders, especially from Sub-Saharan Africa.[16, 17, 21] One study from South Africa assessed post-TB chronic bronchitis (cough and phlegm ≥ 3 months) through a national survey in 2004, but did not include other respiratory symtopms or chest x-ray abnormalities.[22] Few studies in general have related structural lung damage to respiratory symptoms.[4] To contribute to the evidence on post-TB lung disorders, this study assessed a range of chronic respiratory symptoms and radiological abnormalities among the general population of Uganda using data from the most recent national TB prevalence survey.

METHODS

Study design and population

This study used data from the national TB prevalence survey of Uganda conducted in 2014-2015 by the Ministry of Health together with Makerere University, WHO and Centers for Disease Control and Prevention.[23] In the original survey, a national representative sample was obtained using the entire country as the sampling frame and villages as the sampling units. Villages were stratified by rural and urban settings and a total of 70 villages with between 550 and 680 eligible respondents were selected with probability proportionate to population size. All households in a selected village were included. All consenting permanent residents and those visiting the residence since more than two weeks aged 15 years and above were eligible.

Ethical approval of the original survey was granted by the Institutional Review Boards of the Higher Degree Research and Ethics Committee (HDREC) at the Makerere University School of Public Health and the Uganda National Council of Science and Technology (UNCST), under reference number IRB00011353.

Data collection

Data for the original household survey was collected from October 2014 to July 2015. Participants were interviewed with a questionnaire on demographics, clinical symptoms, smoking behaviour, and current and past TB treatment (see Box 1). Subsequently, all people received a chest x-ray to assess lung abnormalities as per WHO guidelines. The films were read by radiology consultants from the national lung hospital. Participants with cough for two weeks or more and/or an abnormal chest x-ray were asked to provide two sputum samples for bacteriological tests for active TB disease (smear microscopy, GeneXpert, culture). Participant data from questionnaires, chest x-rays and laboratory tests were entered, cleaned, verified and anonymised in an electronic database using EpiInfo version 3.51.

For the present study, people with current TB were excluded, i.e. those who reported to be taking anti-TB drugs or who were diagnosed with active TB disease during the survey. People with a history of TB were those who self-reported to ever have been treated for TB in their lifetime but did not have current TB disease. Regions represented statistical groupings of districts without administrative or political status as used in the 2002 Uganda Census.[24]

Outcomes

Respiratory symptoms

Respiratory symptoms were recorded as self-reported presence or absence and duration in days of: cough; phlegm; haemoptysis; and chest pain. A composite binary outcome for chronic respiratory symptoms (presence or absence) was constructed based on cough and phlegm: people who reported both cough and phlegm of two weeks or more were classified as having chronic respiratory symptoms. Haemoptysis was not included in the composite outcome because this is a rare symptom of severe chronic respiratory disease. Chest pain, although potentially linked to respiratory problems, is not a distinguishing symptom of chronic lung disease.[9]

Lung abnormalities

Radiological lung abnormalities were based on chest x-ray reports, which for this analysis were converted from a categorical to a binary variable, i.e.: reports of inactive/healed TB, suggestive active TB disease and other lung abnormalities, whether or not they were thought to be consistent with TB, were regrouped as presence of lung abnormalities; normal readings and extra-pulmonary abnormalities were regrouped as absence of lung abnormalities; poor x-ray/not read and missing readings were recoded as missing.

Statistical analysis

The proportion of chronic respiratory symptoms and radiological lung abnormalities was presented for the overall study population and for people with and without a history of TB. This study had 90% power at a two-sided 5% significance level to detect a proportional difference of 2.5% for the main outcomes between people with and without a history of TB. Crude odds ratios of the association between past TB and both outcomes were calculated with 95% confidence intervals and Chi-square tests. Multivariable logistic regression models were used to adjust for age, gender, smoking, education, region and setting. Multi-collinearity between these variables was assessed using variance inflation factors (VIF) and variables were dropped from the model if VIF>10. Adjustment for village clustering was done using a random effects model. Effect modifiers were included in the final model if the effect on outcomes varied dramatically (i.e. reverse direction) across variable subgroups. Finally, population attributable risk fractions were calculated for the two main outcomes using standard formulas. Statistical analyses were performed using STATA version SE14.

Sensitivity analyses were performed to explore the impact of different outcome definitions. First, we estimated the odds ratios for chronic respiratory symptoms using a three-month cut-off point rather than two weeks, as GOLD guidelines do not specify the minimum duration of respiratory

symptoms for classification of e.g. COPD.[9] Secondly, we estimated the odds ratio of radiological lung abnormalities reclassifying people with 'inactive/healed TB' as having no lung abnormalities, since some ex-TB patients could have for example calcified lymph nodes without ever developing respiratory disorders.

RESULTS

Of 45,293 eligible individuals, 41,154 (90.9%) received symptoms screening and/or chest x-ray scans. After excluding 205 people with current TB, 40,949 people remained of whom 204 (<1%) had missing chest x-ray data (respiratory symptom data was complete). Table 1 shows the characteristics of the study population. A total of 798 out of 40,949 people (1·9%) reported a history of TB and 40,151 (98·1%) reported no history of TB. People with a history of TB were more often male (52·9%), living in the north (31·3%) or central region (35·3%), living in urban settings (47·1%), past (20·9%) or current smokers (10·0%), and older than people without a history of TB.

Table 2 shows the proportion of people with chronic respiratory symptoms (individual and composite) and radiological lung abnormalities. As many as 21% of the general population reported chest pain. Among people with a history of TB, 16% reported cough and phlegm, 41% had lung abnormalities and 9% had both. A history of TB was crudely associated with cough and phlegm (OR 4·95, 95%CI: 4·06-6·05), as well as lung abnormalities (OR 21·79, 95%CI: 18·60-25·53). Although symptoms and lung damage were highly correlated ($p<0.0001$), the majority of people with lung abnormalities did not report cough and phlegm (78%; 253/326), and some with symptoms had no lung abnormalities (41%; 50/123). Still, people with past TB and lung abnormalities had 2.41 (95%CI: 1.62-3.58) times the odds of respiratory symptoms than those with no x-ray abnormalities.

Age, smoking, gender, region, setting and education were included as potential confounders in a multivariable logistic regression model. None of the variables showed multi-collinearity (all VIF<1·2). Table 3 shows that after adjusting for these factors, as well as for village clustering effect, there was still a significant association between a history of TB and respiratory symptoms. People with a history of TB had 4·02 (95%CI: 3·25-4·96; p<0·001) times the odds of chronic cough and phlegm than people without a history of TB. The odds of having respiratory symptoms also increased with older age and smoking, while living in the western region of the country and having a higher education decreased the odds. The within-village correlation coefficient (rho=0.041, 95%CI: 0.026-0.064, p<0·001) indicated that people living within the same village were indeed more similar than people living in different villages.

Table 4 shows that after adjusting for all variables and village clustering effect, people with a history of TB had 17·52 (95%CI:14·76-20·79) times the odds of lung abnormalities than people without a history of TB. The village clustering effect was again significant (rho=0·020, 95%CI: 0·011-0·036, p<0·001). While the odd ratio of lung abnormalities varied widely across age groups (LRT p=0.0001), from 27·34 (95%CI: 16·49-45·34) among 15-24 year olds to 8·18 (95%CI: 5·11-13·11) among 65+ year olds, age did not actually reverse the effect of TB history on lung abnormalities and was therefore not included as effect modifier in the final model. Besides a history of TB, the odds of having lung abnormalities increased with older age and past or current smoking, while living in the western region of the country and higher education decreased the odds. Women had only half the odds of having lung abnormalities than men.

A history of TB attributed an estimated 6% of the population's risk of chronic respiratory symptoms and 24% of the risk of radiological lung abnormalities. In comparison, older age (65+ years) imposed the largest population risk on both outcomes (14% and 42%, respectively), while current

smoking had a similar impact on respiratory symptoms (7%) and a much smaller impact on lung abnormalities (5%) than a history of TB.

A sensitivity analysis around chronic respiratory symptoms showed that using a cut-off point of three months rather than two weeks actually increased the crude odds ratio from 4·95 to 7·54 (95%CI: 5·14-11·07) and the fully-adjusted odds ratio from 4·02 to 5·19 (95%CI: 3·43-7·84), which suggested a stronger impact of a history of TB on long-term rather than short-term respiratory symptoms. A sensitivity analysis around radiological lung abnormalities showed that excluding people with 'inactive/healed TB' on chest x-ray would reduce the crude odds ratio from 21·79 to 8·67 (95%CI: 7·21-10·43) and the fully-adjusted odds ratio from 17·52 to 5·87 (95%CI: 4·81-7·15). This was driven by the association between a history of TB and radiological signs of previous TB disease. Further inspection revealed that 74% of people with 'inactive/healed TB' had atelectasis (lung collapse) and 42% had fibrosis, both commonly associated with respiratory disorders, thus excluding them would underestimate the effect of a history of TB on lung abnormalities.

DISCUSSION

This study assessed the scope of post-TB chronic respiratory symptoms and lung abnormalities among the general population of Uganda and found that people with a history of TB had four times the odds of having chronic respiratory symptoms and 18 times the odds of radiological lung abnormalities compared to people without a history of TB. Chronic cough, phlegm, chest pain and haemoptysis were all significantly more prevalent among people with than without a history of TB. At individual level, a history of TB was a very strong predictor of respiratory problems even before older age and smoking. At population level, a history of TB was at par with smoking and only surpassed by old age in terms of attributable risk. Our sensitivity analyses showed that even when

chronic symptoms and lung abnormalities were defined more conservatively, strong evidence for an impact of past TB as a risk factor remained. These findings are consistent with a previous study from South Africa, which found odds ratios for chronic bronchitis of 4·9 (95%CI:2·6-9·1) for men and 6·6 (95%CI:3·7-11·7) for women with past TB.[22] Those findings may have been slightly overestimated as the study did not exclude people with active TB disease. Most other studies on respiratory symptoms or lung abnormalities have been conducted in occupational or clinical settings and were less comparable. This is the first study to report on the national proportion of post-TB lung abnormalities and compare it with respiratory symptoms. The fact that the majority of people with lung abnormalities did not report respiratory symptoms indicates that lung damage, although doubling the risk, does not always lead to respiratory disease.

Men had almost twice the odds of lung abnormalities than women after controlling for other factors including TB history and smoking. This warrants further exploration as we are not aware of any studies reporting a similar finding. Occupational exposure could be higher in men, but would likely be outweighed by women being more exposed to household air pollution. Delays to diagnosis of TB, potentially leading to increased lung damage, also tend to be higher among women.[25] People with higher levels of education were less prone to post-TB problems possibly because they were on average wealthier, had better access to health services, and less often used biomass fuel for cooking. People living in the western region of Uganda had reduced risks, which might be due to environmental, cultural or genetic variations that can be explored in further studies. Older age increases the risk of respiratory disorders because of deterioration of the lungs over a lifetime and cumulative lung damage resulting from environmental exposures and other lung insults. Smoking is known to be the most common cause of chronic airflow obstruction in high income countries.[26] Interestingly, this study has brought to light that eliminating TB disease in the population of Uganda could result in at least as large a reduction of chronic respiratory symptoms as eliminating smoking.

The strength of this study was the large, nationally representative sample of over 40,000 people. The study population was similar to the general population of Uganda as measured by the 2014 Census in terms of gender (51% females), age (5% 65+ years) and education (19% without formal education).[27] The findings are therefore likely to be generalizable to the whole country and to other countries with similar TB epidemiology and demographics. This study also had some limitations. First, this study was not able to control for potential confounding by household smoke exposure, outside air pollution, occupational exposure to e.g. dust or silica, diabetes and HIV status. Although rural/urban setting could partly serve as proxy for inside/outside air pollution and occupational expsoure, positive confounding by these factors cannot be excluded. Secondly, there was a risk of recall bias due to the fact that TB history and respiratory symptoms were self-reported and not verified by clinical assessments or historical records. People with either of these may remember and report the presence of the other more actively, which could potentially have slightly overestimated our associations. Thirdly, there may have been a small risk of selection bias as 9% of the study population was excluded due to missing data. However, since the excluded group was on average younger, including them would likely have increased the association between a history of TB and lung abnormalities. Lastly, there was a risk of survival bias as only those people who survived longer post-TB will have been included in the survey and those might be the ones with milder respiratory problems. If this study missed some people with severe chronic lung disorders due to premature mortality, then our already strong associations would have been underestimated. Future cohort studies should evaluate the potential effect of time since last TB treatment and potential confounders such as indoor and outdoor air pollution and co-morbidities. Future population based studies that enquire about chronic respiratory symptoms should also include measures of lung function (spirometry), dyspnoea and wheeze in order to diagnose disorders like COPD and bronchiectasis.

While post-TB chronic lung disorders can primarily be reduced by adequate and timely treatment and prevention of active TB disease, it is equally imperative to monitor and manage respiratory problems after cure of TB. People at risk of chronic respiratory problems should be identified as early as possible in order to optimize prognosis and treatment outcomes, for example by offering clinical symptom assessment, chest x-ray scans and lung function tests immediately or a few months after being cured of TB. They are likely to benefit most from interventions including smoking cessation, patient education for self-management, pulmonary rehabilitation and bronchodilator therapy.[9, 28] The tremendous expense and disability associated with chronic lung diseases in North America and Europe has important implications for the future of low resource countries like Uganda.[29] Even though international guidance is lacking, Uganda has very recently included the issue of post-TB lung disorders into its national TB programme guidelines. Also, a preliminary study of pulmonary rehabilitation showed major improvements in dyspnoea, exercise capacity and chest pains among ex-TB patients.[30] It is important for more high burden TB countries and international policy makers and researchers to consider and address the issue of post-TB lung disorders if we are to reduce overall TB-related morbidity and mortality.

Funding

This work was supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care of the South West Peninsula (PenCLAHRC); and the European Research Council (starting grant number 757699 to RMGJH). The original survey was funded by the Global Fund against AIDS, Tuberculosis, and Malaria. The views expressed are those of the authors and not necessarily those of the UK's National Health Services (NHS), the NIHR or the Department of Health and Social Care.

Acknowledgements

The authors would like to thank the Ministry of Health of Uganda and Makerere University College of Health Sciences in Kampala for their kind authorization to use the database of the national TB prevalence survey 2014-2015 for this project.

Conflict of interest

RJ has received personal fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, GSK and Novartis, and non-financial support from Nutricia, unrelated to this work. The other authors declare to have no conflict of interests.

REFERENCES

1. WHO. Global tuberculosis report 2017. Geneva: World Health Organization; 2017. http://www.who.int/tb/publications/global_report/en/ (accessed 1 June 2018)

2. WHO. Tuberculosis country profiles; Uganda. Geneva: World Health Organization; 2016. http://www.who.int/tb/country/data/profiles/en/ (accessed 1 June 2018)

3. Plit ML, Anderson R, Van Rensburg CEJ, Page-Shipp L, Blott JA, Fresen JL, et al. Influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis. European Respiratory Journal. **1998**;12(2): 351-6. doi:10.1183/09031936.98.12020351

4. Meghji J, Simpson H, Squire SB, Mortimer K. A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease. PLoS One. **2016**;11(8): e0161176. doi:10.1371/journal.pone.0161176

5. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. European Respiratory Journal. **2010**;35(1): 27-33.

6. Sarkar M, Srinivasa, Madabhavi I, Kumar K. Tuberculosis associated chronic obstructive pulmonary disease. Clin Respir J. **2017**;11(3): 285-95. doi:10.1111/crj.12621

7. Akkara SA, Shah AD, Adalja M, Akkara AG, Rathi A, Shah DN. Pulmonary tuberculosis: the day after. Int J Tuberc Lung Dis. **2013**;17(6): 810-3. doi:10.5588/ijtld.12.0317

8. Chung K-P, Chen J-Y, Lee C-H, Wu H-D, Wang J-Y, Lee L-N, et al. Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis. Clinics. **2011**;66(4): 549-56. doi:10.1590/s1807-59322011000400005

9. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J. **2017**;49(3). doi:10.1183/13993003.00214-2017

10. de la Mora IL, Martinez-Oceguera D, Laniado-Laborin R. Chronic airway obstruction after successful treatment of tuberculosis and its impact on quality of life. Int J Tuberc Lung Dis. **2015**;19(7): 808-10. doi:10.5588/ijtld.14.0983

11. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. Int J Tuberc Lung Dis. **2015**;19(1): 10-20. doi:10.5588/ijtld.14.0446

12. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. **2015**;5(2): 020415. doi:10.7189/jogh.05-020415

13. van Gemert F, Kirenga B, Chavannes N, Kamya M, Luzige S, Musinguzi P, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. The Lancet Global Health. **2015**;3(1): e44-e51. doi:10.1016/s2214-109x(14)70337-7

14. Amaral AF, Coton S, Kato B, Tan WC, Studnicka M, Janson C, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. Eur Respir J. **2015**;46(4): 1104-12. doi:10.1183/13993003.02325-2014

15. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. Eur Respir J. **2007**;30(6): 1180-5. doi:10.1183/09031936.00083507

16. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. Respiration. **2013**;86(1): 76-85. doi:10.1159/000350917

17. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. Int J Infect Dis. **2015**;32: 138-46. doi:10.1016/j.ijid.2014.12.016

18. Harries AD, Ade S, Burney P, Hoa NB, Schluger NW, Castro JL. Successfully treated but not fit for purpose: paying attention to chronic lung impairment after TB treatment. Int J Tuberc Lung Dis. **2016**;20(8): 1010-4. doi:10.5588/ijtld.16.0277

19. Chakaya J, Kirenga B, Getahun H. Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. **2016**;3: 10-2. doi:10.1016/j.jctube.2016.03.001

20. Van Kampen SC, Wanner A, Edwards M, Harries AD, Kirenga B, Chakaya J, Jones R. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. BMJ Global Health (in press).

21. Ehrlich RI, Adams S, Baatjies R, Jeebhay MF. Chronic airflow obstruction and respiratory symptoms following tuberculosis: a review of South African studies. International Journal of Tuberculosis & Lung Disease. **2011**;15(7): 886-91.

22. Ehrlich R, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Predictors of chronic bronchitis in South African adults. International Journal of Tuberculosis & Lung Disease. **2004**;8(3): 369-76.

23. MOH. The Uganda national tuberculosis prevalence survey, 2014-2015: survey report. Kampala: Ministry of Health; **2014**. http://health.go.ug/content/uganda-national-tuberculosis-prevalence-survey-2014-2015-survey-report (accessed 1 June 2018)

24. UBOS. Uganda population and housing census: population dynamics. Kampala: Uganda Bureau of Statistics; **2002**. https://ubos.org/wp-content/uploads/publications/03_20182002_CensusPopndynamicsAnalyticalReport.pdf (accessed 1 June 2018)

25. Karim F, Islam MA, Chowdhury AM, Johansson E, Diwan VK. Gender differences in delays in diagnosis and treatment of tuberculosis. Health Policy Plan. **2007**;22(5): 329-34. doi:10.1093/heapol/czm026

26. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. The Lancet. **2007**;370(9589): 741-50. doi:10.1016/s0140-6736(07)61377-4

27. UBOS. The national population and housing census 2014: main report. Kampala: Uganda Bureau of Statistics; 2016. http://www.ubos.org/2016/03/24/census-2014-final-results/ (accessed 1 June 2018)

28. Munoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis? J Bras Pneumol. **2016**;42(5): 374-85. doi:10.1590/S1806-37562016000000226

29. Chan-Yeung M, Ait-Khaled N, White N, Ip MS, Tan WC. The burden and impact of COPD in Asia and Africa. Int J Tuberc Lung Dis, **2004**;8(1): 2–14.

30. Jones R, Kirenga BJ, Katagira W, Singh SJ, Pooler J, Okwera A, et al. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. Int J Chron Obstruct Pulmon Dis. **2017**;12: 3533-9. doi:10.2147/COPD.S146659

Table 1. Characteristics of the study population and among people with and without a history of TB among the general population of Uganda in 2014-2015

Demographics	Categories	Total (n=40,949)	History of TB (n=798)	No history of TB (n=40,151)	Crude association	Chi-square test
		n (%)	*n (%)*	*n (%)*	*Odds ratio (95% CI)*	*p-value*
Age	15-24 years	14738 (35·99)	109 (13·66)	14629 (36·43)	1.00	-
	25-34 years	10494 (25·63)	170 (21·30)	10324 (25·71)	2.21 (1.73, 2.82)	<0·0001
	35-44 years	6785 (16·57)	175 (21·93)	6610 (16·46)	3.55 (2.79, 4.52)	<0·0001
	45-54 years	4246 (10·37)	179 (22·43)	4067 (10·13)	5.91 (4.64, 7.53)	<0·0001
	55-64 years	2203 (5·38)	79 (9·90)	2124 (5·29)	4.99 (3.72, 6.70)	<0·0001
	65+ years	2483 (6·06)	86 (10·78)	2397 (5·97)	4.82 (3.61, 6.42)	<0·0001
Gender	Male	17340 (42·35)	422 (52·88)	16918 (42·14)	1·54 (1·34, 1·77)	<0·0001
	Female	23609 (57·65)	376 (47·12)	23233 (57·86)	1·00	-
Education [a]	None	6959 (16·99)	177 (22·18)	6782 (16·89)	1·13 (0·84, 1·52)	0·423
	Primary	19780 (48·30)	353 (44·24)	19427 (48·38)	0·79 (0·60, 1·04)	0·087
	Senior 1-4	9897 (24·17)	173 (21·68)	9724 (24·22)	0·77 (0·57, 1·04)	0·083
	Senior 5-6	1655 (4·04)	35 (4·39)	1620 (4·03)	0·93 (0·61, 1·42)	0·752
	Tertiary	2655 (6·48)	60 (7·52)	2595 (6·46)	1·00	-
Region [b]	Central	13876 (33·89)	282 (35·34)	13594 (33·86)	1·47 (1·19, 1·82)	0·0003
	East	8960 (21·88)	136 (17·04)	8824 (21·98)	1·09 (0·86, 1·39)	0·466
	North	8752 (21·37)	250 (31·33)	8502 (21·18)	2·09 (1·69, 2·59)	<0·0001
	West	9360 (22·86)	130 (16·29)	9230 (22·99)	1·00	-
Setting	Rural	23705 (57·89)	422 (52·88)	23283 (57·99)	1·00	-
	Urban	17244 (42·11)	376 (47·12)	16868 (42·01)	1·23 (1·07, 1·42)	0·004
Smoking [c]	Never smoked	35290 (86·19)	551 (69·05)	34739 (86·53)	1·00	-
	Past smoker	2674 (6·53)	167 (20·93)	2507 (6·24)	4·20 (3·51, 5·02)	<0·0001
	Current smoker	2979 (7·28)	80 (10·03)	2899 (7·22)	1·74 (1·37, 2·21)	<0·0001

[a] Education level: missing for 3 out of 40,949 participants (0·007%)

[b] Region as per 2002 Uganda population and housing census [24]: missing for 1 out of 40,949 participants (0·002%)

[c] Smoking: missing for 6 out of 40,949 participants (0·01%)

Table 2. Proportion and unadjusted crude associations between having a history of TB and chronic respiratory proportion among the general population of Uganda in 2014-2015

Outcomes	Categories	Total (n=40949)	History of TB (n=798)	No history of TB (n=40151)	Crude association	Chi-square test
		n (%)	*n (%)*	*n (%)*	*Odds ratio (95% CI)*	*p-value*
Cough	Yes	2610 (6·37)	155 (19·42)	2455 (6·11)	3·70 (3·09, 4·43)	<0·0001
>2 weeks	No	38339 (93·63)	643 (80·58)	37696 (93·89)	1·00	--
Phlegm	Yes	1692 (4·13)	129 (16·17)	1563 (3·89)	4·76 (3·91, 5·79)	<0·0001
>2 weeks	No	39257 (95·87)	669 (83·83)	38588 (96·11)	1·00	--
Haemoptysis	Yes	112 (0·27)	17 (2·13)	95 (0·24)	9·18 (5·45, 15·46)	<0·0001
>2 weeks	No	40837 (99·73)	781 (97·87)	40056 (99·76)	1·00	--
Chest pain	Yes	8578 (20·95)	257 (32·21)	8321 (20·72)	1·82 (1·56, 2·11)	<0·0001
>2 weeks	No	32371 (79·05)	541 (67·79)	31830 (79·28)	1·00	--
Chest x-ray results	Normal	38,421 (93·8)	450 (56·39)	37971 (94·57)	N/A	N/A
	Inactive/healed TB	265 (0·7)	165 (20·68)	100 (0·25)		
	Extra-pulmonary abnormalities	758 (1·9)	17 (2·13)	741 (1·85)		
	Active TB diseases suggestive	146 (0·4)	56 (7·02)	90 (0·22)		
	Other findings consistent with TB	294 (0·7)	44 (5·51)	250 (0·62)		
	Other findings not consistent with TB	861 (2·1)	61 (7·64)	800 (1·99)		
	Poor x-ray/not read	56 (0·1)	1 (0·13)	55 (0·14		
	Missing	148 (0·4)	4 (0·50)	144 (0·36)		
Main outcomes						
Cough and phlegm >2 weeks [a]	Yes	1562 (3·81)	124 (15·54)	1438 (3·58)	**4·95 (4·06, 6·05)**	<0·0001
	No	39387 (96·19)	674 (84·46)	38713 (96·42)	1·00	--
Radiological lung abnormalities [b]	Yes	1566 (3·84)	326 (41·11)	1240 (3·10)	**21·79 (18·60, 25·53)**	<0·0001
	No	39179 (96·16)	467 (58·89)	38712 (96·90)	1·00	--

[a] Composite outcome for respiratory symptoms, combining people with cough and phlegm lasting 14 days or more

[b] Combining people with inactive/healed TB, active TB diseases, or other lung conditions whether consistent or not consistent with TB; missing for 204 participants (<1%)

Table 3. Multivariable logistic regression model for the association between a history of TB and respiratory symptoms adjusted for confounding and clustering

Variables included in the final model for COUGH AND PHLEGM > 2 WEEKS	**Fully-adjusted association**	**Wald test**
	Odds ratio (95% CI)	*p-value*
History of TB	**4·02 (3·25, 4·96)**	**<0·001**
Age group (15-24 years)	--	--
25-34 years	1·29 (1·10, 1·52)	0·002
35-44 years	1·48 (1·24, 1·75)	<0·001
45-54 years	1·75 (1·46, 2·11)	<0·001
55-64 years	1·93 (1·55, 2·41)	<0·001
65+ years	3·75 (3·10, 4·53)	<0·001
Smoking (never smoked)	--	--
Past smoker	1·48 (1·24, 1·77)	<0·001
Current smoker	2·00 (1·70, 2·36)	<0·001
Region [a] (central)	--	--
East	0·99 (0·74, 1·32)	0·943
North	1·11 (0·83, 1·47)	0·482
West	0·56 (0·42, 0·75)	<0·001
Setting (rural)	--	--
Urban	0·86 (0·69, 1·07)	0·172
Education (no education)	--	--
Primary	0·74 (0·65, 0·85)	<0·001
Senior 1-4	0·53 (0·45, 0·64)	<0·001
Senior 5-6	0·35 (0·23, 0·54)	<0·001
Tertiary	0·35 (0·26, 0·49)	<0·001
Gender (male)	--	--
Female	0·90 (0·80, 1·01)	0·087
Village clustering effect	*Rho (95% CI)*	*LRT [b] p-value*
Correlation coefficient	0.041 (0.026, 0.064)	<0.001

[a] Region as per 2002 Uganda population and housing survey [24]

[b] LRT; likelihood ratio test

Table 4. Multivariable logistic regression model for the association between a history of TB and radiological lung abnormalities adjusted for confounding and clustering

Variables included in the final model for RADIOLOGICAL LUNG ABNORMALITIES	**Fully-adjusted association**	**Wald test**
	Odds ratio (95% CI)	*p-value*
History of TB	**17·52 (14·76, 20·79)**	**<0·001**
Age group (15-24 years)	--	--
25-34 years	1·90 (1·54, 2·34)	<0·001
35-44 years	3·20 (2·60, 3·94)	<0·001
45-54 years	4·85 (3·92, 5·99)	<0·001
55-64 years	6·74 (5·34, 8·52)	<0·001
65+ years	13·16 (10·61, 16·32)	<0·001
Smoking (never smoked)	--	--
Past smoker	1·43 (1·22, 1·68)	<0·001
Current smoker	1·66 (1·41, 1·95)	<0·001
Region [a] (central)	--	--
East	0·93 (0·76, 1·13)	0·474
North	0·94 (0·77, 1·13)	0·498
West	0·73 (0·60, 0·88)	0·001
Setting (rural)	--	--
Urban	1·09 (0·94, 1·26)	0·263
Education (no education)	--	--
Primary	0·87 (0·75, 1·00)	0·048
Senior 1-4	0·70 (0·58, 0·85)	<0·001
Senior 5-6	0·48 (0·31, 0·73)	0·001
Tertiary	0·72 (0·55, 0·94)	0·018
Gender (male)	--	--
Female	0·47 (0·42, 0·54)	<0·001
Village clustering effect	*Rho (95% CI)*	*LRT [b] p-value*
Correlation coefficient	0.011 (0.0045, 0.025)	0.001

463 [a] Region as per 2002 Uganda population and housing survey [24]

464 [b] LRT; likelihood ratio test

465