Effect of parenchymal abnormalities on bio-aerosol production by patients with tuberculosis

Fatima B. Wurie[*†], Stephen D. Lawn[§x], Helen Booth[‡], Pam Sonnenberg[+], Andrew C. Hayward[*]

Author affiliations:

[*]Institute of Epidemiology and Health Care, University College London, United Kingdom

[§]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom

[x]Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town. South Africa.

[‡]TB Service, University College London Hospitals NHS Trust, London, United Kingdom

[+]Institute for Global Health, University College London, United Kingdom

[†]To whom correspondence may be addressed – f.wurie@ucl.ac.uk

Conflicts of interest: None

Word count: 953 words (excluding tables, acknowledgements and references)

Dear Editor,

In 2016 we provided evidence intra-thoracic tuberculosis increases bio-aerosol production in the 1-5µm range, that could plausibly transport *M.tuberculosis* during normal breathing and that there is substantial variation in production within tuberculosis patients that may plausibly relate to the degree of infectivity[1]. We also showed that extrathoracic tuberculosis and latent tuberculosis infection increase exhaled bioaerosols in the 1-5µm range but to a lesser degree than intrathoracic tuberculosis.

It is widely accepted that aerosol (<5µm) spread of *M.tuberculosis* from an index case with pulmonary cavitatory or laryngeal tuberculosis to susceptible contacts underpins communicable transmission of tuberculosis and is most strongly associated with infectivity[2,3]. In this further analysis we investigate whether latent tuberculosis, extrathoracic tuberculosis and intrathoracic increase submicron bioaerosol production as well as production in the 1-5um range and test the hypothesis that, in those with intrathoracic tuberculosis, more extensive parenchymal damage may promote higher bio-aerosol generation than those with milder TB lung pathology at pre-treatment.

Full details of recruitment and measurement of bioaerosols are previously reported.[1]. Briefly, we recruited four groups: healthy/un-infected volunteers recruited as a convenience sample of university personnel (group 1)[4]; healthy/*M. tuberculosis*-infected patients: non-infectious with no evidence of active tuberculosis as evidenced by a significant reaction (≥10 mm induration) to a Mantoux tuberculin skin test and/or a positive interferon-γ-release assay (IGRA) result (group 2); patients with active extra-thoracic tuberculosis (clinical, radiological and pathological evidence of granulomatous lesions external to the thoracic cavity and positive cultures for *M.tuberculosis* but with no clinical or radiological evidence of pulmonary or hilar or mediastinal involvement) (group 3); patients with active intra-thoracic tuberculosis (radiological and pathological evidence of lung cavitation and/or caseating and non-caseating granulomas, tubercles and fibro-caseous lesions in lung and/or hilar and/or mediastinal lymph nodes) confirmed by positive cultures and/or PCR for *M.tuberculosis* (group 4). For participants with intrathoracic tuberculosis chest x-ray data was obtained from the imaging department of University College London Hospital NHS Foundation Trust. The quality of the chest x-ray films, extent and severity of disease were based on radiographic abnormalities observed in parenchymal, pleural and central thoracic regions were assessed using a standardised chest radiograph reading and recording system (CRRS)[5]. This is a previously validated recording tool which categorises radiological patterns. The radiographic data were obtained from chest x-rays that were conducted on dates that were either on, or prior to the date that baseline bio-aerosol measurements were obtained. These data were used to subclassify intrathoracic tuberculosis according to the presence or absence of radiographic parenchymal abnormalities.

An optical particle counter (Exhalair [model 102580-AK], Pulmatrix Inc. Massachusetts, USA) was used to measure aerosol size and concentration coupled with respiratory flow rate and volume measurements. Exhaled particles (range 0.3 to 20µm in diameter) over the course of 15 tidal breaths were measured. Three bio-aerosol measurement cycles were obtained from the start of anti-tuberculous treatment (at baseline). Exhaled bio-aerosols were collected and arranged into four channels according to size ranges: ≥0.3 to ≤0.5µm; >0.5 to ≤1µm; >1 to ≤5µm; >5µm. Each cycle lasted up to two minutes to complete.

Ethical approval for the initial cohort study for group 1 participants was received by University College London Ethics Committee (reference number 1564/001). Ethical approval for groups 2-4 was secured from National Research Ethics Service (NRES) – City & East (REC study reference number 11/LO/1601). All participants provided written informed consent.

Data from 188 participants were obtained pre-treatment (baseline). High particle production was defined as any particle count above the median particle count among all study participants (median 1-5µm count = 2 counts/L; median submicron particle count = 39.2 counts/L). Table 1 shows the relationship between

the four groups and bioaerosol exhalation in the submicron and 1-5um range as well as a sub-analysis of intrathoracic cases with and without radiographic evidence of parenchymal abnormalities.

This shows an association between latent and intrathoracic tuberculosis with increased particle production in the 1-5µm range and in addition we find that intrathoracic tuberculosis (but not other forms of tuberculosis) is also associated with increased particle production in the submicron range. This implies that there are different mechanisms at play affecting the generation of larger and submicron bioaerosols, which is determined by the tuberculosis status.

It is not assumed *M.tuberculosis* bacilli (which are larger than 1µm) will transmit in a submicron particle size range, but this requires further exploration, particularly as this size range is important to reach the alveolar layer to initiate infection.[6] Submicron bioaerosols may be important for the transmission of viral infections such as COVID-19 potentially making patients with intrathoracic tuberculosis at greater risk of transmitting respiratory viruses. This may have implications for nosocomial transmission of respiratory viruses.

Contrary to our initial hypothesis, intrathoracic tuberculosis with parenchymal abnormalities was associated with low risk of being a high-particle producer of 1 to 5µm (crude OR: 0.32; 95%CI: 0.10 - 1.0; p=0.05) and submicron bio-aerosols (crude OR: 0.15; 95%CI: 0.05 - 0.50; p<0.002) compared to intrathoracic tuberculosis without parenchymal abnormalities.

Intrathoracic tuberculosis with degradation of parenchymal architecture may lead to liquid bridge formation and luminal occlusion progressing to airway closure. This may restrict the exit of bio-aerosols from the respiratory passages. Conversely, the absence of parenchymal damage or milder disease and high bio-aerosol production could be driven by an inflammatory response and mechanical efforts to destabilise the mucous layer of the airway lining may promote the formation of more bio-aerosols.

The lower bioaerosol production in those with greater parenchymal damage may limit infectivity but this more severe disease may be accompanied with higher bacillary load having the opposite effect.

Further characterisation of bioaerosol production and bacillary load in exhaled particles is merited on larger cohorts with varying degrees of parenchymal abnormalities to explore whether these findings can be replicated and to explore the impact on infectivity.

Acknowledgments

We thank the optical particle counter manufacturer, Pulmatrix for technical support throughout the study period. We also acknowledge Prof Robin Wood for providing expert advice and guidance. We thank all of the clinicians at the UCLH TB service for all their efforts in supporting the recruitment process and referral of patients during the study period. We also want to thank Prof Joy Lawn, the late Prof Steve Lawn's widow for her courage, tireless support and encouragement during the development of this letter with Steve during his final weeks.

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Crude analysis of the association of tuberculosis status and risk of high production of 1-5 micron bio-aerosols and submicron bio-aerosols at baseline using logistic regression

TB status of participants	Number of participants (n)	Proportion of cases identified as 1 to 5 micron high-particle producers* n (%)	Crude odds ratio (95% CI)	p-value	Proportion of cases identified as submicron high-particle producers* n (%)	Crude odds ratio (95% CI)	p-value
Healthy/uninfected controls	83	24 (28.9)	1		36 (43.4)	1	
Healthy/Mycobacterium-infected cases	25	14 (56.0)	3.1 (1.2 - 7.9)	0.02	10 (37.0)	0.8 (0.3 - 1.9)	0.56
Extra-thoracic cases	11	6 (54.6)	3.0 (0.8 - 10.6)	0.097	5 (45.5)	1.1 (0.3 - 3.9)	0.90
Intrathoracic cases	63	44 (69.8)	5.7 (2.8 – 11.6)	<0.001	41 (65.1)	2.4 (1.2 – 4.8)	0.01
Sub analysis comparing intrathoracic cases with and without parenchymal abnormalities detected							
No parenchymal zones affected	32	26 (81.3)	1		27 (84.4)	1	
Parenchymal zones affected	31	18 (58.1)	0.32 (0.1 – 1)	0.05	14 (45.2)	0.15 (0.05 – 0.5)	0.002

*High particle production was defined as any particle count above the median particle count among all study participants (median 1-5µm count = 2 counts/L; median submicron particle count = 39.2 counts/L).