Received: June 26 2013 | Accepted after revision: Oct 31 2013 | First published online: Dec 5 2013

Support statement: The Wheezing Illnesses STudy LEidsche Rijn received grant 2100.0095 from The Netherlands Organisation for Health Research and Development (ZonMw). An unrestricted grant was received from GlaxoSmithKline. Additionally, this work was financially supported by the UMC Utrecht Vascular Prevention Project.

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Acknowledgements: The authors gratefully acknowledge all parents and children who participated, C. Geerts (Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands) and L. van der Feltz-Minkema (Dept of Paediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht) for their major contribution to the data collection, M. Olling-de Kok (Dept of Paediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht) for secretarial support, J. Zwerver (Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht) for data management and the Vascular Imaging Centre for assistance in the vascular measurements.

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Eur Respir J 2014; 43: 1189–1192 | DOI: 10.1183/09031936.00149613 | Copyright ©ERS 2014

The association between public transport and active tuberculosis in Lima, Peru

To the Editor:

While there have been impressive gains in the global control of tuberculosis (TB) over the past two decades, TB remains a leading cause of death and efforts to decrease its burden have been limited by the rise of drug resistant strains [1]. As drug-resistant TB remains exceedingly difficult and costly to treat, more research is needed to identify areas for improving primary prevention of TB.

The risk of TB transmission is increased whenever there is overcrowding, poor ventilation and exposure to an infected individual, and public transport has been identified as a potential setting with increased risk for TB transmission [2]. Indeed, recent research demonstrates the fraction of rebreathed air on public transport is mathematically correlated with a higher risk of contracting TB [3].

Previous investigations using cross-sectional data in Lima, Peru, have demonstrated that community, rather than household, transmission may account for up to 70% of incident infections [4]. Studies conducted in Lima found an increased risk of TB infection among individuals who rode minibuses [5] and those who worked on public transport [6]. However, these studies were limited by misclassification of TB diagnosis, imprecise time variables and wide confidence intervals.

The objective of our study was to assess the association between use of public transportation and active TB using a detailed transportation questionnaire, multiple control groups and improved TB diagnostics.

We used a matched case–control design and enrolled treatment-naïve individuals newly diagnosed with TB on the day of diagnosis from three peripheral health centres in the Lima metropolitan area. Three controls without TB were individually matched by age and sex for each incident case: a patient with a symptomatic respiratory syndrome from the same clinic as the incident case, a person living in the same household as the case and a person from the same neighbourhood as the case using random number sampling. Controls were excluded if they had a prior history of TB, were HIV positive or pregnant, or were currently living with anyone with active TB (with the exception the incident case for household controls). Cases and symptomatic controls underwent confirmatory testing with solid and liquid cultures to decrease misclassification.

Each participant completed a survey assessing demographic and socioeconomic factors, risk factors for TB and transport habits. As transport usage was likely to vary throughout the year, subjects were also asked about transport usage during the prior week. To reduce confounding by indication, cases and symptomatic respiratory controls were asked about transport usage the week before onset of respiratory symptoms. The association between use of public transport and active TB was modelled with logistic regression. Each covariate was evaluated and included in the model if it had an independent association between cases and controls ($p \leqslant 0.05$) and all covariates were tested for multicollinearity. Time spent on public transport was converted to quintiles due to skewing of the mean by public transport workers, who reported spending >920 min per week on public transport.

We enrolled 86 cases from 86 households situated in 86 neighbourhoods and 85 symptomatic respiratory syndrome controls. Control groups did not vary significantly from each other and were therefore pooled in the analysis. Compared with controls, cases had lower body mass index (BMI), had a history of exposure to a household member with TB, differing occupations and more frequent travel between 15:00 h and 18:59 h. Other TB risk factors including income, number of household inhabitants, years of education, bacille Calmette–Guérin history, alcohol or tobacco use, diabetes and perception of TB exposure outside of the home did not significantly vary between case and control. There was also no significant difference between transport types. The significant covariates were included in a multivariate logistic regression model to assess transportation during the past week or past year with the risk of developing TB (table 1).

In the model assessing transport usage during the prior week, an increase in one quintile of time spent in public transportation increased the odds ratio of having TB by 34% (OR 1.34, 95% CI 1.08–1.65; $p=0.007$). There was also an association between transport usage over the past year and risk of TB, but it was not significant (OR 1.19, 95% CI 0.97–1.46; $p=0.093$). Lower BMI, previous cohabitation with a person with TB and being divorced or widowed were associated with a higher risk of TB, while working as a professional in professions requiring certification, such as healthcare, business and education, was associated with a lower risk of TB. There was an association between increased risk of TB with travel during 15:00 h and 18:59 h, which was statistically significant for the year-long model, but not for the past-week model. There was no significant effect modification among any of the covariates tested with duration of time spent on public transport.

Our study design decreased misclassification of active TB by using highly sensitive and specific TB culturing techniques, recruiting a larger sample size and using a detailed survey of public transport parameters. These attributes and the control of the known TB risk factors of prior cohabitation with a person infected with TB and BMI [7] lend further support to the likelihood that public transport is an independent risk factor for TB transmission. While risk of TB from prior household contact exceeded the risk associated with transport usage, our study did not assess other potential venues of community TB transmission, such as workplace environments, sporting events and marketplaces.

Although our analysis did not detect a significant association between travel duration and TB over the year-long period, this information was self-reported and, therefore, resulted in a simplified estimation of transport usage over the past year, leading to nondifferential misclassification of the exposure towards the null. This is a documented challenge among questionnaires that require recall over a year-long period [8]. A more accurate estimation of transport usage would require the use of prospective travel logs, but this was not feasible for the scope of this study.

In the year-long mode, there was an increased risk of TB among those travelling between the hours of 15:00 h and 18:59 h. This time frame encompasses the typical evening rush hour period in Lima, where there is increased transport usage and overcrowding. This finding suggests that certain routes and time frames may be linked with increased TB risk and serve as a medium for transmitting TB to other neighbourhoods. This hypothesis is supported by the finding in another study that specific bus routes traverse areas clustered with TB [9].

TABLE 1 Adjusted association between time spent on public transport and active pulmonary tuberculosis (TB) in Lima, Peru

Characteristic	Transport usage in the week prior to enrolment[#]		Transport usage per week during the past year[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
BMI kg·m^{-2}	0.78 (0.69–0.88)	<0.001	0.78 (0.70–0.87)	<0.001
Past household TB exposure[¶]	3.28 (1.83–5.89)	<0.001	3.38 (1.90–6.04)	<0.001
Marital status				
Single	1.00[f]		1.00[f]	
Married	0.66 (0.14–3.17)	0.603	0.62 (0.14–2.83)	0.545
Cohabitation	0.70 (0.33–1.47)	0.346	0.64 (0.30–1.36)	0.242
Divorced/widowed	5.25 (1.39–19.7)	0.015	5.13 (1.36–19.4)	0.016
Occupation				
Student	1.00[f]		1.00[f]	
Professional	0.16 (0.03–0.79)	0.025	0.18 (0.04–0.88)	0.034
Labourer	1.13 (0.53–2.38)	0.753	1.13 (0.53–2.40)	0.757
Commercial	1.30 (0.50–3.38)	0.584	1.29 (0.49–3.42)	0.608
Domestic	0.92 (0.28–3.00)	0.886	0.93 (0.29–2.98)	0.906
Public transport worker	0.20 (0.04–1.07)	0.059	0.27 (0.47–1.59)	0.148
Unemployed	1.61 (0.42–6.15)	0.483	1.81 (0.50–6.55)	0.364
Travel between 15:00 h and 18:59 h	1.77 (0.99–3.14)	0.053	1.85 (1.03–3.31)	0.038
Time spent on public transport[+,§]				
Quintile 1	1.00[f]		1.00[f]	
Quintile 2	1.09 (0.43–2.74)	0.861	1.86 (0.78–4.47)	0.163
Quintile 3	2.00 (0.85–4.73)	0.115	1.52 (0.66–3.46)	0.324
Quintile 4	2.81 (1.12–7.07)	0.028	2.56 (1.06–6.20)	0.037
Quintile 5	2.60 (0.99–6.78)	0.050	1.82 (0.70–4.93)	0.241
Each quintile	1.34 (1.08–1.65)	0.007[##]	1.19 (0.97–1.46)	0.093[##]

BMI: body mass index. [#]: n=343. [¶]: living with someone who had TB previously. [+]: during past week: quintile 1, <120 min; quintile 2, 120–279 min; quintile 3, 280–539 min; quintile 4, 540–919 min; and quintile 5, ⩾920 min. [§]: per week during the past year: quintile 1, <180 min; quintile 2, 180–319 min; quintile 3, 320–599 min; quintile 4, 600–899 min; and quintile 5 ⩾900 min. [f]: reference. [##]: for trend.

With respect to the post-2015 World Health Organization goal of TB elimination, defined as fewer than one case per million population, by 2050, identifying and prioritising treatment of individuals with latent TB at high risk of progression is essential to prevention [10]. Given the demonstrated risk conveyed by prior household TB exposure, our study affirms the importance of household contact tracing for TB and latent TB case finding and treatment. It also identifies public transportation as a source of community transmission. Further study of the correlation of transport time, type, route and degree of congestion with the risk of TB is merited to identify targeted preventative interventions and ascertain the role of these interventions in existing prevention programmes.

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Case control study in Lima, Peru correlates public transport usage with developing active TB
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Received: Sept 19 2013 | Accepted after revision: Nov 17 2013 | First published online: Dec 5 2013

Support statement: This study was funded and supported by the University of Washington Dept of Global Health, Instituto Nacional de Salud of Peru, and University of San Marcos.

Conflict of interest: None declared.

Acknowledgements: The authors thank Lizbeth Hidalgo and Juan Carlos Llontop (Dirección de Salud IV Lima Este, Lima, Peru); Elizabeth Peinado, Elena Castillo and Amelia Chavez (Dirección de Salud II Lima Sur, Lima); Osvaldo Mariñas

(Instituto Nacional de Salud, Centro Nacional de Salud Pública, Lima); Edith Castillo (Direccion Regional de Salud del Callao, Laboratorio de Referencia Regional de Tuberculosis, Callao, Peru); and Thanh Ton (Dept of Global Health, University of Washington, Seattle, WA, USA) for their contribution to this work.

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Eur Respir J 2014; 43: 1192–1195 | DOI: 10.1183/09031936.00164813 | Copyright ©ERS 2014

Diffusion capacity and *BMPR2* mutations in pulmonary arterial hypertension

To the Editor:

Pulmonary arterial hypertension (PAH) is a disease in which remodelling of the small pulmonary arteries leads to an increase in pulmonary artery pressure (PAP). The most important genetic predisposing factor related to PAH is a mutation in the bone morphogenetic protein receptor type 2 gene (*BMPR2*) [1, 2]. *BMPR2* mutation carriers are known to present with disease at an earlier age and with worse haemodynamics [3]. We recently showed in a cohort of patients with idiopathic and hereditary PAH that a very low diffusion capacity for carbon monoxide (D_{LCO}) is exclusively found in some of the patients without identified *BMPR2* mutations, whereas *BMPR2* mutation carriers have a relatively preserved D_{LCO} [4]. D_{LCO} is a noninvasive marker of the quality of the alveolar capillary structure [5] and the observed difference in D_{LCO} supports the hypothesis that distinct vascular disease processes are at play in *BMPR2* mutation-related PAH and non *BMPR2* mutation-related idiopathic PAH. Until recently, insufficient availability of lung samples has prohibited the performance of a detailed comparison of the pulmonary vascular pathologies in these two disease groups [6]. Therefore, we sought, in the present study, to confirm the previously found influence of *BMPR2* mutations on diffusion capacity in a much larger multinational patient cohort.

We performed a retrospective collaborative study at the VU University Medical Center in Amsterdam, the Netherlands and the Université Paris-Sud, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France. Patients were eligible for this study when classified in the database with idiopathic or familial PAH, and when the results from *BMPR2* mutation analysis and D_{LCO} measurements were available. Patients were diagnosed with idiopathic PAH according to current clinical guidelines [7]. Familial PAH was diagnosed when at least one family member had confirmed PAH. Patients with a family history of PAH and no mutations identified in the *BMPR2* gene were not included in this study. In total 64 patients were selected from the Dutch idiopathic and familial PAH population and 85 patients were drawn from the French population. Comorbidities of all these patients were reviewed, as was the amount of tobacco exposure. In addition, patients were reassessed for the likelihood of pulmonary veno-occlusive disease (PVOD). Patients were excluded when they had a tobacco exposure >20 pack-years or a medical history mentioning

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