Tuberculosis in London: the convergence of clinical and social complexity

Charlotte Anderson[1], Sarah R Anderson[2], Helen Maguire[1,3], Andrew C Hayward[3], Alistair Story[4]

1. Field Epidemiology Service – South East and London, Public Health England London UK
2. North West London Health Protection Team, Public Health England London UK
3. UCL Department of Infectious Disease Informatics, University College London, London UK
4. Find&Treat, University College Hospitals NHS Foundation Trust, London UK

Corresponding author:
Charlotte Anderson
Public Health England Field Epidemiology Service
Zone C, Floor 3 Skipton House
80 London Road
London SE1 6LH
charlotte.anderson@phe.gov.uk
Tel: 07827 369789

Keywords:

Tuberculosis; epidemiology; drug resistance

Word count: 1200 words

In large European cities the tuberculosis (TB) epidemic is characteristically concentrated in vulnerable and under-served populations.[1] London has the highest number and annual incidence of TB in Europe and implemented routine surveillance on homelessness, drug and alcohol misuse and imprisonment among TB patients in 2009.[2] This paper describes the clinical, public health and epidemiological characteristics of TB cases and the public health impact of social risk factors including risk of infectiousness, onward transmission, poor treatment adherence and drug resistance.

We analysed a cohort of adult London TB patients (2009-12) including clinical and laboratory surveillance information. This was improved by matching against the Find&Treat team's database, who support TB patients across London with complex social needs.[3] Homelessness, imprisonment, drug and alcohol misuse were defined as per national guidance.[4] Multi-drug resistant (MDR) TB was defined as per WHO and poor treatment outcome was defined as not completing treatment within 12 months for rifampicin sensitive patients, or within 24 months for rifampicin resistant patients[5]. Recent migrants were defined as entering the UK less than two years before diagnosis. UN world region of birth was amended to a TB surveillance classification.

Risk factors were identified for smear positive pulmonary disease; isoniazid and MDR (restricted to culture confirmed cases); non-adherence to treatment; and poor treatment outcomes (restricted to individuals notified 2009-11). Univariable analysis generated Odds Ratios (ORs), with 95% Confidence Intervals and (χ^2) test for significance. Multivariable logistic regression was used to generate adjusted ORs, built using likelihood ratio tests (LRT). Variables were retained in the final model if they improved the fit of the model ($p<0.05$) or confounded a different exposure. Potential interactions were investigated based on a priori knowledge. Data were analysed using Stata 12.

Of the cohort of 12,908 adult TB cases, 10% (1321) had one or more social risk factor: homelessness (550, 4%), imprisonment (349, 3%), drug (436, 3%) or alcohol misuse (581, 5%). Cases with social risk factors were more often male (79% vs. 55%, $p<0.001$) UK born (29% vs. 12%, $p<0.001$) white (25% vs. 9%, $p<0.001$) or black Caribbean (7% vs. 3%, $p<0.001$). Multiple factors were common (393 patients, 30%, reported two or more).

We stratified the multivariable analysis for infectious disease by drug use due to the interaction between drug use and homelessness (LRT $p=0.0071$). No further interactions were identified.

Infectious disease

Among 4,501 pulmonary patients with no history of drug use: 58% (134/231) of homeless patients were smear positive. Homelessness was independently associated with being sputum smear positive (aOR 1.8, 95% CI 1.4-2.4), as was being aged under 45. Those born in South Asia were

less likely to have infectious TB (than those born elsewhere). Among the 173 cases reporting drug misuse, no further characteristics were associated with infectiousness.

Drug resistance

Nineteen percent (73/393) of homeless patients had isoniazid resistant and 5% (20/393) had MDRTB. Homelessness was an independent risk factor for isoniazid (aOR 1.9, 95%CI1.4-2.6) and MDR disease (aOR 2.9, 95% CI1.6-5.2), while problem drug use was associated with isoniazid resistance. Being born in East Europe or East Asia, and a previous history of TB was also associated with drug resistance. Recent migrants were more likely to be MDR, while patients aged 65 or more were less likely to have drug resistance.

Non-adherence and not completing treatment

Almost half of all homeless patients were non-adherent (258/550), and 72% (303/420) completed treatment. Homelessness was associated with non-adherence (aOR 10.2, 95% CI 7.9-13.2) and not completing treatment (aOR 2.6, 95% CI 2.0-3.3). The other social risk factors were also independently associated with non-adherence, as was young age (under 25 years), pulmonary disease, a previous history of TB and being born in Central and West Europe.

Other characteristics associated with not completing treatment were being aged under 25 years or older than 54, male, born in East Europe, having pulmonary disease and being a recent migrant.

The increased risk of infectious TB among patients with social risk factors may relate to lung damage from smoking tobacco and/or crack cocaine, or delayed diagnosis.[6,7] Risk of drug resistance for those born in East Europe or East Asia reflects the burden of drug resistant TB in those areas. The increased risk of drug resistant TB among homeless people and drug users, after controlling for country of birth and previous treatment, suggests transmission of drug resistant disease in London, where homelessness is also a known risk factor for clustering.[8]

All social risk factors were associated with non-adherence. Patients experiencing homelessness were most at risk (aOR 10.2, 95% CI 7.9-13.2). This increased with social complexity: 83% of patients with four factors were non-adherent compared to 16% with one risk factor.

Homelessness was associated with not completing treatment. Males and those born in East Europe were also less likely to complete treatment, possibly due to under-reporting of social risk factors. Poor outcomes among recent migrants may reflect a preference to return to home countries for treatment, and among older patients the impact of co-morbidities.

TB patients with social risk factors have a disproportionate public health impact. Just 4% experienced homelessness but this was 16% of MDR and 36% of non-adherent patients. This supports UK guidance recommending assessing and supporting patient social risk factors, maintaining adequate staffing to support socially complex cases, and using cohort review as a quality assurance tool.[4,9] UK guidance for homeless people and drug-users also recommends targeted TB case finding using mobile digital chest radiology; integrated screening and treatment for latent TB infection, hepatitis C and HIV; and enhanced case management through diagnosis and treatment.[9]

It has been recognised that TB control efforts in low incidence countries should focus in big urban centres.[10] The implementation of targeted approaches was reviewed in an international survey of TB elimination practices in low incidence European countries, and followed by a consensus statement of the ECDC TB in big cities working group. This detailed recommendations to improve early case finding, case holding and treatment completion, especially among vulnerable groups.[11,12] Despite the mostly low incidence, the economic cost of TB in the EU remains considerable (total costs of €536,890,315 accumulated in 2012).[13]

Limitations to our study include that surveillance likely underestimates the prevalence of social risk factors. We increased by 24% the proportion known as homeless after matching to a specialist outreach service database (445 to 550). Patients missing information were assumed to not have that factor, which may have weakened associations identified. Other missing information reduced the study power to identify risk factors for infectiousness (sputum smear missing for 22% of pulmonary patients) and drug resistance (susceptibility unknown for 42% of patients). Individual HIV status was unknown: however co-infection estimates were low at approximately 4% of TB patients during this time period (personal communication, PHE National Infection Service January 2016).

Our study confirms that TB patients in London with social risk factors are more likely to be infectious, drug resistant, and not complete treatment and reveals homelessness as an independent risk factor for MDR disease. This convergence of clinical and social complexity presents an immense challenge and underlines the need for investment in specialist outreach services to tackle TB among vulnerable and medically under-served populations. We welcome the Collaborative Tuberculosis Strategy for England 2015 to 2020 which committed new investment to tackling TB in under-served populations.[14]

Acknowledgements

We would like to thank London TB clinic staff and patients for providing information to the London TB surveillance system; Find&Treat staff for providing information on patients referred to their service; PHE Field Epidemiology Service team for supporting the London TB surveillance system; PHE National Mycobaterium Reference Laboratory for providing information on culture and drug susceptibility; PHE National Infection Service TB section for linking case reports to laboratory data.

Authors' contributions

CA carried out the analysis and wrote the first draft of the manuscript. CA and AS developed the analysis plan. All authors contributed to interpretation of the findings, drafting of paper, approval for publication and are accountable for the quality and integrity of the work.

Conflict of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval was not required as this study was based on routine surveillance data held by Public Health England. Public Health England has Health Research Authority approval to hold and analyse national surveillance data for public health purposes.

REFERENCES

1. Lönnroth K, Migliori GB, Abubakar I et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J.* 2015 Apr;45(4):928-52.

2. de Vries G, Aldridge RW, Caylà JA et al., the Tuberculosis in European Union Big Cities Working Group. Epidemiology of tuberculosis in big cities of the European Union and European Economic Area countries. *Euro Surveill*. 2014;19(9):20726.

3. Jit M, Stagg HR, Aldridge RW, White PJ et al. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ* 2011;343:d5376.

4. Royal College of Nursing. Tuberculosis Case Management and Cohort Review. London, March 2012. Accessed November 2015. http://www.rcn.org.uk/__data/assets/pdf_file/0010/439129/004204.pdf

5. World Health Organization, Geneva. Tuberculosis factsheet March 2016. Accessed March 2016. http://www.who.int/mediacentre/factsheets/fs104/en/

6. Ward HA, Marciniuk DD, Pahwa P et al. Extent of pulmonary tuberculosis in patients diagnosed by active compared to passive case finding. *Int J Tuberc Lung Dis* 2004;8(5):593-7.

7. Story A, Bothamley G, Hayward A. Crack cocaine and infectious tuberculosis. *Emerg Infect Dis.* 2008;14(9):1466-9.

8. Love J, Sonnenberg P, Glynn JR, Gibson A, Gopaul K, Fang Z, Le Brun F, Pitman R, Hayward AC, Innes J, Van den Bosch C, Delpech V, Drobniewski F, Watson JM. Molecular epidemiology of tuberculosis in England, 1998. *Int J Tuberc Lung Dis.* 2009;13(2):201-7.

9. National Institute for Health and Clinical Care Excellence. NICE Guidance PH37, Identifying and managing tuberculosis among hard to reach groups. 2012. Accessed November 2015 http://guidance.nice.org.uk/PH37

10. Sotir MJ, Parrott P, Metchock B, Bock NN, McGowan JE Jr, Ray SM, Miller LP, Blumber HM. Tuberculosis in the inner city: impact of a continuing epidemic in the 1990s. *Clin Infect Dis.* 1999;29(5):1138-44

11. D'Ambrosio L, Dara M, Tadolini M Centis R, Sotgiu G, van der Werf MJ, Gaga M, Cirillo D, Spanevello A, Raviglione M, Blasi F, Migliori GB; European national programme representatives. Tuberculosis elimination: theory and practice in Europe. *Eur Respir J*. 2014;43(5):1410-20.

12. Van Hest NA, Aldridge RW, de Vries G, Sandgren A, Hauer B, Hayward A, Arrazola de Onate W, Haas W, Codecasea LR, Cayla JA, Story A, Antoine D, Gori A, Quabeck L, Jonsson J, Wanlin M, Orcau A, Rodes A, Dedicoat M, Antou F, van Deutekom H, Keizer ST, Abubaker I. Tuberculosis control in big cities and urban risk groups in the European Union: a consensus statement. *Euro Surveill.* 2014;19(9).

13. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. *Eur Respir J.* 2014;43(2):554-65.

14. Public Health England and NHS England. Collaborative Tuberculosis Strategy for England 2015 to 2020. London January 2015. Accessed November 2015.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/403231/Collaborative_TB_Strategy_for_England_2015_2020_.pdf

Table 1: Multivariable analysis of patient characteristics associated with infectiousness, drug resistance, non-adherence and poor outcomes

Patient characteristics (n) N=12908		Sputum smear positive* n=2179		Isoniazid resistant** n=646		Multi-drug resistant** n=127		Non-adherent n=717		Did not complete*** n=1207	
		aOR (95% CI)#	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	16-24 (2289)	1.2 (1.0-1.4)	0.059	1.0 (0.8-1.3)	0.877	2.0 (1.2-3.1)	0.004	1.5 (1.2-1.9)	0.001	1.2 (1.1-1.4)	0.001
	25-34 (4200)	Ref		Ref		Ref		Ref		Ref	
	35-44 (2512)	0.8 (0.7-1.0)	0.051	1.1 (0.8-1.4)	0.598	0.9 (0.5-1.6)	0.702	0.8 (0.6-1.1)	0.183	0.9 (0.8-1.1)	0.408
	45-54 (1638)	0.7 (0.6-0.9)	0.004	1.2 (0.9-1.5)	0.273	1.1 (0.6-2.1)	0.772	0.8 (0.6-1.1)	0.216	1.2 (1.0-1.5)	0.074
	55-64 (980)	0.7 (0.6-0.9)	0.012	1.0 (0.7-1.5)	0.957	0.6 (0.21.8)	0.383	0.7 (0.5-1.1)	0.158	1.4 (1.1-1.7)	0.013
	65+ (1289)	0.6 (0.5-0.7)	<0.001	0.6 (0.4-0.8)	0.005	0.1 (0.01-0.8)	0.030	0.5 (0.3-0.7)	0.001	2.6 (2.2-3.2)	<0.001
Male (7470)										1.3 (1.1-1.4)	0.0006
World region of birth†	Central Europe (317)	1.9 (1.4-2.5)#	<0.001	0.8 (0.5-1.4)	0.435	1.7 (0.8-3.9)	0.194	2.0 (1.3-3.1)	0.002	1.3 (0.9-1.9)	0.100
	East Asia (147)	1.8 (1.2-2.7)#	0.008	1.9 (1.0-3.4)	0.045	3.7 (1.5-9.1)	0.004	1.6 (0.8-3.3)	0.182	1.4 (0.9-2.3)	0.154
	East Europe (84)	2.1 (1.3-3.6)#	0.005	4.0 (2.2-7.2)	<0.001	7.6 (3.4-17.0)	<0.001	1.9 (0.9-4.1)	0.116	1.9 (1.1-3.3)	0.026
	East Mediterranean (97)	1.2 (0.6-2.5)#	0.570	-	-	-	-	0.3 (0.1-1.4)	0.128	1.5 (0.8-2.9)	0.253
	North Africa (112)	1.3 (0.7-2.4)#	0.450	-	-	-	-	0.7 (0.3-1.9)	0.504	0.5 (0.2-1.1)	0.072
	North America & Oceania (26)	0.9 (0.3-2.7)#	0.811	-	-	-	-	0.9 (0.1-7.0)	0.926	1.1 (0.3-3.6)	0.931
	South Asia (5888)	Ref		Ref		Ref		Ref		Ref	
	South East Asia (393)	1.4 (1.0-1.9)#	0.032	1.1 (0.7-1.8)	0.738	1.0 (0.3-2.7)	0.93	1.6 (1.0-2.6)	0.077	1.1 (0.8-1.5)	0.690
	South, Central America & the Caribbean (297)	2.3 (1.7-3.2)#	<0.001	0.8 (0.4-1.5)	0.523	-	-	1.6 (0.9-2.8)	0.081	0.9 (0.6-1.4)	0.651
	Sub-Saharan Africa (3023)	1.2 (1.1-1.4)#	0.004	0.8 (0.6-1.0)	0.068	0.6 (0.4-1.0)	0.045	1.0 (0.8-1.2)	0.74	0.7 (0.6-0.9)	<0.001
	West Europe‡ (1948)	1.9 (1.7-2.3)#	<0.001	1.1 (0.9-1.4)	0.318	0.6 (0.3-1.1)	0.073	1.3 (1.0-1.7)	0.046	1.1 (0.9-1.3)	0.248
Recent migrant (<2 years)* (1981)						1.7 (1.1-2.8)	0.023			1.5 (1.3-1.8)	<0.0001
Previous TB (772)				1.5 (1.1-2.2)	0.026	4.4 (2.6-7.5)	<0.001	1.7 (1.2-2.3)	0.0029		
Pulmonary (6184)		-	-					1.7 (1.4-2.0)	<0.0001	1.2 (1.1-1.4)	0.0013
Social risk factors	Problem drug use (436)	-	-	2.4 (1.7-3.3)	<0.000			3.0 (2.2-4.1)	<0.0001		
	Alcohol (581)	1.4 (1.1-1.8)#	0.0140					2.9 (2.2-3.9)	<0.0001		
	Prison (349)							2.3 (1.6-3.2)	<0.0001		
	Homelessness (550)	1.8 (1.4-2.4)#	<0.0001	1.9 (1.4-2.6)	0.0003	2.9 (1.6-5.2)	<0.001	10.2 (7.9-13.2)	<0.0001	2.6 (2.0-3.3)	<0.0001

*among pulmonary cases only

**among culture confirmed cases only

***did not complete an un-interrupted course of treatment within 12 months if rifampicin sensitive, and 24 months if rifampicin resistant

#among patients without problem drug use. Among patients with problem drug use, no further characteristics were associated with sputum smear positive disease

† world region of birth is based on UK ETS classification, based on country of birth. Central

‡76% of patients from West Europe were born in the UK