Delays and Pathways to Final Tuberculosis Diagnosis in Patients from a Referral Hospital in Urban China

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Abstract. China is among the countries with the largest epidemic of drug susceptible and resistant tuberculosis globally. We investigated the locations tuberculosis patients visited before being diagnosed, total diagnostic delay, and risk factors associated with total delay from a large tuberculosis referral hospital in Nanjing, China. We conducted a retrospective cohort study among tuberculosis patients who initiated anti-tuberculosis treatment within 3 months prior to the study date. Patient information regarding time and locations visited while seeking care for tuberculosis-related symptoms was collected through face-to-face interviews. Crude and adjusted Cox proportional hazard ratios of factors associated with time to diagnosis were calculated. Of 179 bacteriologically confirmed patients, 37% were women and median age was 41 (interquartile range [IQR], 26–62). Public hospitals were the most commonly visited health-care institution and repeated visits to them were common. The mean days to tuberculosis diagnosis were 50.3. Female patients (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.04–1.48) or patients who contacted a health-care provider 2 weeks after becoming symptomatic (HR, 1.59; 95% CI, 1.43–1.70) were significantly less likely to have a timely diagnosis. In a referral hospital in urban China, we found that female tuberculosis patients took significantly more time to reach diagnosis than males and patients often cycled in public hospitals for multiple visits before reaching final diagnosis. Health professionals at public hospitals in Nanjing should be encouraged to refer potential tuberculosis patients as soon as possible to avoid nosocomial transmission.

INTRODUCTION

Tuberculosis (TB) disease is largely preventable; however, approximately nine million individuals newly develop the disease globally every year.¹ Since 1994, global TB control has relied predominantly on identifying and treating new TB cases through patient self-referral to health institutions with able diagnostic and clinical resources.² Despite widespread application of these methods, approximately one out of three new TB cases remains undiagnosed and untreated.^{3,4} Consequently, these cases are concealed from national TB surveillance programs. Individuals with TB who remain undiagnosed for extended periods of time can develop adverse clinical outcomes,⁵ carry increased individual monetary cost,⁶ and contribute to persistent community transmission.^{5,7} Understanding setting-specific characteristics explaining delays in diagnosis and health institutional pathways that patients use can improve TB control.

Diagnostic and patient time delay surveys among TB patients have been implemented previously^{8–10} and have found that many TB patients revisit the same, mostly informal, providers multiple times before reaching a health provider with the capability to diagnose TB. Individual-level factors that have been shown to influence delay in diagnosis include gender, education, poor TB knowledge, socioeconomic status, among others.^{9,10} China has a model TB control program that has performed far better than most high-burden countries, successfully achieving the set pri-

mary targets of 70% case detection and 85% treatment completion.^{11–13} However, China still has the second largest number of TB cases and the most multi-drug-resistant cases globally.¹⁴ The persistent burden of TB in China could be partly explained by patient delays in receiving diagnosis and a loss of patient follow-up during diagnostic evaluation by the health system. For example, migrant workers constitute a large proportion of TB patients in some cities in China and they are often hard to trace during evaluation or after treatment is initiated.^{15,16} Additionally, public hospital settings have been criticized previously for inadequate TB treatment, leading to drug resistance.^{13,14} We aimed to investigate specific health-care-based locations that TB patients visit prior to diagnosis. We also examined the influence of gender, treatment status, or residence on the diagnostic delays in diagnosis among patients from a large, referral TB-specialized hospital in urban China.

METHODS

Study population. We conducted a retrospective cohort study on TB patients in Nanjing Chest Hospital, a large referral hospital in southeastern China. Nanjing Chest Hospital is one of the six TB-referral hospitals in Nanjing. Nanjing is the capital of Jiangsu Province and has approximately eight million inhabitants. Although the city is heavily urbanized, a large influx of migrant workers consistently cycle in and out of the city.¹⁷ Infectious disease control regulation in China designates that all patients with presumptive TB should be referred to TB-specialized hospitals. Presumptive TB patients are commonly classified when they have symptoms characteristic of TB (prolonged cough for ≥ 2 weeks, hemoptysis, fatigue, weight loss, etc.) or through abnormal chest radiographical findings. All presumptive TB

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patients sent to Nanjing Chest Hospital receive a physical and clinical examination, radiographical imaging, and a TB laboratory diagnostic evaluation. If a patient is positively diagnosed, they are given standard directly observed anti-TB treatment of 6 months.

Eligibility criteria. In our study, participants were recruited consecutively and enrolled if they had bacteriologically confirmed pulmonary TB, 18 years or older, and initiated anti-TB treatment within 3 months of survey implementation. Participants were excluded if they were too ill to complete the questionnaire, failed to complete all survey questions, were smear and culture negative but radiologically diagnosed with TB, or did not have corresponding medical records at the time of survey completion. Patients with negative bacteriologic results but diagnosed with TB through chest X-rays infrequently have TB symptoms and for this reason were excluded. Delays in TB diagnosis (patient delay, diagnostic delay, and total delay) were measured when TB symptoms were first recognized by the patient.

Key definitions. When categorizing TB cases, we followed standardized definitions when available.¹⁸ A new TB case was defined as a patient who had never taken anti-TB drugs for more than 1 month or who has never been treated for TB. Previously treated cases were defined as any patient who has taken anti-TB drugs for 1 month or more in the past. A previous diagnosis was collected through self-report and confirmed from patient medical records. A provider network was defined as any health-care institution that a patient communicated while seeking help for their TB symptoms. Total delay to diagnosis was defined as total time (in days) from onset of TB-related symptoms to final diagnosis. The total delay is constituted by two components: patient and diagnostic delay. Patient delay was defined as time (in days) from symptom onset of the TB case to seeking care in any informal or formal health system. Diagnostic delay was defined as the time from first attempting to seek care in the health system (formal or informal) to the time of final diagnosis of TB. Because we found patient delay within our study was minimal and patients reached the health-care system early after becoming symptomatic, our analysis concentrated on diagnostic delay. The diagnostic pathway of TB patients was defined as the sequence of health providers visited prior to being diagnosed; these providers included private clinics, public hospitals, private referral hospitals, or Nanjing Chest Hospital; an alternative provider included village health workers, drugs stores, or herbal healers. Only Nanjing Chest Hospital had the diagnostic capability to identify TB with microbiological confirmation.

Study exposures and outcome. The main study exposures were gender, TB treatment status, and whether a person resided in a rural or urban location. The main outcome of interest was total time to diagnosis or "total delay."

Data collection and quality assurance. We conducted face-to-face interviews using a pre-tested questionnaire administered by trained interviewers. The questionnaires were pre-tested in a pilot study on 16 TB patients to evaluate the survey for patient understanding and consistency of patient responses. Survey data were collected about patients' health experiences after becoming symptomatic with their current TB disease event. Institutions were collected to form a step-by-step process of the pathways a

patient takes to reach an ultimate TB diagnosis. Survey interviewers used standard prompts on questions regarding institutional locations in which patients visited, previous TB history, smoking, comorbidities, and other important questionnaire criteria throughout the interview to improve recollection of each patients' specific diagnostic pathway. A TB knowledge score was evaluated on a five-point scale based on answers from five questions regarding characteristics and symptoms of TB disease. Each correctly answered question gave one point. After each consecutive day of recruitment, questionnaires were entered into Microsoft Excel (Microsoft Corp., Redmond, WA) on-site by a study coordinator (Leonardo Martinez). To ensure high-quality data, surveys were then independently entered by two field workers. On completion of the study, the three versions of data extraction were compared for discrepancies and differences were resolved by reviewing the original questionnaires for accuracy.

Statistical analysis. First, we performed descriptive analyses of sociodemographic characteristics of the study sample. The total time to diagnosis in days was calculated for each patient and then by each of our main exposures (gender, treatment status, and residence) and for several other relevant characteristics such as age, other comorbidities, marital status, employment, smoking status, and TB knowledge score. We used a semiparametric, Cox proportional hazard models^{19–21} to investigate associations with increased total days to reach a TB diagnosis. In our analysis, we constructed "time-to-event" data corresponding to time for a TB patient to reach a confirmed diagnosis as has been seen elsewhere.^{22,23} In our analysis, a hazard less than 1 corresponded to the higher likelihood of a final TB diagnosis and a hazard greater than 1 signifies a higher total diagnostic delay. Because all TB patients in our sample reached a final diagnosis, there were no censoring events. The proportional hazards assumption was met and hazard ratios (HRs) from various models are presented. Cox models were calculated for the overall sample after which stratification among important characteristics and risk factors was performed. Wilcoxon rank sum tests were used to test for differences between groups. Statistical significance was assessed using 95% confidence intervals (CIs) in all models. We conducted all statistical analysis using Stata version 12.1 (Stata Corp., College Station, TX).

Ethical approval. This study was approved by University of Georgia Institutional Review Board (IRB ID, STUDY00000986) and the ethics committee of Jiangsu Provincial Center for Disease Control and Prevention. Written informed consent was obtained from all TB patients before study enrollment.

RESULTS

We recruited a total of 225 confirmed TB patients, of which 46 (20%) were solely diagnosed radiologically. Because patients diagnosed radiologically were asymptomatic, they were excluded from final analyses, leaving a total of 179 bacteriologically confirmed TB patients for analysis. Of enrolled participants, the median age was 44 years, 63% were male, 70% were married, and less than 30% were currently used. One-third of patients reported a history of smoking; however, only four subjects (2.2%) stated that they currently

TABLE 1

Characteristics of symptomatic tuberculosis patients in Nanjing, China

Characteristic	Frequency	Percent*
All	179	100
Median age (IQR)	41 (26–62)	NA
Sex		
Male	112	62.6
Female	67	37.4
Residence		
Inside Nanjing	144	80.5
Outside Nanjing	35	19.6
Mean monthly income (Yuan)†	3,549	NA
Marital status		
Single	49	27.4
Married	126	70.4
Widowed	4	2.2
Employment		
Used	52	29.1
Unemployed	127	70.9
Cigarette smoking‡		
Smoker	61	34.1
Never smoker	118	65.9
Comorbidities		
Diabetes	17	9.5
Hypertension	21	11.7
Both	6	3.4
None	148	82.7
Other	2	1.1
Cell phone ownership		
Yes	168	93.9
No	11	6.1
Previous treatment		
New case	154	86.0
Retreatment case	25	14.0

IQR = interquartile range; NA = Not applicable.

*Characteristic-specific percentages may not add up to 100% due to integer rounding.

†One Yuan is equivalent to 16 U.S. cents.

‡Smoker refers to having ever smoked cigarettes.

TABLE 2

Days to diagnosis to tuberculosis diagnosis of symptomatic patients from a referral hospital in Nanjing, China

Characteristic	Mean days to diagnosis*† (95% CI)
All	50.3 (42.0–58.6)
Age group	
18–24	41.7 (27.1–56.3)
25–34	45.1 (32.6–57.6)
35–44	62 (30.5–93.5)
≥ 45	53.8 (39.3–68.2)
Sex	
Male	44.6 (35.8–53.5)
Female	59.9 (43.1–76.6)
Residence	
Inside Nanjing	45.8 (38.4–53.3)
Outside Nanjing	68.8 (38.7–98.9)
Time to first contact health care	
< 2 weeks	35.4 (27.2–43.7)
≥ 2 weeks	79.1 (62.4–95.8)
Marital status	
Single	51.3 (31.2–71.4)
Married	50.6 (41.6–59.7)
Widowed	28.5 (4.2–52.8)
Employment	
Yes	57 (40.7–73.3)
No	47.6 (37.8–57.4)
Cigarette smoking‡	
Smoker	49.4 (36.3–62.6)
Non-smoker	50.8 (40.0–61.6)
Comorbidities	
Hypertension	51.0 (24.2–77.7)
Diabetes	40.2 (24.3–56.1)
None	51.1 (41.6–60.5)
Either	46.9 (28.8–65.1)
Cell phone ownership	
Yes	50.8 (42.0–59.6)
No	43.3 (22.2–64.3)
Previous treatment	
New case	49.1 (40.4–57.9)
Retreatment case	57.8 (30.4–85.2)
TB knowledge§	
0	53.7 (43.7–63.6)
≥ 1	36.7 (24.5–48.9)

CI = confidence interval; No. = number; TB = tuberculosis.

*Characteristic-specific percentages may not add up to 100% due to integer rounding.

†Measured in days from symptoms to diagnosis.

‡Smoking refers to having ever smoked cigarettes.

§Evaluated based on answers from five questions regarding characteristics or symptoms of tuberculosis disease. Patients were classified into those that answered one or more questions correctly or no questions correctly.

smoke. Over 80% of participants lived in urban or periurban areas, whereas 19% lived outside the city. In all, 154 patients (86%) were new cases, whereas 25 patients were retreatment cases (Table 1). The mean total delay taken to diagnosis was 50.3 days (95% CI, 42.0–58.6) (Figure 1; Table 2). When TB patients waited 2 weeks or more before contacting a health provider, their diagnosis took a longer time compared with

FIGURE 1. Total number of days between tuberculosis symptoms and initiation of tuberculosis treatment in tuberculosis patients ($N = 179$) from a referral hospital in Nanjing, China.

patients that waited less than 2 weeks (79.1 versus 35.4 days) (Table 2).

A wide variety of locations were first visited by participants after becoming symptomatic (Figure 2). Thirty participants (16.8%) visited Nanjing Chest Hospital directly, 115 (64.2%) visited a surrounding general public hospital, 28 patients (15.6%) visited a drug store, and six patients (3.4%) visited a private clinic. Patient delay, the time before a TB patient reaches the health-care system and instead contacts their individual social network, including family and friends, was largely unreported by participants as avenues in which they sought assistance. This occurred even after interviewer prompting of TB patients. Compared with other institutions, patients that visited public hospitals were substantially more likely to have a repeat, follow-up visit at the same institution. In univariate analysis (Table 3), spending more than 2 weeks before contacting a health provider was heavily associated with taking more total time to diagnosis (HR, 1.58; 95% CI, 1.42–1.69; $P < 0.0001$).

FIGURE 2. Health-care institutions and frequency of visits of tuberculosis patients from a referral hospital in Nanjing, China. Nanjing Chest Hospital is the only institution able to definitively diagnose tuberculosis in this study. Other institutions acted as referrals if tuberculosis was suspected.

Female sex and living in Nanjing were minimally associated with an increased amount of time before diagnosis but did not reach statistical significance. Patients with a TB knowledge score one or above were diagnosed in less time ($P = 0.08$), although this was not statistically significant. Other variables were not suggestively influential toward TB diagnosis.

After adjustment of HRs for potential confounders, waiting 2 weeks or more before first reaching a health provider (HR, 1.59; 95% CI, 1.43–1.70; $P < 0.0001$) and female sex (HR, 1.29; 95% CI, 1.04–1.48; $P = 0.03$) remained associated with a longer overall time to TB diagnosis (Table 3). Having a high TB knowledge score was not significant ($P = 0.12$).

DISCUSSION

Currently, global TB control is largely reliant on two factors: individual patient behavior to report to health care after becoming symptomatic and the effectiveness of health systems to properly identify and diagnose patients once

TABLE 3

Cox proportional hazard models by total days to reach diagnosis among tuberculosis patients in a referral hospital in Nanjing, China*

Characteristic	Time to tuberculosis diagnosis†	
	Hazard ratio (95% CI), <i>P</i> value	Adjusted hazard ratio (95% CI), <i>P</i> value
Age group		
18–24	1 (Reference)	
25–34	1.05 (0.52–1.40), 0.809	
35–44	1.27 (0.74–1.57), 0.261	
≥ 45	1.15 (0.73–1.43), 0.427	
Sex		
Male	1 (Reference)	1 (Reference)
Female	1.25 (0.97–1.45), 0.073	1.29 (1.03–1.48), 0.029
Residence		
Inside Nanjing	1 (Reference)	1 (Reference)
Outside Nanjing	1.29 (0.94–1.52), 0.091	1.20 (0.81–1.46), 0.227
Time to first contact health care		
< 2 weeks	1 (Reference)	1 (Reference)
≥ 2 weeks	1.58 (1.42–1.61), < 0.001	1.58 (1.43–1.70), < 0.001
Marital status		
Single	1 (Reference)	
Married	1.06 (0.68–1.33), 0.736	
Widowed	0.49 (0.09–1.46), 0.434	
Employment		
Yes	1 (Reference)	
No	0.79 (0.33–1.12), 0.247	
Smoking status		
Never smoker	1 (Reference)	
Smoker‡	0.98 (0.61–1.25), 0.913	
Comorbidities		
None	1 (Reference)	
Hypertension	1.01 (0.44–1.37), 0.965	
None	1 (Reference)	
Diabetes	1.15 (0.70–1.91), 0.579	
None	1 (Reference)	
Either	0.94 (0.45–1.28), 0.771	
Cell phone ownership		
Yes	1 (Reference)	
No	0.96 (0.08–1.44), 0.904	
Previous treatment		
New case	1 (Reference)	
Retreatment case	1.14 (0.68–1.44), 0.495	
TB knowledge§		
0	1 (Reference)	1 (Reference)
≥ 1	0.60 (0.07–1.04), 0.080	0.68 (0.08–1.09), 0.147

CI = confidence interval; TB = tuberculosis.

*A hazard is defined as a diagnosis of tuberculosis. Therefore a hazard ratio higher than 1 indicates a later diagnosis. A hazard ratio less than 1 signifies a faster diagnosis.

†Measured in days from symptoms to diagnosis.

‡Smoker in this instance signifies ever smoker.

§Evaluated based on answers from five questions regarding characteristics and symptoms of tuberculosis disease. Patients were classified into those that answered one or more questions correctly or no questions correctly.

they reach their provider network. Understanding the pathways that TB patients use after becoming symptomatic and the amount of delay can generate insights for potential interventions to prevent TB transmission. Although a majority of the patients in the study chose a health-seeking pathway that included a public hospital, they still experience a large amount of total time delay to reach final diagnosis. This could be explained by the differences in the public health institutions and their approach to TB care. It was evident from our analysis that patients made repeated cycles through these public hospitals.

The mean total time to diagnosis of 50.3 days found in our study was high but is comparable to two recent systematic reviews.^{9,10} Conversely, a recent study done in Ugandan patients found nearly twice as many steps along the pathway to final TB diagnosis, with most of the steps constituted by visits to private clinics or social contacts.²² This key difference may suggest that the structure of the help seeking pathways within the patients' provider and social networks vary by specific cultural context and setting. Although patient delay, through which TB patients reached out to their social network, did not occur in our Chinese study population, nearly two-thirds did contact family members, friends, or coworkers in Uganda.²² Although the overall time delay may be relatively congruent to those found in other studies, our study highlights several unique and important features about TB diagnosis in China.

We found that women took significantly more total days to reach diagnosis than men. A systematic review of diagnostic delay studies from China found that gender affects patient delay only in rural areas and not in urban areas.²⁴ Our primary outcome was total time in days to diagnosis (total delay), a measurement not covered in this review. Reasons for delays in diagnosis and low notification among women are not completely understood, but is likely multifactorial and setting specific. A population-based study in Vietnam found more than three times higher case detection rate among men compared with women.²⁵ Stigma among women of TB has been one proposed source of these gender discrepancies.^{9,26,27} In some settings, women with TB are more likely to conceal their disease,^{28,29} are at risk for social and community isolation,^{28,30} or are not screened for TB by health-care professionals despite having TB symptoms.³¹ Causes for these gender differences, specifically in Nanjing, China, should be further investigated through qualitative studies.

In Nanjing, public hospitals are not designated to diagnose TB, but were the most commonly visited health-care institution by patients after first becoming aware of symptoms. Over one-third of participants in our study went to a public hospital on their first or second health-care seeking visit and many of them made multiple repeat visits before being classified as having presumptive TB and then referred to Nanjing Chest Hospital. Patient cycling in the health system while seeking TB diagnosis is common⁸ and improvements in prompt referral from public hospitals may assist to reduce acquired drug resistance among TB patients.¹⁴

Finally, while enrolling study participants, we found a high proportion (20% of all TB diagnosed patients) with negative culture and smear results diagnosed through physician inspected radiographical examinations. Radiographical examinations were also commonly used for TB diagnosis in a

large national prevalence survey in China.¹³ Compared with laboratory-based diagnostic methods, chest radiography has certain advantages including rapid results and low overall cost for detecting pulmonary abnormalities.³² Despite these advantages, radiographical examination is not widely recommended when laboratory tests to diagnose pulmonary TB are available due to their low specificity.^{33,34} Scoring systems that combine radiographical examinations and individual patient clinical features, such as TB symptoms or a positive tuberculin skin test, have been inadequately explored, but may be a more accurate diagnostic technique.³³ Because of the large number of patients diagnosed through this method in our study, diagnostic accuracy studies of radiographical examinations for pulmonary TB in China should be implemented. Recent investigations in other settings have shown heterogeneous results.^{32,33,35}

There are some limitations to consider. First, much of our data were collected through participant recollection through face-to-face interview style questionnaires and therefore recall bias is possible. We attempted to deal with this limitation through multiple approaches. Interviewers were trained to consistently and carefully prompt participants about locations they visited before diagnosis throughout the survey interview. We also limited our eligibility criteria to include only patients who began anti-TB treatment within 3 months of survey implementation to limit memory lapses. Finally, we corroborated clinical information given by participants through inspection of medical records and, when inconsistent, followed up with participants. Second, Nanjing Chest Hospital is one of several referral hospitals in Nanjing and results may be distinct in other parts of the city. Third, locations that patients visited on becoming symptomatic were collected through participant self-reporting, which may be vulnerable to social desirability biases.

In conclusion, we found that TB patients who were women and those that delayed more than 2 weeks after becoming symptomatic took significantly more time before being diagnosed in a referral hospital in urban China. Public hospitals were the most commonly visited health-care institution and were often frequented several times before referral to a health-care facility with TB diagnostic capability.

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REFERENCES

- Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, Ravignone MC, 2010. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 375: 1814–1829.
- World Health Organization, 1994. *Framework for Effective Tuberculosis Control*. Geneva, Switzerland: World Health Organization.
- Theron G, Jenkins HE, Cobelens F, Abubakar I, Khan AJ, Cohen T, Dowdy DW, 2015. Data for action: collection and use of local data to end tuberculosis. *Lancet* 386: 2324–2333.
- Pai M, Dewan P, 2015. Testing and treating the missing millions with tuberculosis. *PLoS Med* 12: e1001805.
- Ward H, Marciniuk D, Pahwa P, Hoepfner V, 2004. Extent of pulmonary tuberculosis in patients diagnosed by active compared to passive case finding. *Int J Tuberc Lung Dis* 8: 593–597.
- Pan H, Bele S, Feng Y, Qiu SS, Lü JQ, Tang SW, Shen HB, Wang JM, Zhu LM, 2013. Analysis of the economic burden of diagnosis and treatment of tuberculosis patients in rural China. *Int J Tuberc Lung Dis* 17: 1575–1580.
- Golub J, Bur S, Cronin WA, Gange S, Baruch N, Comstock GW, Chaisson RE, 2006. Delayed tuberculosis diagnosis and tuberculosis transmission. *Int J Tuberc Lung Dis* 10: 24–30.
- Storla DG, Yimer S, Bjune GA, 2008. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 8: 1.
- Li Y, Ehiri J, Tang S, Li D, Bian Y, Lin H, Marshall C, Cao J, 2013. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Med* 11: 1.
- Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J, 2009. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infect Dis* 9: 1.
- Wang L, Cheng S, Xu M, Huang F, Xu W, Li R, Chin DP, 2009. Model collaboration between hospitals and public health system to improve tuberculosis control in China. *Int J Tuberc Lung Dis* 13: 1486–1492.
- Wang L, Liu J, Chin DP, 2007. Progress in tuberculosis control and the evolving public-health system in China. *Lancet* 369: 691–696.
- Wang L, Zhang H, Ruan Y, Chin DP, Xia Y, Cheng S, Chen M, Zhao Y, Jiang S, Du X, He G, Li J, Wang S, Chen W, Xu C, Huang F, Liu X, Wang Y, 2014. Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data. *Lancet* 383: 2057–2064.
- Zhao Y, Xu S, Wang L, Chin DP, Wang S, Jiang G, Xia H, Zhou Y, Li Q, Ou X, Pang Y, Song Y, Zhao B, Zhang H, He G, Guo J, Wang Y, 2012. National survey of drug-resistant tuberculosis in China. *N Engl J Med* 366: 2161–2170.
- Long Q, Li Y, Wang Y, Yue Y, Tang C, Tang S, Squire SB, Tolhurst R, 2008. Barriers to accessing TB diagnosis for rural-to-urban migrants with chronic cough in Chongqing, China: a mixed methods study. *BMC Health Serv Res* 8: 1.
- Wang Y, Long Q, Liu Q, Tolhurst R, Tang S, 2008. Treatment seeking for symptoms suggestive of TB: comparison between migrants and permanent urban residents in Chongqing, China. *Trop Med Int Health* 13: 927–933.
- Bele S, Jiang W, Lu H, You H, Fan H, Huang L, Wang Q, Shen H, Wang J, 2014. Population aging and migrant workers: bottlenecks in tuberculosis control in rural China. *PLoS One* 9: e88290.
- World Health Organization, 2013. *Definitions and Reporting Framework for Tuberculosis: 2013 Revision*. Geneva, Switzerland: World Health Organization.
- Concato J, Peduzzi P, Holford TR, Feinstein AR, 1995. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. *J Clin Epidemiol* 48: 1495–1501.
- Peduzzi P, Concato J, Feinstein AR, Holford TR, 1995. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 48: 1503–1510.
- Cai J, Zeng D, 2008. *Cox Proportional Hazard Model*. Wiley Encyclopedia of Clinical Trials. Hoboken, NJ: John Wiley and Sons, Inc.
- Sekandi JN, Zalwango S, Martinez L, Handel A, Kakaire R, Nkwata AK, Ezeamama AE, Kiwanuka N, Whalen CC, 2015. Four degrees of separation: social contacts and health providers influence the steps to final diagnosis of active tuberculosis patients in Urban Uganda. *BMC Infect Dis* 15: 1.
- Copas AJ, Farewell VT, 2001. Incorporating retrospective data into an analysis of time to illness. *Biostatistics* 2: 1–12.
- Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M, 2014. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 18: 255–266.
- Thorson A, Hoa N, Long N, Allebeck P, Diwan V, 2004. Do women with tuberculosis have a lower likelihood of getting diagnosed? Prevalence and case detection of sputum smear positive pulmonary TB, a population-based study from Vietnam. *J Clin Epidemiol* 57: 398–402.
- Yang W-T, Gounder CR, Akande T, De Neve JW, McIntire KN, Chandrasekhar A, de Lima Pereira A, Gummedi N, Samanta S, Gupta A, 2014. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberc Res Treat* 2014: 461935.
- Somma D, Thomas B, Karim F, Kemp J, Arias N, Auer C, Gosoni GD, Abouihia A, Weiss MG, 2008. Gender and socio-cultural determinants of TB-related stigma in Bangladesh, India, Malawi and Colombia. *Int J Tuberc Lung Dis* 12: 856–866.
- Onifade DA, Bayer AM, Montoya R, Haro M, Alva J, Franco J, Sosa R, Valiente B, Valera E, Ford CM, Acosta CD, Evans CA, 2010. Gender-related factors influencing tuberculosis control in shantytowns: a qualitative study. *BMC Public Health* 10: 381.
- Johansson E, Long N, Diwan V, Winkvist A, 2000. Gender and tuberculosis control: perspectives on health seeking behaviour among men and women in Vietnam. *Health Policy* 52: 33–51.
- Long NH, Johansson E, Diwan VK, Winkvist A, 2001. Fear and social isolation as consequences of tuberculosis in Viet Nam: a gender analysis. *Health Policy* 58: 69–81.
- Smith A, Burger R, Claassens M, Ayles H, Godfrey-Faussett P, Beyers N, 2016. Health care workers' gender bias in testing could contribute to missed tuberculosis among women in South Africa. *Int J Tuberc Lung Dis* 20: 350–356.
- Van't Hoog A, Meme H, Van Deutekom H, Mithika AM, Olunga C, Onyino F, Borgdorff MW, 2011. High sensitivity of chest radiograph reading by clinical officers in a tuberculosis prevalence survey. *Int J Tuberc Lung Dis* 15: 1308–1314.
- Pinto LM, Pai M, Dheda K, Schwartzman K, Menzies D, Steingart KR, 2013. Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. *Eur Respir J* 42: 480–494.
- Koppaka R, Bock N, 2004. How reliable is chest radiography? Frieden T, ed. *Toman's Tuberculosis*. Geneva, Switzerland: World Health Organization, 51.
- Story A, Aldridge R, Abubakar I, Staggs HR, Lipman M, Watson JM, Hayward AC, 2012. Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. *Int J Tuberc Lung Dis* 16: 1461–1467.