

Delayed Tuberculosis Diagnosis in a Low Incidence Country and its Effect on Cost of Care

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Abstract

Background

Tuberculosis elimination (TB) is a global priority that requires high-quality timely care to be achieved. In low TB incidence countries such as Ireland, delayed diagnosis is common. Despite cost being central to policy making, it is not known if delayed care affects care cost among TB patients in a low-incidence setting.

Methods

Health care records of patients with signs and symptoms of TB evaluated by a tertiary service in Ireland between July 1st 2018 and December 31st 2019 were reviewed to measure and determine predictors of patient-related delays, health care-provider related delay and the cost of TB care. Benchmarks against which the outcomes were compared were derived from the literature.

Results

Thirty-seven patients were diagnosed with TB and 51% (19/37) had pulmonary TB (PTB). The median patient-related delay was 60 days among those with PTB, greater than the benchmark derived from the literature (38 days). The median health care provider-related delay among patients with PTB was 16 days and, although similar to the benchmark (median 22 days, minimum 11 days, maximum 36 days) could be improved. The health care-provider related delay among patients with EPTB was 66 days, greater than the benchmark (42 days). The cost of care was €8298, and while similar to that reported in the literature (median €9,319, minimum €6,486, maximum €14,750) could be improved. Patient-related delay among those with PTB predicted care costs.

Conclusion

Patient-related and health care-related delays in TB diagnosis in Ireland must be reduced. Initiatives to do so should be resourced.

Introduction

In 2020, 10 million people were infected with tuberculosis (TB), a preventable infectious disease [1]. Despite being treatable, 1.3 million people died with TB in 2020. TB elimination (an incidence less than 1 case per million [2]) is a global priority [3][4]. Internationally, there is a growing consensus that to achieve this, a paradigm shift from a focus on only TB care coverage to one that includes care quality is needed [1][2][5]. High-quality TB care includes timely diagnosis and treatment initiation. Delays in TB treatment are associated with more severe disease, greater mortality, and a risk of ongoing transmission [6, 7][8]. Therefore, TB programmes must be able to identify not only people at-risk of TB disease but those most at-risk of delayed diagnosis and treatment. However, due to the low visibility of TB in countries with a low incidence, programmatic activities to enable timely diagnosis and treatment are often not prioritised by health care managers or policy makers for resourcing [2]. Delays in the diagnosis and treatment of TB have been reported in Ireland [9][10]. In countries with a low incidence of TB, such as Ireland, how delayed TB care effects cost of care is not known despite cost being central to many policy decisions. The primary aim of this evaluation was to determine factors that predict patient-related and health care provider-related delays in TB diagnosis and treatment and to establish if the cost of TB care in a low-incidence country is affected by delays in care.

Methods

A retrospective review of the health care records of patients evaluated by a tertiary centre TB service in Ireland was performed. Patients who were referred with symptoms or signs of active TB between the 1st of July 2018 and the 31st of December 2019 were included. Patients with non-tuberculosis mycobacteria infection were excluded. Data extraction was performed by author 1 and author 2, with author 1 reviewing all data collected for accuracy. Data collected included age, sex, nationality and TB disease site, microbiological characteristics (culture, GeneXpert and smear status on presentation), human immunodeficiency virus (HIV) status, place of first presentation (primary care, outpatient clinic, emergency department), and resource utilisation (Appendix 1). Patient-related delays were defined as the time from symptom onset to first presentation to health care services. Health care-related delays were defined as the time from first presentation to health care services to treatment initiation. Pulmonary TB (PTB) cases were defined as any patient with involvement of the lung parenchyma or the tracheobronchial tree [11]. Extra-pulmonary TB cases (EPTB) were those with TB not captured by the definition of PTB. Treatment outcomes were reported according to WHO definitions [11].

Cost calculations considered direct costs, those that relate to TB diagnosis and treatment. These included the cost of radiological (radiographs, computed tomography imaging, magnetic resonance imaging, ultrasonography, positron-emission tomography), haematological (full blood counts), biochemical (renal and liver function profiles), immunological (interferon gamma release assay), virological (hepatitis B, hepatitis C, HIV testing) and microbiological (TB smear and culture, GeneXpert testing) investigations. Investigation costs (Appendix 1) were sourced primarily from the laboratory directorate, literature published from Ireland, and for radiological tests, the National Health Service cost collection [12]. Anti-tuberculosis medications and pyridoxine reimbursement costs were sourced from the Health Service Executive (HSE) (Appendix 1). Where drug costs were unavailable from the HSE, costs were sourced first from MIMS Ireland or second from the British National Formulary. The drug costs to the health system were calculated following guidance from the National Centre for Pharmacoeconomics [13]. Cost data were inflated to 2019 values and costs in British Pounds Sterling were converted to Euro using Organization for Economic Co-operation and Development (OECD) purchasing power parity figures following national guidance from the Health Information and Quality Authority [14]. The cost of outpatient TB and ophthalmology clinics were calculated according to national costing guidelines and HSE salary scales [15][16](Appendix 1). Hospitalisations due to TB, either known or unknown at the time of admission, were costed following guidance from the Healthcare Pricing Office [17] and included elective, emergency and rehabilitation related hospitalisations (Appendix 1).

A structured review of the literature was performed to identify studies which reported patient-related delays, health care provider-related delays and direct costs of TB care (Appendix 2). Outcomes from this evaluation were benchmarked against those reported in the literature from other low incidence countries to determine if care was delayed or more costly.

The median and interquartile range of patient related-delays, health care provider-related delays and direct costs of care for patients with TB were reported. Analyses were conducted separately for patients with PTB and EPTB. Multivariable regression was performed with patient-related delay as the dependent variable and age, sex, nationality, and HIV status as the independent variables. Multivariable regression was performed with health care provider-related delay as the dependent variable and age, sex, nationality, HIV status, culture status, drug resistance status and acute hospitalisation requirement as the independent variables. Multivariable regression was also performed with direct cost of care as the dependent variable and age, sex, nationality, HIV status, culture status, patient-related delays, and health care-provider related delays as the independent variables. The median, minimum and maximum reported values in studies retrieved from the literature review for patient-related delays, health care provider-related delays and cost of drug-susceptible TB care were reported. Costs reported in the literature were inflated to 2019 values using Organization for Economic Co-operation and Development (OECD) consumer price index data [18] and then converted to Euros using the purchasing power parity index as reported by the OECD [19].

Results

Fifty-four patients were assessed for TB during the reference period. Most patients (69% (37/54)) referred had a diagnosis of TB made. Over half (51% (19/37)) of patients with TB had PTB (Table 1). Males comprised 57% (21/37) of patients. The median age of TB patients was 41.7 years (Interquartile range 35.1-46.3). Sixty per cent of patients (22/37) were from a country with a high incidence of TB (≥ 40 cases annually per 100,000 of population). Most patients (87% (32/37)) reviewed had a risk factor for TB. While screening for HIV in the TB clinic was imperfect, only 8% (3/37) of TB patients had a diagnosis of HIV. No TB patient had a history of treatment for LTBI.

Table 1
Patient characteristics

	Tuberculosis (n=37)	Pulmonary tuberculosis (n=19)	Extrapulmonary tuberculosis (n=18)
Median age (IQR)	41.7 (35.1-46.3)	41.4 (33.3-54)	42.1 (37.7-50)
Male sex (percentage)	21(57%)	12 (63%)	9 (50%)
Any TB risk factor (percentage)	32 (87%)	15 (79%)	16 (89%)
Born in a country of high TB incidence (percentage)	22 (60%)	8 (42%)	14 (78%)
HIV Positive (percentage)	3 (8%)	2 (11%)	1 (6%)
HIV Negative (percentage)	29 (78%)	14 (74%)	15 (83%)
Not tested for HIV (percentage)	5 (14%)	3 (16%)	2 (11%)
Immunosuppression (percentage)	4 (11%)	1 (5%)	3 (17%)
Homeless (percentage)	2 (5%)	2 (11%)	0
Asylum seeker (percentage)	1 (3%)	0	1 (6%)
Person who uses drugs (percentage)	2 (5%)	2 (11%)	0
History of incarceration	0	0	0
Healthcare worker (percentage)	5 (14%)	2 (11%)	3 (17%)
Recent TB contact (percentage)	4 (11%)	4 (21%)	0
History of active TB	0	0	0
History of negative LTBI screen (percentage)	3 (8%)	3 (16%)	0
Diabetes mellitus (percentage)	3 (8%)	3 (16%)	0
Alcohol misuse (percentage)	4 (11%)	4 (21%)	0

Bacteriological confirmation of TB infection occurred in 95% (35/37) of patients and the majority (78% (29/37)) were culture positive. Nearly two-thirds of patients (63% (12/19)) with PTB were smear positive at diagnosis. Drug-resistant TB was found in 16% (6/37) of patients, five of whom had isoniazid resistance and one of whom had pyrazinamide resistance. None had rifampicin resistant or multi-drug resistant TB. Treatment success was achieved in 95% (35/37) of patients, 92% (34/37) and 3% (1/37) of whom had treatment completion and cure, respectively. Two patients (5%) were not evaluated, because they transferred their care elsewhere.

Among patients who remained under the care of the TB service, hospitalization occurred in 91% (32/35) of patients and amounted to 1484.5 bed-days. Over half (51% (18/35)) of all TB patients had an emergency hospitalization. Illness due to undiagnosed TB requiring management or investigation was the reason for 86% (44/51) of hospitalizations and the remainder of admissions related to rehabilitation in patients treated for TB (6% (3/51)) or management of disease or treatment-related complications (8% (4/51)).

Patient-related delays

Forty-six percent (17/37) of patients presented first to their primary care physician with their symptoms prior to diagnosis, 41% (15/37) presented with their symptoms directly to an emergency department and 13% (5/37) patients presented their symptoms to a physician while attending another hospital outpatient clinic. Overall, 59% (22/37) of patients had their diagnosis established by attending the emergency department.

In patients with PTB, the median patient-related delay was 60 days (IQR 30-180). In a multivariable regression model (Table 2), neither age, sex, nationality, or HIV status predicted patient-related delay among those with PTB. In patients with EPTB the median patient-related delay was 30 days (IQR 21-60) and in a multivariable progression model that included age, sex, nationality, and HIV status, only HIV infection predicted patient-related.

Table 2
Multiple regression models for predictors of delays among patients with tuberculosis

Patient-related delay	Coef.	Std. Err.	T	P>t	95% Confidence Interval (Lower Limit)	95% Confidence Interval (Upper Limit)
Multiple regression model for predictors of patient-related delay among patients with pulmonary TB						
Age at first presentation	2.78	1.96	1.42	0.18	-1.46	7.02
Male sex	19.24	57.90	0.33	0.75	-105.84	144.32
Irish nationality	-20.20	62.17	-0.32	0.75	-154.50	114.11
HIV infected	48.69	80.32	0.61	0.56	-124.83	222.20
_cons	-30.56	89.26	-0.34	0.74	-223.40	162.27
Multiple regression model for predictors of patient-related delay among patients with extrapulmonary TB						
Age at first presentation	1.71	1.48	1.15	0.27	-1.55	4.97
Male sex	64.65	33.98	1.90	0.08	-10.13	139.43
Irish nationality	70.18	60.90	1.15	0.27	-63.86	204.22
HIV infected	285.79	68.38	4.18	0.00	135.28	436.30
_cons	-61.42	61.92	-0.99	0.34	-197.70	74.85
Multiple regression model for predictors of health care provider-related delay among patients with pulmonary TB						
Age at first presentation	1.35	1.24	1.09	0.31	-1.46	4.16
Male sex	-40.56	36.47	-1.11	0.30	-123.06	41.93
Irish nationality	-39.88	39.63	-1.01	0.34	-129.52	49.76
HIV infected	-46.31	47.60	-0.97	0.36	-153.99	61.37
Culture-positive TB	-240.37	68.57	-3.51	0.01	-395.48	-85.27
Drug-resistant TB	-16.57	50.25	-0.33	0.75	-130.25	97.11
Acutely hospitalized	-32.35	33.71	-0.96	0.36	-108.62	43.91
_cons	291.16	86.85	3.35	0.01	94.70	487.62
Multiple regression model for predictors of health care provider-related delay among patients with extrapulmonary TB						
Age at first presentation	5.79	13.02	0.44	0.67	-23.67	35.26
Male sex	111.70	175.54	0.64	0.54	-285.39	508.80
Irish nationality	-319.50	563.40	-0.57	0.59	-1594.00	954.99
HIV infected	-94.37	497.42	-0.19	0.85	-1219.62	1030.87
Culture-positive TB	-130.02	191.05	-0.68	0.51	-562.21	302.17
Drug-resistant TB	-109.82	270.67	-0.41	0.69	-722.11	502.47
Acutely hospitalized	-32.39	297.81	-0.11	0.92	-706.09	641.30
_cons	40.84	559.54	0.07	0.94	-1224.92	1306.60

Health care provider-related delays

The median health care provider-related delay among patients with PTB was 16 days (IQR 2-54). In a multivariable regression model including age, sex, nationality, HIV status, culture status, drug resistance status and being acutely hospitalized, culture-positivity was associated with a shorter health care provider-related delay (coefficient -240.37, standard error 68.57, 95% -395.48- -85.27, P<0.05) among patients with PTB (Table 2). The median health care provider-related delay among patients with EPTB was 66 days (IQR 24-176) and in a

multivariable regression model including age, sex, nationality, HIV status, culture status, drug-resistance status and being acutely hospitalized, no variable was found to predict health care provider-related delay among patients with EPTB.

Direct cost of care

The total direct cost of TB care was €1,216,712. Hospitalizations consisted of 92.1% (€1,120,576) of costs, the majority of which (60.2%) related to emergency hospitalizations. Outpatient care comprised the remaining 7.9% of costs. The median cost of care among all patients with TB treated successfully who remained under the care of the TB service (n= 30) was €8298 (IQR 4,344-19,641). The median cost of care among patients with PTB with a successful treatment outcome (n=16) was €10,162 (IQR 4,898-19,549). The median cost of care among patients with EPTB with a successful treatment outcome (n=14) was €7,534 (IQR 3,730-18,057). In a multivariable model that included age, sex, nationality, HIV status, culture status, patient-related delays, and health care provider-related delays only patient-related delays predicted a higher cost of care among patients with PTB who completed treatment (Table 3). In a multivariable model that included age, sex, nationality, HIV status, culture status, patient-related delay, and health care provider-related delay, no variable predicted the cost of TB care among patients with EPTB.

Table 3
Multiple regression models for predictors of direct cost of care among patients with tuberculosis

Multiple Regression model for predictors of direct cost of pulmonary TB care						
Patient-related delay	Coef.	Std. Err.	T	P>t	95% Confidence Interval (Lower Limit)	95% Confidence Interval (Upper Limit)
Age at first presentation	2880.08	1319.81	2.18	0.06	-105.55	5865.70
Male sex	24231.74	39247.73	0.62	0.55	-64552.80	113016.30
Irish nationality	-24453.15	41362.82	-0.59	0.57	-118022.30	69116.05
HIV infected	-31595.83	51704.20	-0.61	0.56	-148558.90	85367.19
Culture-positive TB	-80597.39	114364.10	-0.70	0.50	-339307.00	178112.20
Patient-related delay	424.05	187.03	2.27	0.05	0.96	847.15
Health care provider-related delay	-305.31	365.80	-0.83	0.43	-1132.82	522.20
_cons	-43701.31	129315.30	-0.34	0.74	-336232.80	248830.20
Multiple Regression model for predictors of direct cost of extrapulmonary TB care						
Age at first presentation	-466.4403	446.8027	-1.04	0.337	-1559.727	626.8466
Male sex	-4199.576	9388.936	-0.45	0.67	-27173.48	18774.32
Irish nationality	46504.35	32452.2	1.43	0.202	-32903.33	125912
Culture positive TB	-4861.437	8622.483	-0.56	0.593	-25959.89	16237.02
Patient-related delay	-60.13667	85.82541	-0.7	0.51	-270.1439	149.8705
Health care provider-related delay	0.790151	14.51181	0.05	0.958	-34.71897	36.29927
_cons	30585.9	17349.45	1.76	0.128	-11866.67	73038.47

Comparison of evaluation outcomes with benchmarks

The results of the literature search are reported in Appendix 2. Studies reported the median patient-related delay among patients with PTB as being 7, 10, 18, 21, 30, 36 and 38 days [20][21][22][23][24][25]. Therefore, the median, minimum and maximum patient-related delay among patients with PTB reported in the literature are 21 days, 7 days, and 38 days, respectively. The median patient-related delay in this evaluation of 60 days among those with PTB suggests patient-related delays were prolonged. The health care-related delay among patients with PTB was reported in the included studies as 11, 14, 15, 22, 26, 27 and 36 days [23][24][26][22][27][20]. The median, minimum and maximum health care-related delays among patients with PTB are 22 days, 11 days, and 36 days, respectively. The median health care provider related delay among patients with PTB in this evaluation of 16 days is similar to that reported in the literature but suggests it could be improved.

With regard to patients with EPTB, there was significant variation in the patient-related delay reported in the literature among differing EPTB disease sites and symptom complexes. Therefore, a benchmark for EPTB patient-related delay could not be reliably defined for comparison

with the outcomes reported in this evaluation. Among patients with EPTB, the health care-related delays reported in the included studies were 32, 39 and 42 days [22][28], all lesser than the health care-related delay among patients with EPTB in this evaluation of 66 days.

Regarding the direct cost of TB care, the median, minimum and maximum costs of non-rifampicin resistant non-multidrug resistant TB care reported in the included studies were €9,319, €6,486, and €14,750, respectively (Table 4). Therefore, the cost of care reported in this evaluation (€8298), while similar to that in other low incidence countries, suggests it could be improved.

Table 4
Direct cost of tuberculosis care reported in the literature

Study (year)	Country	Drug-susceptible TB cost (€)
Diel et al. (2020) [29][30]	Germany	9,455
De Vries et al. (2013) [31]	The Netherlands	9,319
Deuffic-Burban et al. (2010) [32]	France	6,486
Department of Health (2009) [33]	United Kingdom	7,199
Chan et al. (2017) [34]	Australia	6,952
Marks et al. (2014) [35]	USA	14,750
Pina et al. (2013) [36]	Spain	10,557
Median		9,319
Minimum		6,486
Maximum		14,750

Discussion

This evaluation described the timeliness and cost of TB care in a low incidence country, determined predictors of delayed care and, for patients with PTB, demonstrated that longer patient-related delays resulted in increased care costs. Patient-related delays were substantial, particularly among patients with PTB. Although patient-related delays for those with EPTB were not compared with outcomes reported in the literature, the absolute value reported in this study of 30 days was long. Patient characteristics such as age, sex, nationality, or HIV status did not predict patient-related delays among those with PTB. HIV infection predicted patient-related delays among those with EPTB. This highlights a need to ensure HIV is diagnosed early and that people living with HIV are kept engaged in HIV care services that can diagnose TB and provide patients with education about its signs and symptoms. Other factors, such as the absence of universal health care in Ireland, may have contributed to the long patient-related delays reported in this evaluation. Cost and long-waiting times have been reported as barriers to accessing health care in Ireland [37][38], particularly in vulnerable groups who may face additional challenges to accessing health care services. In this evaluation, only 46% of patients presented first to their primary care physician supporting the assertion that the absence of universal health care may have been a factor. Health care provider-related delays for patients with TB were prolonged, particularly for patients with EPTB (66 days). Culture positivity predicted a shorter health care provider-related delay among those with PTB, demonstrating the importance of performing culture of respiratory specimens for TB early in symptomatic patients. Increasing patient-related delays in those with PTB resulted in increased care costs, with each day of delay increasing costs by €424. Although the median cost of TB care was similar to that reported in the literature, it could be improved, particularly for PTB, which was more costly than EPTB care in this evaluation. This study adds to the literature on TB care in low-incidence countries where delays in accessing and diagnosing TB are a well-recognised challenge [23][24][25], which has also been reported in other studies in Ireland [9][10]. The association between increasing costs of PTB care and patient-related delays has not previously been reported in the literature from countries with a low incidence of TB.

A limitation of this study was the retrospective means by which data were collected from healthcare records. Additional healthcare resource utilisation in primary care or private health facilities may not have been documented in these records. Therefore, the cost of care reported in this study could be an underestimate of the true value. The single-centre nature of this study may limit the generalisability of the cost estimates. However, hospitalizations were the greatest component of TB care cost (92.1%) and a similar proportion of TB cases being hospitalized has been reported nationally, as in this study [39], supporting the generalisability of the direct cost estimates to TB care in other centres in Ireland. There were no patients with rifampicin or multidrug-resistant TB, meaning the results cannot be generalised to these patient cohorts.

Future research is needed in Ireland to better understand the causes of patient-related and health care provider-related delays in TB diagnosis and treatment, many of which will be country and population specific. Patient-pathway analysis has been useful in other countries in doing this [40]. Qualitative research that evaluates patients' experiences of seeking care prior to diagnosis should be performed to identify barriers to utilising and accessing health care with their symptoms, particularly in primary care. The national TB programme in Ireland should initiate such research studies to determine how TB care in primary and secondary care services can meet the needs and expectations of patients with TB prior, during, and after their diagnosis. By doing so, appropriate initiatives to reduce patient-related and health care-provider related delay can be implemented.

The findings of this study have implications for the national TB programme in Ireland, which should be ensuring patients with TB receive high-quality timely and effect care. Researchers, healthcare professionals and medical organisations have regularly highlighted insufficient resourcing for TB services in Ireland, where there is no dedicated funding for the TB program [9]. Unless initiatives to reduce TB care delays are identified and resourced, patients with TB in Ireland will continue to have prolonged morbidity, ongoing opportunities for transmission, and incur higher care costs. In this context, TB elimination will likely not be achieved nationally.

Conclusion

Patient-related and health care-related delays in TB diagnosis and treatment in Ireland must be reduced. Initiatives to do so should be resourced nationally and if effective could reduce the cost of PTB care.

Declarations

Funding

The salary of the first author of this evaluation was funded by the Royal College of Surgeons in Ireland.

Conflicts of interest/Competing interests

The authors have no conflicts of interest to declare.

Availability of data and material

The datasets generated during and/or analysed during the current study are not publicly available because they were collected as part of a quality of care evaluation but are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Ethics approval

This study was a quality of care service evaluation and it was registered with the Beaumont Hospital Office of Clinical Audit (approved audit number 880).

Authors' contributions

James O'Connell: Conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing -original and draft, writing-review and editing, visualisation, project administration.

Niamh Reidy: methodology, validation, investigation, data curation, writing- review and editing, project administration

Cora McNally: Conceptualisation, methodology, writing- review and editing, visualisation, project administration, supervision.

Debbi Stanistreet: Conceptualisation, methodology, writing- review and editing, visualisation, supervision.

Samuel McConkey: Conceptualisation, methodology, writing- review and editing, visualisation, project administration, supervision.

Eoghan de Barra: Conceptualisation, methodology, writing- review and editing, visualisation, project administration, supervision.

Consent to participate

Not applicable

Consent for publication

Not applicable.

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