

# Delayed Tuberculosis Treatment and Cost of Care in a Low-Incidence Country

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**Background.** Tuberculosis (TB) elimination requires high-quality, timely care. In countries with a low incidence of TB, such as Ireland, delayed diagnosis is common. This evaluation aimed to determine the factors that predict patient-related and health care provider–related delays in TB management and to establish how TB care cost is affected by care delays.

*Methods.* Health care records of patients with signs and symptoms of TB evaluated by a tertiary service in Ireland between July 1, 2018, and December 31, 2019, were reviewed to measure and determine predictors of patient-related delays, health care provider-related delays, and the cost of TB care. Outcomes were compared against benchmarks 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, €9319; minimum, €6486; maximum, €14750), could be improved. Patient-related delays among those with PTB predicted care costs.

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

Keywords. cost; communicable disease; Ireland; quality; tuberculosis.

In 2020, nearly 10 million people were infected with tuberculosis (TB), a preventable infectious disease [1]. Despite being treatable, 1.5 million people died of TB in 2020 [1]. TB elimination (an incidence <1 case per million) is a global priority that many high-income, low-incidence (<10 cases per 100 000) countries are well positioned to progress toward [2]. Lowincidence countries, such as Ireland (incidence of 5.6 cases per 100 000 in 2019 with 267 cases [3]), tend to have low rates of TB transmission, few missing cases of TB annually, and a low burden of drug-resistant TB and HIV–TB coinfection [2]. In low-incidence countries, TB is increasingly concentrated in vulnerable groups, and occasional outbreaks are observed [2]. Internationally, there is a growing consensus that to address TB, a paradigm shift from a focus on only TB care coverage to one

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that includes care quality is needed [1, 2, 4]. 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 [5-7]. Therefore, TB programs 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 prioritized by health care managers or policy-makers for resourcing [2]. In Ireland, delays in the diagnosis and treatment of TB have been reported [8, 9], and understanding the cost of this delayed care may be informative when making resource allocation decisions for TB care in Ireland. The primary aims of this evaluation were to determine the factors that predict patient-related and health care provider-related delays in TB diagnosis and treatment and to establish how 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 center TB service in Ireland was performed. Patients who were referred with symptoms or signs of active TB between July 1, 2018, and December 31, 2019, were included. Data extraction was performed by author 1 and

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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 utilization (Supplementary 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 [10]. Extrapulmonary TB cases (EPTB) were those with TB not captured by the definition of PTB. Treatment outcomes were reported according to World Health Organization (WHO) definitions [10].

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), hematological (full blood counts), biochemical (renal and liver function profiles), immunological (interferongamma release assay), virological (hepatitis B, hepatitis C, HIV testing), and microbiological (TB smear and culture, GeneXpert testing) investigations. Investigation costs (Supplementary Appendix 1) were sourced primarily from the laboratory directorate, literature published from Ireland, and, for radiological tests, the National Health Service cost collection [11]. Antituberculosis medications and pyridoxine reimbursement costs were sourced from the Health Service Executive (HSE) (Supplementary Appendix 1). Where drug costs were unavailable from the HSE, costs were sourced first from the Monthly Index of Medical Specialties (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 [12]. Cost data were inflated to 2019 values, and costs in British pounds sterling were converted to euros using Organization for Economic Co-operation and Development (OECD) purchasing power parity figures following national guidance from the Health Information and Quality Authority [13]. The cost of outpatient clinics (which included those for the investigation of undiagnosed TB and those for the management of known TB in or outside of the tertiary center) were calculated according to national costing guidelines and HSE salary scales (Supplementary Appendix 1) [14, 15]. Hospitalizations due to TB (which included those in or outside of the tertiary center that at the time of admission related to undiagnosed TB and those for the management of known TB in or outside of the tertiary center) were costed following guidance from the Healthcare Pricing Office [16] and included elective, emergency, and rehabilitation-related hospitalizations (Supplementary Appendix 1).

A structured review of the literature was performed to identify studies that reported patient-related delays, health care provider–related delays, and direct costs of TB care (Supplementary Appendix 2). Outcomes from this evaluation were benchmarked against those reported in the literature from other lowincidence 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. Patients with nontuberculosis mycobacteria infection were excluded from data analysis. Multiple regression was performed with patientrelated delay as the dependent variable and age, sex, nationality, and HIV status as the independent variables. Multiple regression was performed with health care provider-related delay as the dependent variable and age, sex, nationality, HIV status, culture status, sputum smear status, GeneXpert test performance, drug resistance status, and acute hospitalization requirement as the independent variables. Multiple 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 and then converted to euros using the purchasing power parity index as reported by the OECD [17].

# 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 (interquartile range [IQR]) was 41.7 (35.1–46.3) years. Sixty percent of patients (22/37) were from a country with a high incidence of TB (≥40 cases annually per 100 000 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 latent tuberculosis infection (LTBI), and only 8% (3/37) had a documented history of being screened for LTBI (all of whom were found to not have LTBI).

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

## Table 1. Patient Characteristics

	Tuberculosis	Pulmonary Tuberculosis	Extrapulmonary Tuberculosis
	(11 = 37)	(11 = 19)	(11 = 10)
Median age (IQR), y	41.7 (35.1–46.3)	41.4 (33.3–54)	42.1 (37.7–50)
Male sex, No. (%)	21 (57)	12 (63)	9 (50)
Any TB risk factor, No. (%)	32 (87)	15 (79)	16 (89)
Born in a country of high TB incidence, No. (%)	22 (60)	8 (42)	14 (78)
HIV positive, No. (%) HIV negative, No. (%) Not tested for HIV, No. (%)	3 (8) 29 (78) 5 (14)	2 (11) 14 (74) 3 (16)	1 (6) 15 (83) 2 (11)
Immunosuppression, No. (%)	4 (11)	1 (5)	3 (17)
Homeless, No. (%)	2 (5)	2 (11)	0
Asylum seeker, No. (%)	1 (3)	0	1 (6)
Person who uses drugs, No. (%)	2 (5)	2 (11)	0
History of incarceration	0	0	0
Health care worker, No. (%)	5 (14)	2 (11)	3 (17)
Recent TB contact, No. (%)	4 (11)	4 (21)	0
History of active TB, No. History of LTBI screen, No. (%)	0 3 (8)	0 3 (16)	0 0
Diabetes mellitus, No. (%)	3 (8)	3 (16)	0
Alcohol misuse, No. (%)	4 (11)	4 (21)	0

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; LTBI, latent tuberculosis infection; TB, tuberculosis.

resistance and one of whom had pyrazinamide resistance. None had rifampicin-resistant or multidrug-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 before diagnosis, 41% (15/37) presented with their symptoms directly to an emergency department, and 13% (5/37) of 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.

Among patients with PTB, the median patient-related delay (IQR) was 60 (30–180) days (Table 2). In a multiple regression model (Table 3), age, sex, nationality, and HIV status did not predict patient-related delay among those with PTB. Among patients with EPTB, the median patient-related delay (IQR) was 30 (21–60) days, and in a multiple regression model that included age, sex, nationality, and HIV status, only HIV infection predicted patient-related delay.

## **Health Care Provider–Related Delays**

The median health care provider–related delay among patients with PTB (IQR) was 16 (2–54) days. In a multiple 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% CI, –395.48 to –85.27; P < .05) among patients with PTB (Table 3). There was no evidence from multiple regression

	Table 2.	Care (	Costs and	Delays	Among	Patients	With	Tuberculo	sis
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Variable	Pulmonary Tuberculosis	Extrapulmonary Tuberculosis
Median patient-related delay (IQR), d	60 (30–180)	30 (21–60)
Mean patient-related delay (SD), d	101 (100)	83 (112)
Median health care–related delay (IQR), d	16 (2–54)	66 (24–176)
Mean health care–related delay (SD), d	50 (76)	157 (227)
Median cost of care (IQR), €	10 162 (4898–19 549)	7535 (3730–18 057)
Mean cost of care (SD), €	32 955 (77 117)	40 005 (98 308)
Mean cost of care (SD), €	32955 (77117)	40 005 (98 308)

Abbreviations: d, days; IQR, interquartile range

## Table 3. Multiple Regression Models for Predictors of Delays Among Patients With Tuberculosis

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

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; TB, tuberculosis.

controlling for age, sex, and nationality that sputum smear positivity after presenting to health care services predicted health care provider-related delays among patients with PTB (coefficient, -84.7; standard error, 42.6; 95% CI, -176.73 to 7.33; P = .07). The median health care provider-related delay among patients with EPTB (IQR) was 66 (24-176) days, and in a multiple 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. Although GeneXpert testing was performed on samples from 78% (29/37) of patients and 84% (16/19) of those with PTB, there was no evidence from multiple regression controlling for age, sex, and nationality that GeneXpert testing predicted health care providerrelated delay (PTB: coefficient, 18.78; standard error, 53.7; 95% CI, -97.23 to 134.8; P = .73; EPTB: coefficient, 22.58; standard error, 141.43; 95% CI, -282.97 to 328.13; P = .88).

# **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) (IQR) was €8298 (€4344-€19 641). The median cost of care among patients with drug-susceptible PTB with a successful treatment outcome (n = 16) (IQR) was €10162 (€4898–€19549). The median cost of care among patients with drug-susceptible EPTB with a successful treatment outcome (n = 14) (IQR) was  $\notin$ 7535 (€3730–€18057). In a multiple regression model that included age, sex, nationality, HIV status, culture status, patient-related delays, and health care provider-related delays, only patientrelated delays predicted a higher cost of care among patients with drug-susceptible PTB who completed treatment (Table 4). In a multiple regression 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 drug-susceptible EPTB.

### **Comparison of Evaluation Outcomes With Benchmarks**

The results of the literature search are reported in Supplementary Appendix 2. Studies reported the median patient-related delay

Table 4.	Multiple Regression	Models for Predictors	of Direct Cost of Care	Among Patients Wit	h Tuberculosis
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Multiple Regression Model for Predictors of Direct Cost of Pulmonary TB Care						
Patient-Related Delay	Beta Coefficient	Standard Error	95% CI (Lower Limit)	95% CI (Upper Limit)	Т	P> <u>_</u> t
Age at first presentation	2880.08	1319.81	-105.55	5865.70	2.18	0.06
Male sex	24 231.74	39 247.73	-64 552.80	113 016.30	0.62	0.55
Irish nationality	-24 453.15	41 362.82	-118 022.30	69 116.05	-0.59	0.57
HIV infected	-31 595.83	51 704.20	-148 558.90	85 367.19	-0.61	0.56
Culture-positive TB	-80 597.39	114 364.10	-339 307.00	178 112.20	-0.70	0.50
Patient-related delay	424.05	187.03	0.96	847.15	2.27	0.05
Health care provider–related delay	-305.31	365.80	-1132.82	522.20	-0.83	0.43
Constant	-43 701.31	129 315.30	-336 232.80	248 830.20	-0.34	0.74
Multiple regression model for predict	tors of direct cost of ext	trapulmonary TB care				
Age at first presentation	-466.4403	446.8027	-1559.727	626.8466	-1.04	0.337
Male sex	-4199.576	9388.936	-27 173.48	18 774.32	-0.45	0.67
Irish nationality	46 504.35	32 452.2	-32 903.33	125 912	1.43	0.202
Culture-positive TB	-4861.437	8622.483	-25 959.89	16 237.02	-0.56	0.593
Patient-related delay	-60.13667	85.82541	-270.1439	149.8705	-0.7	0.51
Health care provider–related delay	0.790151	14.51181	-34.71897	36.29927	0.05	0.958
Constant	30 585.9	17 349.45	-11 866.67	73 038.47	1.76	0.128

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; TB, tuberculosis.

among patients with PTB as being 7, 10, 18, 21, 30, 36, and 38 days [18–23]. Therefore, the median, minimum, and maximum patient-related delays 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 that 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 [18, 20–22, 24, 25]. 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 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 [20, 26], all less 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 nonrifampicin/nonmultidrug-resistant TB care reported in the included studies were  $\notin$ 9319,  $\notin$ 6486, and  $\notin$ 14 750, respectively (Table 5). Therefore, the cost of care reported in this evaluation ( $\notin$ 8298), while similar to that in other low-incidence countries, could be improved.

# 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 patientrelated delays predicted increased care costs. Patient-related delays were substantial, particularly among patients with PTB. Although patient-related delays for those with EPTB were not

	Table 5.	Direct Cost	of Nonrifam	picin	/Nonmultidrug	I-Resistant TE	3 Care Re	eported in the	Literature
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Study (Year)	Country	Nonrifampicin/Nonmultidrug-Resistant TB Cost, €
Diel et al. (2020) [27, 28]	Germany	9455
De Vries et al. (2013) [29]	The Netherlands	9319
Deuffic-Burban et al. (2010) [30]	France	6486
Department of Health (2009) [31]	United Kingdom	7199
Chan et al. (2017) [32]	Australia	6952
Marks et al. (2014) [33]	USA	14 750
Pina et al. (2013) [34]	Spain	10 557
Median		9319
Minimum		6486
Maximum		14 750

Abbreviation: USA, United States of America

compared with outcomes reported in the literature, the absolute value reported in this study of 30 days was long. There was no evidence that patient characteristics such as age, sex, nationality, or HIV status predicted patient-related delays among those with PTB. HIV infection predicted patient-related delays among those with EPTB. This highlights a need to ensure that HIV is diagnosed early and that people 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 wait times have been reported as barriers to accessing health care in Ireland [35, 36], particularly in vulnerable groups, who may face additional changes when accessing health 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. In other low-burden settings, depending on how well performing existing diagnostic algorithms for TB are, GeneXpert testing can reduce health care provider-related delays [37]. However, this evaluation did not demonstrate such an association. Increasing patient-related delays in those with PTB predicted 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. However, TB care should aspire to be more than timely and efficient; it should aim to prevent TB among those at risk. Despite most patients in this evaluation having a risk factor for TB, few had a documented history of being screened for LTBI. This suggests that TB prevention should be improved, but guidance and support for TB services on programmatic LTBI management in Ireland are lacking [38]. This study adds to the literature on TB care in low-incidence countries where delays in treating TB are a well-recognized challenge [21-23], which has also been reported in other studies in Ireland [8, 9]. The association between increasing costs of PTB care and patient-related delays has been previously infrequently reported in the literature from countries with a low incidence of TB. This evaluation provides the first estimates of the cost of TB disease in adults in Ireland.

The major limitation of this evaluation was the small sample size (n = 37), which represented only ~9% of an estimated 424 cases notified nationally from July 2018 to December 2019 (267 in 2019 plus half of the 315 in 2018 [3]). For this reason, type II errors in the analyses cannot be excluded. A limitation of this study was the retrospective means by which data were collected from health care records. Additional health care resource

utilization 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 tertiary center nature of this study limits the generalizability of the findings to other centers, particularly TB care in nontertiary centers. However, with regard to the cost estimates reported, hospitalizations were the greatest component of TB care cost (92.1%), and a similar proportion of TB cases being hospitalized has been reported nationally [39], supporting the generalizability of the direct cost estimates to TB care in other tertiary centers in Ireland. There were no patients with rifampicin- or multidrug-resistant TB, meaning the results cannot be generalized to these patient cohorts. This evaluation did not consider the patient perspective on the cost of TB disease, which is likely to be significant in both monetary and nonmonetary terms due to out-of-pocket expenditures, prolonged symptoms, stigma, loss of housing and employment, and post-TB sequelae [1].

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 causes of delayed care are likely country- and population-specific. Patient-pathway analysis has been useful in other countries [40]. Qualitative research that evaluates patients' experiences of seeking care before diagnosis should be performed to identify barriers to utilizing and accessing health care with their symptoms, particularly in primary care. The national TB program 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 before, 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 program in Ireland, which should be ensuring that patients with TB receive high-quality, timely, and effective care. Researchers, health care professionals, and medical organizations have regularly highlighted insufficient resourcing for TB services in Ireland, where there is no dedicated funding for the TB program [8]. Unless initiatives to reduce TB care delays are identified and resourced, patients with TB in Ireland will continue to have prolonged morbidity, to have ongoing opportunities for transmission, and to incur higher care costs. In this context, TB elimination will likely not be achieved nationally.

## CONCLUSIONS

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.

#### **Supplementary Data**

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of

the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. James O'Connell: conceptualization, methodology, validation, formal analysis, investigation, data curation, writingoriginal and draft, writing-review and editing, visualization, project administration. Niamh Reidy: methodology, validation, investigation, data curation, writing-review and editing, project administration. Cora McNally: conceptualization, methodology, writing-review and editing, visualization, project administration, supervision. Debbi Stanistreet: conceptualization, methodology, writing-review and editing, visualization, supervision. Samuel McConkey: conceptualization, methodology, writingreview and editing, visualization, project administration, supervision. Eoghan de Barra: conceptualization, methodology, writingreview and editing, visualization, methodology, writingreview and editing, visualization, project administration, supervision.

*Availability of data and material.* The data sets generated during and/ or analyzed 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.

*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).

## References

- World Health Organization. Global tuberculosis report 2020. 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng. pdf. Accessed 5 August 2021.
- L nnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J 2015; 45:928–52.
- Health Protection Surveillance Centre. Annual epidemiological report for tuberculosis 2019. 2019. Available at: https://www.hpsc.ie/a-z/vaccinepreventable/ tuberculosistb/tbdataandreports/2019\_Q1-4\_TB\_v1.0.pdf. Accessed 8 August 2021.
- Pai M, Temesgen Z. Quality: the missing ingredient in TB care and control. J Clin Tuberc Other Mycobact Dis 2019; 14:12–3.
- Asres A, Jerene D, Deressa W. Delays to treatment initiation is associated with tuberculosis treatment outcomes among patients on directly observed treatment short course in Southwest Ethiopia: a follow-up study. BMC Pulm Med 2018; 18:64.
- Virenfeldt J, Rudolf F, Camara C, et al. Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. BMJ Open 2014; 4:e004818.
- Golub J, Bur S, Cronin W, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. Int J Tuberc Lung Dis 2006; 10:24–30.
- O'Meara M. An evaluation of TB service delivery in the Northern Area Health Board: thesis submitted as part requirement for the membership of the Faculty of Public Health Medicine of the Royal College of Physicians of Ireland. 2007. Available at: https://www.lenus.ie/handle/10147/263892. Accessed 8 August 2021.
- Grant C, McHugh J, Ryan C, et al. Symptoms to script: delays in tuberculosis treatment in the west of Ireland. Ir J Med Sci 2021; 19:295–300.
- World Health Organization. Reporting framework for tuberculosis—2013 revision, updated December 2014 and January 2020. 2020. Available at: https://www. who.int/publications/i/item/9789241505345. Accessed 5 August 2021.
- National Health Service. National Cost Collection. Available at: https://improvement.nhs.uk/resources/national-cost-collection/. Accessed 13 May 2020.
- National Centre for Pharmacoeconomics. Guidelines for inclusion of drug costs in pharmacoeconomic evaluations, version 2.1. 2020. Available at: http://www. ncpe.ie/submission-process/hta-guidelines/guidelines-for-inclusion-of-drugcosts/. Accessed 6 August 2021.
- Health Information and Quality Authority. Guidelines for the economic evaluation of health technologies in Ireland 2014. 2014. Available at: https://www. hiqa.ie/reports-and-publications/health-technology-assessment/guidelineseconomic-evaluation-health. Accessed 6 August 2021.

- Government Accounting Unit, Department of Public Expenditure and Reform. Public spending code E.01 calculation of staff costs. 2019. Available at: https:// govacc.per.gov.ie/wp-content/uploads/Public-Spending-Code-Consolidated-Document.pdf. Accessed 7 March 2021.
- Health Service Executive. Consolidated salary scales 2019. 2019. Available at: https://www.hse.ie/eng/staff/benefitsservices/pay/. Accessed 7 March 2021.
- Healthcare Pricing Office. Admitted patient price list 2019. 2019. Available at: http://www.hpo.ie/abf/ABF2019AdmittedPatientPriceList.pdf. Accessed 13 May 2020.
- Organisation for Economic Co-operation and Development. Purchasing power parities for GDP and related indicators. Available at: https://stats.oecd.org/Index. aspx?DataSetCode=PPPGDP. Accessed 29 November 2020.
- Gagliotti C, Resi D, Moro M. Delay in the treatment of pulmonary TB in a changing demographic scenario. Int J Tuberc Lung Dis 2006; 10:305–9.
- Peri AM, Bernasconi DP, Galizzi N, et al. Determinants of patient and health care services delays for tuberculosis diagnosis in Italy: a cross-sectional observational study. BMC Infect Dis 2018; 18:690.
- Dale K, Tay E, Trauer J, Trevan P, Denholm J. Gender differences in tuberculosis diagnosis, treatment and outcomes in Victoria, Australia, 2002-2015. Int J Tuberc Lung Dis 2017; 21:1264–71.
- Quattrocchi A, Barchitta M, Nobile CG, et al. Determinants of patient and health system delay among Italian and foreign-born patients with pulmonary tuberculosis: a multicentre cross-sectional study. BMJ Open 2018; 8:e019673.
- Auer C, Kiefer S, Zuske M, et al. Health-seeking behaviour and treatment delay in patients with pulmonary tuberculosis in Switzerland: some slip through the net. Swiss Med Wkly 2018; 148:w14659.
- Van der Werf M, Chechulin Y, Yegorova O, et al. Health care seeking behaviour for tuberculosis symptoms in Kiev City, Ukraine. Int J Tuberc Lung Dis 2006; 10:390–5.
- 24. Jurcev-Savicevic A, Mulic R, Kozul K, et al. Health system delay in pulmonary tuberculosis treatment in a country with an intermediate burden of tuberculosis: a cross-sectional study. BMC Public Health **2013**; 13:250.
- Leutscher P, Madsen G, Erlandsen M, et al. Demographic and clinical characteristics in relation to patient and health system delays in a tuberculosis low-incidence country. Scand J Infect Dis 2012; 44:29–36.
- Mathiasen VD, Andersen PH, Johansen IS, Lillebaek T, Wejse C. Clinical features of tuberculous lymphadenitis in a low-incidence country. Int J Infect Dis 2020; 98:366–71.
- Diel R, Nienhaus A. Cost of illness of non-multidrug-resistant tuberculosis in Germany: an update. ERJ Open Res 2020; 6:00329-2020.
- Diel R, Sotgiu G, Andres S, Hillemann D, Maurer F. Cost of multidrug resistant tuberculosis in Germany—an update. Int J Infect Dis 2021; 103:102–9.
- De Vries G, Baltussen R. Kosten van tuberculose en TBC—bestrijding in Nederland. Tegen Tuber 2013; 109:3–7.
- Deuffic-Burban S, Atsou K, Viget N, Melliez H, Bouvet E, Yazdanpanah Y. Costeffectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. Int J Tuberc Lung Dis 2010; 14:471–81.
- Department of Health. Supply of TB drugs to patients changes to regulations and advice on implementation. Available at: https://webarchive.nationalarchives. gov.uk/+/http://www.dh.gov.uk/en/Publichealth/Communicablediseases/ Tuberculosis/DH\_078136. Accessed 29 November 2020.
- Chan E, Nolan A, Denholm J. How much does tuberculosis cost? An Australian healthcare perspective analysis. Commun Dis Intell Q Rep 2017; 41:E191–4.
- Marks SM, Flood J, Seaworth B, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. Emerg Infect Dis 2014; 20:812–21.
- Pina J, Clotet L, Ferrer A, et al. Cost-effectiveness of rifampin for 4 months and isoniazid for 9 months in the treatment of tuberculosis infection. Eur J Clin Microbiol Infect Dis 2013; 32:647–55.
- O'Reilly D, O'Dowd T, Galway KJ, et al. Consultation charges in Ireland deter a large proportion of patients from seeing the GP: results of a cross-sectional survey. Eur J Gen Pract 2007; 13:231–6.
- Connolly S, Wren MA. Unmet healthcare needs in Ireland: analysis using the EU-SILC survey. Health Policy 2017; 121:434–41.
- Sulis G, Agliati A, Pinsi G, et al. Xpert MTB/RIF as add-on test to microscopy in a low tuberculosis incidence setting. Eur Clin Respir J 2018; 51:1702345.
- O'Connell J, de Barra E, McConkey S. Systematic review of latent tuberculosis infection research to inform programmatic management in Ireland. Ir J Med Sci. 2021. doi:10.1007/s11845-021-02779-w.
- O'Connell J, de Barra E, McConkey S. Hospital inpatient care utilization among patients with tuberculosis, Republic of Ireland, 2015-2018. PLoS One 2020; 15:e0238142.
- Masini E, Hanson C, Ogoro J, et al. Using patient-pathway analysis to inform a differentiated program response to tuberculosis: the case of Kenya. J Infect Dis 2017; 216(Suppl 7):S714–23.