



## Infectious Disease Practice

## Tuberculosis incidence in solid organ transplant recipients in Europe: A multicenter TBnet cohort study



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Abbreviations: CI, confidence interval; IGRA, interferon-gamma release assay; IQR, interquartile range; HR, hazard ratio; TBnet, Tuberculosis Network European Trials Group; TPT, tuberculosis preventive therapy; TST, tuberculin skin test; sHR, subdistribution hazard ratio; SIR, standardized incidence ratio; SOT, solid organ transplantation; WHO, World Health Organization

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## SUMMARY

**Background:** Solid organ transplant (SOT) recipients face elevated tuberculosis risk, yet optimal prevention strategies in low- to medium-incidence regions remain unclear.**Methods:** We conducted a multicenter retrospective cohort study of adult SOT recipients transplanted between 2007 and 2012 at 15 European centers, with follow-up through 2018. The primary outcome was microbiologically confirmed post-transplant tuberculosis. Incidence rates were calculated per 100,000 person-years; standardized incidence ratios (SIRs) used World Health Organization country-specific background rates. Cox models assessed risk factors.**Results:** Among 5805 patients (median age 51; 62.7% male; 73.9% renal transplants), 33.8% were tested for tuberculosis infection and 10.3% received tuberculosis preventive therapy (TPT). Over 33,785 person-years, 23 patients (0.4%) developed tuberculosis (68.0/100,000 person-years). Highest incidence occurred in patients with positive screening but no TPT (233.8/100,000). Incidence was higher in Southern vs. Central Europe (251.9 vs. 28.7/100,000), with pooled SIRs of 12.8 and 3.1, respectively. Tuberculosis risk was elevated among Southern European recipients (HR 22.9) and those with migration history (HR 2.7).**Conclusion:** Tuberculosis risk is increased in European SOT recipients. Regionally adapted prevention strategies, including targeted screening in low-incidence areas and universal screening in higher-incidence regions, are warranted.© 2025 The Author(s). Published by Elsevier Ltd on behalf of British Infection Association. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Introduction

Tuberculosis is typically controlled by both innate and adaptive immune responses in healthy individuals. Solid organ transplant (SOT) recipients, who are treated with immunosuppressive therapies to prevent graft rejection, are estimated to have a 20- to 74-fold higher risk of tuberculosis compared with the general population, and incidences have been reported to range from 0.3 to 6.4% in low incidence regions to up to 15% in endemic countries.<sup>1–12</sup> The incidence also depends on the type of organ transplanted, with lung transplant recipients having a significantly higher risk than other SOT groups.<sup>7,13,14</sup>

Most cases of tuberculosis in SOT recipients result from re-activation of a latent infection with *Mycobacterium tuberculosis* (LTBI)<sup>15</sup> – more recently re-defined as “tuberculosis infection”<sup>16</sup> – upon initiation of immunosuppressive therapy. In addition to re-activation of tuberculosis infection, *M tuberculosis* may be transmitted from the donor to the transplant recipient via the allograft,<sup>17,18</sup> particularly if the donor is from a tuberculosis endemic country, and the transplanted organ is the lung.<sup>19,20</sup> Furthermore, *de novo* infection may occur after transplantation.<sup>20,21</sup> The prevalence of tuberculosis infection among SOT recipients in low-to-medium incidence countries has been reported to be 6% in Japan,<sup>22</sup> 19% to 30% in Brazil,<sup>23,24</sup> 20% in South Korea,<sup>25</sup> 9% to 14% in the USA,<sup>26,27</sup> 18% in Iran,<sup>28</sup> 24% to 44% in Spain,<sup>29–31</sup> 47% in Turkey,<sup>12</sup> 5% in Australia,<sup>32</sup> and 9.0 to 20.0% in a multicenter TBnet study across 17 European healthcare facilities.<sup>33</sup> Although there is considerable variation in these figures, they are generally consistent with the estimated prevalence of tuberculosis infection in the general population of the World Health Organization (WHO) European Region of 13.7%.<sup>34</sup>

The risk of active tuberculosis (now termed “tuberculosis disease”<sup>16</sup>) is reported to be high early after transplantation, with a median onset of nine months after initiation of immunosuppression.<sup>4</sup> Tuberculosis in SOT recipients is associated with a higher incidence of extrapulmonary and disseminated infections and more severe manifestations with a higher mortality of up to 29%.<sup>1,2,4,5,11,35</sup> The management of tuberculosis in SOT recipients is challenging due to the underlying immunosuppression required to maintain the graft<sup>3</sup> and the risk of drug-drug interactions.<sup>36</sup>

Despite the considerable impact of tuberculosis in SOT recipients, the optimal strategy for tuberculosis prevention remains a complex and evolving challenge. A previous TBnet consensus statement recommended tuberculosis preventive therapy (TPT) without prior tuberculosis infection screening for all transplant recipients in regions with high tuberculosis incidence ( $\geq 100/100,000$  population) and tuberculosis infection screening and TPT for those with confirmed infection for all transplant recipients in regions with moderate tuberculosis incidence ( $\geq 20$  and  $< 100/100,000$  population).<sup>21</sup> In regions with low tuberculosis incidence ( $< 20/100,000$  population), the decision to screen for tuberculosis infection and administer TPT should include an individual risk assessment, and screening should be performed at least in candidates with additional risk factors for tuberculosis infection. In contrast, most international guidelines, including those from low-incidence countries, recommend universal screening for tuberculosis infection in all transplant candidates.<sup>37–39</sup> On the one hand, tuberculosis infection screening and TPT have been shown to be generally safe and to prevent progression to tuberculosis disease.<sup>33,40–45</sup> On the other hand, concerns remain about adverse events, drug-drug interactions and overdiagnosis and overtreatment, especially in low-incidence settings where the positive predictive value of interferon-gamma

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release assays (IGRAs) and tuberculin skin tests (TSTs) may be limited.<sup>28,29,33,45</sup>

Overall, evidence on the management of tuberculosis prevention in solid organ transplant recipients in low-incidence regions is limited, and the impact of different preventive strategies on post-transplant tuberculosis incidence remains uncertain. Therefore, we conducted a multicenter cohort study to evaluate the effect of various tuberculosis prevention approaches on the incidence of post-transplant tuberculosis across European transplant centers, with the goal of providing updated evidence to guide clinical practice in these settings.

## Study population and methods

### Study design

A retrospective cohort study was conducted from 22nd of June 2015 to 31st of December 2018 to investigate the incidence of tuberculosis in SOT recipients across Europe. We followed the STROBE guidelines for reporting of observational studies.<sup>46</sup> Transplant centers in Europe were recruited through the Tuberculosis Network European Trials Group (TBnet, [www.tbnet.eu](http://www.tbnet.eu)) and were eligible for inclusion if the countries had a low- to medium tuberculosis incidence (<100/100,000 population), based on WHO data from 2011.<sup>47</sup> Centers with higher local tuberculosis incidences (e.g., London, United Kingdom) were still included based on national incidence.

The study protocol was approved by the ethical committee of the Ärztekammer des Saarlandes (reference number 134/15) and extended to each participating center. Informed consent was dispensable due to the retrospective nature of the study.

### Data collection

All SOT recipients  $\geq 18$  years of age who underwent SOT between 2007 and 2012 in the participating centers were consecutively enrolled in the study and follow-up data for development of tuberculosis were collected until the end of 2018. Only patients with confirmed tuberculosis were included as cases for further analysis. Confirmed tuberculosis was defined as the presence of clinical signs and symptoms of tuberculosis and the detection of *Mycobacterium tuberculosis* through growth in liquid or solid culture and/or the identification of *M tuberculosis*-complex specific DNA via nucleic acid amplification testing (NAAT) from a biological specimen at the time of diagnosis. Probable tuberculosis was defined as the presence of signs and symptoms with acid-fast bacilli in a sputum smear or caseous necrosis in a tissue-biopsy specimen. Possible tuberculosis was defined as the presence of signs and symptoms without microbiologic or histologic evidence of *M tuberculosis* but with a clinical response to anti-tuberculosis therapy.<sup>48</sup>

Only patients with at least three months of follow-up after SOT were included into further analysis. Patients who developed tuberculosis within three months of transplantation were excluded as prevalent cases. Missing or incomplete datasets were excluded from analysis. No imputation of missing data was performed. Anonymous data were collected per center and per patient in a secure data form. Further details on data collection is given in the [supplementary methods](#).

### Statistical analyses

All statistical analyses were conducted using R (version 4.5.1) within RStudio (version 2025.05.1+513). Categorical variables are presented as absolute numbers and percentages; continuous variables are summarized as medians with interquartile ranges (IQR).

The crude incidence rate of tuberculosis was calculated as the number of cases per 100,000 patient-years during follow-up. Incidence rates were compared descriptively between the first two years after transplantation and the subsequent years. Incidence rates were compared using Poisson exact tests, and 95% confidence intervals were calculated assuming a Poisson distribution.

Survival analysis was performed using the Kaplan–Meier method with time since transplantation as the time scale and incident tuberculosis as the event. Participants were censored at the date they had the event when they were lost to follow up or until December 2018, and death was introduced as a competing event. The log-rank test was applied to compare survival curves between different TPT strategies. Standardized Incidence Ratios (SIRs) were calculated for all participating countries using national tuberculosis incidence data from 2011.<sup>47</sup> National background incidence rates were applied uniformly to all participating centers, including those located in regions with higher local tuberculosis incidence. To assess regional differences, SIRs were also calculated for participating centers from countries in Southern Europe (here including Spain and Portugal) and Central Europe (here defined as Austria, Czech Republic, Germany, the Netherlands, Serbia, and the United Kingdom). Cumulative tuberculosis incidence after transplantation was compared between Central and Southern Europe using Kaplan–Meier estimates and the log-rank test. Details on meta-analysis of SIRs for post-transplant tuberculosis, and on modeling time to tuberculosis diagnosis are given in the [supplementary methods](#) section.

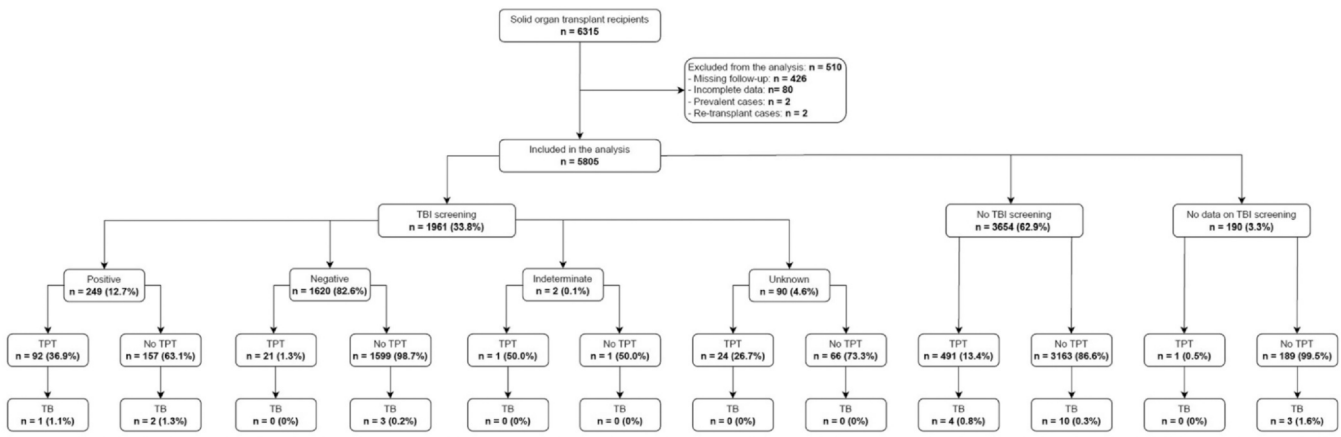
## Results

### Study population

A total of 6315 SOT recipients from 15 transplant centers across eight countries (Austria, Czech Republic, Germany, The Netherlands, Portugal, Serbia, Spain, and the United Kingdom) were enrolled in the study ([Fig. 1](#)). Of these, 510 patients (8.1%) were excluded from the final analysis due to missing follow-up data (n=426), incomplete datasets (n=80), since they underwent re-transplantation and were therefore included only once (n=2), or because they developed tuberculosis within the first three months after SOT (n=2). The final analysis thus included 5805 patients. Patients had a median age of 51 years (IQR 40–59 years) and were predominantly male (n=3641; 62.7%, [Table 1](#)). A total of 780 patients (13.4%) had a history of migration, defined as individuals born outside the country in which they received medical care. The majority of patients were renal transplant recipients (n=4292; 73.9%), followed by liver (n=890; 15.3%), lung (n=498; 8.6%), and heart transplant recipients (n=108; 1.9%). Participants were enrolled from the United Kingdom (n=1749; 30.1%), The Netherlands (n=1661; 28.6%), Spain (n=805; 13.9%), Germany (n=683; 11.8%), Austria (n=336; 5.8%), Portugal (n=304; 5.2%), the Czech Republic (n=151; 2.6%), and Serbia (n=116; 2.0%).

### Incidence of tuberculosis

During a total follow-up time of 33,785 person-years, 23 patients (0.4%) were diagnosed with confirmed tuberculosis, corresponding to an overall crude incidence rate of 68.1 cases per 100,000 person-years (95% CI: 43.2–102.0, [Table 2](#)). In addition, one patient was classified as having probable tuberculosis and another as having possible tuberculosis. Regarding disease manifestation among the patients with confirmed tuberculosis, 12 patients (52.2%) had pulmonary tuberculosis, eight (34.8%) had exclusively extrapulmonary involvement, two (8.7%) had both pulmonary and extrapulmonary disease, and in one case (4.3%) the site of disease was not documented. Nineteen (82.6%) were cured or completed treatment, three



**Fig. 1.** Flow chart of solid organ transplant recipients recruited into the study and cases of active tuberculosis during follow-up depending on screening and tuberculosis preventive treatment. Shown is the number of individuals who were included to assess development of tuberculosis after transplantation (incident cases). One of the two prevalent patients developed tuberculosis two days after lung transplantation, most likely due to donor-derived prevalent disease, the other one was a renal transplant recipient who developed tuberculosis after two months. All individuals with more than 3 months of follow-up were included, with the number of individuals who were or were not screened prior to transplantation shown. Each group is stratified whether patients received TB preventive therapy, and developed active tuberculosis. TB, tuberculosis; TPT, TB preventive therapy.

(13.0%) died, and in one case (4.3%) the outcome was not documented. Among patients with confirmed tuberculosis disease, one case (4.0%) occurred within the first two years after transplantation, while the remaining 22 cases (96.0%) were diagnosed more than two years post-transplant. The incidence rate within the first two years after SOT was 9.1 cases per 100,000 person-years (1 case over 10,953 person-years; 95% CI 0.2–50.9), compared to 96.4 per 100,000 person-years beyond two years (22 cases over 22,832 person-years; 95% CI 60.4–146.0). The incidence rate during the first two years after transplantation was numerically lower than during later follow-up (incidence rate ratio 0.09); however, this difference did not reach statistical significance (Poisson exact test,  $p=0.07$ ).

Of the 23 patients who developed tuberculosis, five had a history of migration, including three from high-incidence countries. In Central Europe, four tuberculosis cases occurred in patients with a history of migration and four in those without. Notably, four of the eight tuberculosis cases reported from Central Europe originated from London, where local background tuberculosis incidence is substantially higher than in most other participating regions.

Tuberculosis incidence varied substantially across countries and regions (Table 2). No tuberculosis cases were observed in Austria, the Czech Republic, Denmark, Germany, or Serbia during the follow-up period. The highest crude incidence rates were recorded in Portugal (352.7 cases per 100,000 person-years), Spain (211.5 cases per 100,000 person-years), followed by the United Kingdom (46.5 per 100,000 person-years) and The Netherlands (31.2 cases per 100,000 person-years). At the regional level, the crude incidence rate was 28.7 per 100,000 person-years in Central Europe (8 cases over 27,830 person-years) and 251.9 per 100,000 person-years in Southern Europe (15 cases over 5956 person-years).

Kaplan–Meier estimates showed a markedly higher cumulative incidence of post-transplant tuberculosis among patients from Southern Europe compared with those from Central Europe, as confirmed by the log-rank test ( $p < 0.0001$ , Fig. S1). While incidence remained low during the first years after transplantation in both regions, cases in Southern Europe continued to accumulate over time, resulting in a substantially higher overall risk by year 10.

#### Tuberculosis infection screening and TPT practices

In total, 1961 patients (33.8%) underwent tuberculosis infection screening prior to SOT (Fig. 1). Annual proportions were 27.9% (n=255) in 2007, 27.4% (n=253) in 2008, 34.4% (n=324) in 2009, 33.1%

(n=327) in 2010, 37.1% (n=332) in 2011 and 41.0% (n=470) in 2012. Moreover, 3654 (62.9%) of patients did not undergo tuberculosis infection screening, and no data on screening were available in 190 (3.3%) of patients. Overall, 630 patients (10.3%) received TPT. In Central Europe, 4697 transplant recipients were included, of whom 1470 (31.3%) underwent screening, while 3139 were not screened. In Southern Europe, 1108 recipients were included, and 491 (44.3%) received screening, whereas 515 did not undergo screening. Among the 1961 screened transplant recipients, the majority (75.5%, n=1480) underwent TST-based screening. IGRA-based screening was performed in 262 recipients (13.3%), while a combination of TST and IGRA was used in 111 cases (5.7%). In another 108 patients (5.5%), the type of screening test remained unknown.

Of the 1961 patients who underwent tuberculosis infection screening, 249 (12.7%) tested positive, but only 92 of those (36.9%) received TPT. Among the 1620 patients who tested negative, 21 (1.3%) still received TPT. The highest tuberculosis incidence rate among patients who underwent screening was observed among patients with a positive screening result who did not receive TPT (233.8 per 100,000 person-years, 95% CI 28.5–844.7), followed by positively screened patients who received TPT (213.7 per 100,000 person-years, 95% CI 5.4–1190.4, Table 3). No tuberculosis cases occurred among patients with a negative IGRA/TST result who nevertheless received TPT. Patients with a negative IGRA/TST result who did not receive TPT had a tuberculosis incidence rate of 34.7 per 100,000 person-years (95% CI 7.2–101.3). Among the 3654 patients (62.9%) who were not screened for tuberculosis infection, 491 (13.4%) nevertheless received TPT (Fig. 1). The clinical reasons for this decision were not systematically documented. Tuberculosis incidence rates among patients who did not receive tuberculosis infection screening were 52.7 per 100,000 person-years (95% CI 25.3–96.9) among those who did not receive TPT and 127.4 per 100,000 person-years (95% CI 34.7–96.9) among those who did receive TPT. Information on screening status was unavailable for 190 patients (3.3%), of whom one patient received TPT. The three patients developing tuberculosis in this group had not received TPT (Fig. 1).

#### Meta-analysis of standardized incidence ratios (SIRs) for post-transplant tuberculosis

Compared to expected background incidence rates, higher standardized incidence ratios (SIRs) were observed in Spain (SIR: 13.2;

**Table 1**  
Demographic characteristics of individuals with and without tuberculosis after solid organ transplantation.

n	Overall cohort	No post-transplant tuberculosis	Post-transplant tuberculosis
	5805	5782	23
<b>Age</b> (mean, SD)	51 (40–59)	51 (40–59) <sup>a</sup>	44 (40–52.5)
<30 years (n, %)	579 (10.0)	577 (10.0)	2 (8.7)
30–44 years (n, %)	1410 (24.3)	1400 (24.2)	10 (43.5)
45–59 years (n, %)	2416 (41.6)	2409 (41.7)	7 (30.4)
≥60 years (n, %)	1391 (24.0)	1387 (23.8)	4 (17.4)
<b>Sex</b> (n, %)			
Male	3641 (62.7)	3631 (62.8)	10 (43.5)
Female	2164 (37.2)	2151 (37.2)	13 (56.5)
<b>Transplant type</b> (n, %)			
Renal	4292 (73.9)	4281 (74.0)	11 (47.8)
Liver	890 (15.3)	882 (15.3)	8 (34.8)
Lung	498 (8.6)	494 (8.5)	4 (17.4)
Heart	108 (1.9)	108 (1.9)	0 (0.0)
Other	17 (0.3)	17 (0.3)	0 (0.0)
<b>Country</b> (n, %)			
United Kingdom	1749 (30.1)	1744 (30.2)	5 (21.7)
The Netherlands	1661 (28.6)	1658 (28.7)	3 (13.0)
Spain	804 (13.9)	795 (13.7)	9 (39.1)
Germany	683 (11.8)	683 (11.8)	0 (0.0)
Austria	337 (5.8)	337 (5.8)	0 (0.0)
Portugal	304 (5.2)	298 (5.2)	6 (26.1)
Czech Republic	151 (2.6)	151 (2.6)	0 (0.0)
Serbia	116 (2.0)	116 (2.0)	0 (0.0)
<b>Ethnicity</b> (n, %)			
White	4407 (75.9)	4390 (75.9)	17 (73.9)
Asian	586 (10.1)	583 (10.1)	3 (13.0)
Black	319 (5.5)	318 (5.5)	1 (4.3)
Hispanic/Latino	70 (1.2)	70 (1.2)	0 (0.0)
Other	89 (1.5)	88 (1.5)	1 (4.3)
Unknown	334 (5.8)	333 (5.8)	1 (4.3)
<b>History of migration</b> (n, %)			
Yes	780 (13.4)	775 (13.4)	5 (21.7)
No	4691 (80.8)	4674 (80.8)	17 (73.9)
Unknown	334 (5.8)	333 (5.8)	1 (4.3)
<b>Diabetes mellitus</b> (n, %)			
Yes	1476 (25.4)	1472 (25.5)	4 (17.4)
No	4329 (74.6)	4310 (74.5)	19 (82.6)
<b>Alcohol abuse</b> (n, %)			
Yes	572 (9.9)	567 (9.8)	5 (21.7)
No	5233 (90.1)	5215 (90.2)	18 (78.3)
<b>Smoker</b> (n, %)			
Yes	1798 (31.0)	1790 (31.0)	8 (34.8)
No	4007 (69.0)	3992 (69.0)	15 (65.2)
<b>Previous tuberculosis</b> (n, %)			
Yes	158 (2.7)	156 (2.7)	2 (8.7) <sup>b</sup>
No	5647 (97.3)	5626 (97.3)	21 (91.3)
<b>Pre-transplantation immunosuppression</b> (n, %)			
Yes	1121 (19.3)	1114 (19.3)	7 (30.4)
No	4684 (80.7)	4668 (80.7)	16 (69.6)
<b>Year of transplantation</b> (n, %)			
2007	913 (15.7)	909 (15.7)	4 (17.4)
2008	922 (15.9)	918 (15.9)	4 (17.4)
2009	941 (16.2)	935 (16.2)	6 (26.1)
2010	989 (17.0)	984 (17.0)	5 (21.7)
2011	895 (15.4)	892 (15.4)	3 (13.0)
2012	1145 (19.7)	1144 (19.8)	1 (4.3)

IQR, interquartile range.

<sup>a</sup> Age was not available for 9 patients without tuberculosis;<sup>b</sup> These patients were not screened prior to transplantation and have not received any TPT.

95% CI: 6.1–25.1) and Portugal (SIR: 12.2; 95% CI: 4.5–26.5), corresponding to an overall regional SIR of 12.8 (95% CI: 7.2–21.1) in Southern Europe (Table S1). In Central Europe, elevated SIRs were recorded in the Netherlands (SIR: 4.3; 95% CI: 0.88–12.5) and the United Kingdom (SIR: 3.6; 95% CI: 1.2–8.3), resulting in a regional SIR of 3.1 (95% CI: 1.4–6.1). The overall SIR was 6.2 (95% CI: 3.9–9.2).

Using a random-effects Poisson generalized linear mixed model, pooled SIRs were estimated for Central and Southern Europe (Fig. 2). The model confirmed a pooled SIR of 3.1 (95% CI: 1.6–6.2) for Central Europe and 12.8 (95% CI: 7.7–21.2) for Southern Europe, with no measurable between-country heterogeneity in either region

( $\tau^2=0.0000$ ,  $I^2=0.0\%$ ). The overall pooled SIR across all countries was 5.4 (95% CI: 2.7–10.8), corresponding to a substantial increase in post-transplant tuberculosis risk compared to national incidence rates. Moderate heterogeneity was observed at the overall level ( $\tau^2=0.256$ ,  $I^2=40.9\%$ ).

#### Modeling time to tuberculosis diagnosis

In the univariable analysis, SOT recipients from Southern Europe had a markedly increased risk of tuberculosis compared with those from Central Europe (HR 15.8, 95% CI 6.0–41.6,  $p < 0.001$ , Table S2).

**Table 2**  
Country- and region-specific incidence rate of post-transplant tuberculosis.

Region/Country	Tuberculosis events	Person-years <sup>a</sup>	Rate per 100,000 person-years	95% CI
<b>Central Europe</b>	<b>8</b>	<b>27,830</b>	<b>28.7</b>	<b>12.4–56.6</b>
Austria	0	2149	0	0–172.0
Czech Republic	0	1090	0	0–338.0
Germany	0	3587	0	0–103.0
The Netherlands	3	9625	31.2	6.4–91.1
Serbia	0	610	0	0–605.0
United Kingdom	5	10,759	46.5	15.1–108.0
<b>Southern Europe</b>	<b>15</b>	<b>5956</b>	<b>251.9</b>	<b>141.0–415.4</b>
Portugal	6	1701	352.7	129.0–768.0
Spain	9	4255	211.5	96.7–402.0
<b>Total</b>	<b>23</b>	<b>33,785</b>	<b>68.1</b>	<b>43.2–102.0</b>

CI, confidence interval.

<sup>a</sup> Person years were calculated as years from transplantation to the date when patients had their last clinical assessment, developed active tuberculosis, or died, whichever occurred first; participating countries in the study were classified as indicated in central and southern Europe, respectively.

Non-renal transplant recipients also had a higher tuberculosis risk (HR 4.9, 95% CI 1.8–13.3,  $p=0.002$ ). In the multivariable Cox model, SOT recipients from Southern Europe (HR 22.9, 95% CI 6.5–80.6,  $p<0.001$ ) and patients with a history of migration (HR 2.7, 95% CI 1.1–6.8,  $p=0.03$ ) had a higher risk of tuberculosis. Age, sex, and transplant type were not independently associated with tuberculosis risk. In a competing risk analysis with robust standard errors and a cluster variable related to the regions patients were coming from, non-renal transplant type (HR 4.3, 95% CI 3.4–5.5,  $p<0.001$ ) was associated with an increased risk of tuberculosis, while male sex (HR 0.46, 95% CI 0.23–0.94,  $p=0.03$ ) and age  $\geq 51$  years (HR 0.52, 95% CI 0.42–0.64,  $p<0.001$ ) were associated with a lower risk (Table S3). Of the 5805 patients included in this analysis, 23 developed post-transplant tuberculosis, 981 died without tuberculosis, and 4801 were censored.

## Discussion

In this European multicenter cohort of 5805 adult SOT recipients, the crude overall incidence of post-transplant tuberculosis was 68.1 cases per 100,000 person-years, corresponding to an SIR of 6.2 (95% CI: 3.9–9.3) and thus markedly elevated compared with background population rates. This aligns with previous smaller studies that have shown a persistently elevated risk of tuberculosis in SOT recipients even in low- to medium-incidence settings.<sup>1–7,10,11</sup> Tuberculosis in SOT recipients was associated with a high case fatality rate of 13.0%, underlining its clinical importance. Notably, apart from two cases diagnosed in the peritransplant time or within the early period after transplantation, all but one incident cases occurred more than two years after transplantation, underscoring potential occurrence of de novo infections after transplantation, and the need for long-term

**Table 3**  
Incidence rates of post-transplant tuberculosis according to tuberculosis infection screening result and preventive treatment strategy.

Subgroup	TPT	n	Events (n)	Person-years <sup>a</sup>	IR/100,000 PY (95% CI)
no screening	no	3163	10	18,975	52.7 (25.3–96.9)
no screening	yes	491	4	3140	127.4 (34.7–96.9)
negative screening	no	1599	3	8656	34.7 (7.2–101.3)
negative screening	yes	21	0	125	0.0 (0–2947.0)
positive screening	no	157	2	855	233.8 (28.3–844.7)
positive screening	yes	92	1	468	213.7 (5.4–1190.4)

This analysis was restricted to patients who underwent tuberculosis infection screening, who had a known valid test result (positive or negative,  $n=1869$ ). CI, confidence interval; IR, incidence rate; CI, confidence interval; TPT, tuberculosis preventive treatment; PY, person-year.

<sup>a</sup> Person-years were calculated as years from transplantation to the date when patients had their last clinical assessment, developed active tuberculosis, or died, whichever occurred first.

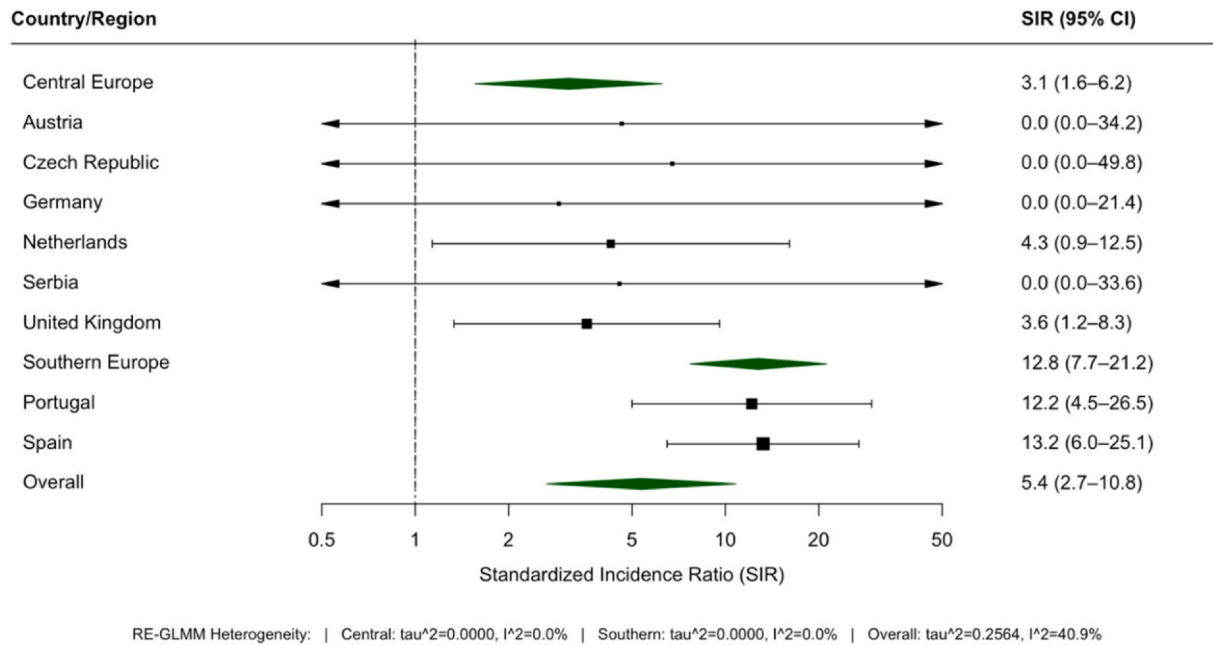
vigilance beyond the early post-transplant period that is typically prioritized in clinical follow-up.

A key finding of our study was regional differences of tuberculosis. Incidence rates and standardized incidence ratios were highest in Southern Europe such as Spain and Portugal, where observed tuberculosis risk exceeded background rates by more than ten-fold. In contrast, no cases were reported in several Central European countries. The clustering of cases in London, where local tuberculosis incidence remains substantially higher than in the rest of the Central European regions, may lead to an overestimation of national SIRs, but underscores the importance of also considering local epidemiology when designing screening and preventive strategies. The association between migration history and post-transplant tuberculosis in our cohort is consistent with previous reports, particularly as three of the five migrant patients originated from high-incidence countries.<sup>49</sup> Among patients without a history of migration outside London, post-transplant tuberculosis in Central Europe was only observed in the Netherlands but in none of the other countries.

Another striking finding of our study concerns tuberculosis prevention practices. Implementation of systematic screening for tuberculosis infection by IGRA/TST and TPT uptake was heterogeneous across centers. Overall, only one third of patients underwent screening for tuberculosis infection. Among patients with a positive IGRA/TST result, fewer than half received TPT. The highest tuberculosis incidence was observed among patients with a positive screening result who did not receive TPT, supporting previous evidence that untreated tuberculosis infection is the main driver of post-transplant tuberculosis disease. However, we did not observe an effect of TPT and the majority of cases occurred more than two years after transplantation, which could represent de novo infection post-transplantation in the presence of immunosuppression. Future studies should address this possibility in order to adapt screening strategies post-transplantation, especially in the context of a higher risk of *M tuberculosis* exposure. During the study period, the proportion of SOT recipients undergoing tuberculosis infection screening increased steadily, possibly reflecting growing awareness of tuberculosis risk in this vulnerable population and increasing confidence in the safety and effectiveness of TPT.<sup>40,43,44</sup>

One of the key strengths of this cohort study is the inclusion of a large number of SOT recipients from numerous clinical centers across Europe, representing a wide range of low- to medium-incidence of tuberculosis. The long follow-up period further allows for the assessment of regional differences in tuberculosis incidence among SOT recipients and in the effectiveness of different screening and prevention strategies.

Several limitations should be considered. First, the study was not sufficiently powered to detect a significant reduction in tuberculosis incidence with TPT, and we were unable to fully disentangle the effect of screening and preventive treatment from other factors influencing tuberculosis risk, such as region of residence, transplant type, or patient demographics. These factors may affect tuberculosis



**Fig. 2.** Standardized incidence ratios (SIRs) for post-transplant tuberculosis with random-effects pooled estimates by region. Country-specific SIRs and pooled estimates for Central Europe, Southern Europe, and overall SIR are displayed. Diamonds indicate random-effects pooled SIRs.

incidence independent of TPT and of the time after transplantation. Furthermore, our data do not allow us to fully distinguish between the potential effects of the type of transplant and the region where patients were transplanted. In addition, the use of national rather than regional background incidence data means that centers located in high-incidence areas such as London may not be fully reflected in the SIR estimates and may lead to an overestimation of national or regional SIRs. In the competing risks regression analysis with clustering at the regional level, non-renal transplantation was independently associated with an increased risk of post-transplant tuberculosis. Due to the small number of TB cases, further stratification by specific organ type was not feasible, and potential effects may still be attributable to different regional and person-specific background risks for tuberculosis in different transplant types. Second, we are unable to explain the high rate of incident tuberculosis in individuals with tuberculosis infection receiving TPT. It is possible that TPT may have been less effective than in other groups of immunocompromised individuals<sup>45</sup> for reasons such as drug-drug-interactions or high-level of immunosuppression, but also due to de novo infections occurring post-transplant, which is supported by the high proportion of tuberculosis cases beyond two years after transplantation. Third, we were unable to ascertain why some patients received TPT despite negative IGRA/TST results, or without documented testing for tuberculosis infection. These decisions may have been based on individual risk assessments, but such information was not systematically collected. The high rate of tuberculosis observed in this group may therefore reflect unmeasured individual risk factors rather than programmatic shortcomings, although this could not be verified. Fourth, although transmission of *M tuberculosis* from the donor organ to the recipient is possible, we lacked systematic information on how tuberculosis and tuberculosis screening were addressed in donors across the individual centers. Consequently, we were unable to determine whether *M tuberculosis* was acquired before transplantation, transmitted via the donor organ, or whether tuberculosis developed as a post-transplant infection. Although speculative, our finding that most tuberculosis cases occurred more than one year after transplantation may on one hand be due to a growing population of patients without a prior history of tuberculosis (as compared to an older generation of patients with a

higher prevalence of infection due to a known or in part unknown history of exposure); moreover, the occurrence of tuberculosis may increasingly be driven by de novo exposure which is more likely in countries or regions with a higher local prevalence. Fifth, we pre-defined any tuberculosis cases occurring within 3 months post-transplantation as prevalent. This approach may have resulted in underreporting of incident cases with tuberculosis as 2 out of 3 cases with tuberculosis diagnosed in the first 2 years post-transplantation occurred within 3 months. Finally, the time between the completion of the study and submission of the manuscript has been delayed due to COVID-19 and lack of funding. Although the incidence of tuberculosis in Europe has decreased since the end of the patient enrollment period, the presented data remain highly relevant in view of ongoing migration to Europe and within European countries. Current guidelines for the management of tuberculosis in SOT recipients are essentially unchanged, and are outdated in view of current findings.

**Conclusion**

In conclusion, our findings confirm that the risk of tuberculosis in SOT recipients is increased even in low- to medium-incidence countries in Europe. Post-transplant tuberculosis carries a high risk of morbidity and mortality, underscoring the importance of preventive measures. We suggest that the optimal approach may vary by region: in settings with very low incidence, targeted screening of risk groups followed by TPT may be the most appropriate strategy, whereas in higher-incidence regions, universal screening of all SOT candidates, regular post-transplant screening, and provision of TPT where indicated could be warranted. Such a nuanced strategy has the potential to substantially reduce the risk of tuberculosis in this vulnerable population.

**Author contributions**

BL, TTB, CL, and MS made a substantial contribution to the conception and design of the work, to the acquisition, analysis and interpretation of data for the work, accessed and verified the data, wrote the manuscript, critically revised the manuscript for

important intellectual content, and gave final approval of the current version to be published. FvL made a substantial contribution to the conception and design of the data analysis plan, and to the interpretation of data for the work, had access to the data, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. JK had access to the data, checked coding of the analysis performed, and provided input into relevant statistical questions. All other authors made a contribution to the acquisition of the data for the work, had access to the data, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Data availability

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others with investigator support. Data can be made available upon reasonable request to the corresponding author after approval of a proposal within the TBnet steering committee.

### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Berit Lange has received grant support by the German DAAD, BMFTR, EU4Health, EU Horizon, and DFG, has received accommodation by the organizers for attending AREVIR in 2024 and 2025, which was supported by Roche, MSD Sharp Dohme, Janssen Cilag and Abbott, and declares membership of several boards (Expert Council 'Health and Resilience', Standing Vaccination Commission at the Robert Koch Institute, Member of the Public Health Advisory Group of the German Ministry for Health) and President of the German Society for Epidemiology. Holger Flick has received financial project support by Revvity, and payments of honoraria for lectures and participation in scientific meetings from Revvity and Qiagen, and Diasorin. He has an unpaid role as head of the expert group on pulmonary infections and tuberculosis at the Austrian Society for Pneumology. Onn Min Kon reports chairing a global TB summit for Qiagen which is not remunerated. Heather Milburn reports having received a grant by the Friends of Guy's Hospital to support payment of dieticians for project investigating whether patients with NTM pulmonary disease need additional nutrition, and by the Welsh Department of Health 2023 for personal expenses in investigating long running TB outbreak in Wales, UK. She is unpaid Trustee for NTM Patient Care in UK. Tomas Reischig reports being supported by the Charles University Cooperatio Program, research areas "Immunity and Infections" and "Internal Disciplines", and has received honoraria for lectures by Takeda, MDS, and Chiesi. Adrián Sánchez-Montalvá has received a grant by Qiagen for the project "Latent TB infection and risk of cardiovascular diseases", and he reports that his wife is working at Novartis and is holding shares of the company. Aiko P.J. de Vries reports consulting activities with Hansa, Vunthera, Memo Therapeutics, and Sanofi, with payments granted to the institution. Dirk Wagner reports participation in advisory boards on NTM-PD. Christoph Lange is supported by the German Center of Infection Research (DZIF) and reports honoraria for presentations at sponsored symposia by Astra Zeneca, Gilead, GSK, Insmmed, Med Update, MedUpdateEurope and Pfizer. He received an honorarium for participating in a scientific advisory board meeting of Insmmed. He participated in advisory boards for MSF. Martina Sester has received grant support by Astellas, Biotest, and Takeda to the institution Saarland University outside of the

submitted work, and has received honoraria for presentations or work in Data Safety monitoring Boards, and travel support for meetings by Biotest, Novartis, Takeda, MSD, and Moderna. All other authors do not declare any conflict of interest.

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### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jinf.2025.106668](https://doi.org/10.1016/j.jinf.2025.106668).

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