LITERATURE REVIEW

Transmission of Mycobacterium Tuberculosis (Mtb)

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CONTENTS

1. EXECUTIVE SUMMARY

This report describes a clinical literature review performed by Nerac, Inc. at the request of the American Association of Tissue Banks (AATB) regarding the risk of *Mycobacterium tuberculosis* (Mtb) transmission through human tissue. This clinical literature evaluation contributes to AATB efforts to proactively monitor an evolving situation regarding Mtb transmission through tissue transplantation, and AATB efforts to evaluate any future recommendations to tissue bank medical directors for relevant updates of the tissue donor screening process if such changes are deemed to be warranted. On June 7, 2021, AATB was notified by an accredited institutional member of a potential Mtb transmission through tissue transplantation. A Human Cells, Tissues, and Cellular and Tissue-Based Product (HCT/P) lot of viable bone matrix recovered from a single donor associated with this transmission was voluntarily recalled and all impacted hospital institutions were contacted—the transmission was subsequently confirmed to be caused by the HCT/P. Under AATB standards, evidence of significant active infection at the time of donation, including "clinically active tuberculosis," is a rule-out condition.

The evidence provided in this clinical literature review is intended to present: 1) Any history, publications and/or experience with Mtb transmission through human tissue described in the literature; 2) Estimated population-based prevalence and incidence of TB and extrapulmonary TB to compile the risk factors for tuberculosis, including extrapulmonary tuberculosis, in the deceased donor pool; and 3) The current testing, with a focus on direct detection of tuberculosis in extrapulmonary specimens and tissue.

This review confirmed that transmission of Mtb through human tissues is unusual, with the last tissue-transplant-associated transmission reported in the published literature in 1981 via homograft aortic valve replacements (1), and the last transmission through bone reported in 1953 (2). Compared to tissue transplantation, Mtb infection identified after solid organ transplantation is more frequent. According to data from the Organ Procurement and Transplantation Network (OPTN) Disease Transmission Advisory Committee (DTAC), between 2008 and 2017 alone there were 11 proven/probable donor-derived tuberculosis transmissions from 9 deceased organ donors (3).

2. BACKGROUND

There are two types of tuberculosis (TB): latent or active. Active TB may be pulmonary or extrapulmonary (4, 5). The term latent TB, characterized by the presence of immune sensitization to Mtb in the absence of clinical or radiological evidence of active disease, was first described in 1909 (6). Latent TB can develop after exposure to aerosolized particles with viable bacilli from an infected individual (5). Initial infection commonly produces no symptoms (latent TB), and is distinguished by small lung lesions that frequently heal and do not develop residual changes except for occasional calcifications within pulmonary or

tracheobronchial lymph nodes (5). Those with latent TB have a lifetime risk of developing active TB of 5%-10%, which may be decreased 65%-80% using preventative treatment (7).

Active TB may develop after infection, with development influenced by risk factors. Active TB may also develop from re-activation of a latent TB infection or re-infection (5) . Since 1909, latent TB has been demonstrated through molecular research to re-activate up to 33 years following exposure (6). Active TB primarily consists of pulmonary TB cases, however 19.3% - 39.3% of individuals develop extrapulmonary TB or concurrent extrapulmonary TB with pulmonary involvement (4).

In active pulmonary TB infection, Mtb primarily resides in intracellular alveolar or interstitial macrophages in the lungs. These lineages have been described as producing different responses following Mtb exposure: "alveolar macrophages upregulate fatty acid uptake and β-oxidation to provide a more nutritionally permissive environment for MTB, whereas interstitial macrophages are highly glycolytically active to exert nutritional restriction and control bacterial growth." Additionally, necropsy studies from those who died of non-TB causes have identified Mtb DNA in perigastric, perinephric, subcutaneous, and pericardial adipose tissue; endothelium, macrophages, and pneumocytes in the lung; convoluted proximal tubules and Bowman's parietal cells in the kidney; sinusoidal endothelial cells and macrophages in the spleen; and sinusoidal endothelium and Kupffer cells from the liver using polymerase chain reaction (PCR). Affected cells were not likely to meet Koch's postulates due to being non-cultivable, and evidence regarding re-activation of non-replicating Mtb and subsequent causation of active infection is insufficient. (6)

Alveolar epithelial cells provide an environment for Mtb to persist and disseminate from the lung prior to the activation of immune response. Mtb may also replicate within fibroblasts, although during latent Mtb infection, evidence regarding harboring of Mtb is currently insufficient to draw conclusions. Mtb may disseminate from the lungs to extrapulmonary regions through circulatory and lymphatic systems. Additionally, Mtb "infects adipocytes via scavenger receptors, with intracellular bacilli observed within membrane-bound vacuoles." Recent research published in 2019 has demonstrated that hematopoietic stem cells obtained from latent-TB-infected individuals or individuals that successfully underwent chemotherapeutic treatment for active TB infection retained intracellular Mtb in a predominantly uncultivable form. This manuscript thoroughly reviewed available literature on Mtb locations during latency, highlighting that mesenchymal and hematopoietic stem cells harbor organisms in sensitized asymptomatic individuals. Mtb has been detected in hematopoietic and mesenchymal stem cells, "implicating the bone marrow as a previously unappreciated niche for the organism" in latent TB infection. This body of evidence suggests wide anatomical distribution of Mtb in latently infected individuals, but systematic research has not been performed to evaluate the presence of Mtb in all tissue types. (6)

Knowledge during much of the 20th century regarding Mtb was that it was restricted to macrophages in quiescent granulomas for those with latent TB infection. However, more

recent research has found Mtb DNA in various non-phagocytic cell types outside of and within the lung. The persistence of Mtb in extracellular locations in latent TB infection is speculated. Recent research has demonstrated that "MTB releases mycobacterial extracellular vesicles that exert diverse effects on the host response, including induction of Toll-like receptor (TLR)-2 signaling;" sustained TLR-2 stimulation may benefit the persistence of extracellular mycobacteria due to potential anti-inflammatory responses and Th1 polarization of CD4+ T cells being inhibited. Additionally, neutrophils that are infected with Mtb "release extracellular vesicles that activate macrophages and promote the clearance of intracellular MTB through early superoxide anion production and autophagy induction." (6)

Extrapulmonary TB is defined as the presence of TB in organs outside of the lungs and can impact any tissue or organ accordingly: pleura (20%), lymph nodes (33%), joints and bones (5%-10%), genitourinary tract (5%-10%), gastrointestinal tract and peritoneum (3.5%), pericardium (2%-3%), and meninges (5%) (4, 5, 8). The third most common sites of extrapulmonary TB are the joints and bones. A retrospective review of 17 patients with joint and bone TB undergoing dialysis demonstrated extrapulmonary TB primarily in the lumbar spine (41.2%), but also in the thoracic spine (29.4%), cervical spine (11.7%), knee (11.7%), hip (5.9%), and multiple sites with concomitant pulmonary involvement (11.7%) (9).

Variations in extrapulmonary definitions or sites were found in the literature. Presently, the exact mechanism(s) for extrapulmonary dissemination is undetermined (4). In addition to the tissues or organs extrapulmonary TB may impact, listed directly above, one study included the skin as an extrapulmonary site of TB infection, and cases of tuberculous pleural effusion or tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) were considered extrapulmonary TB cases (8). The same study assessed disseminated and miliary TB. Disseminated TB was characterized as the diffusion of Mtb from the lungs to various regions of the body through the lymph system or blood (8). Miliary TB was defined by the wide dissemination of Mtb throughout the human body, including small lesions (8).

Common symptoms of active pulmonary TB include cough, fever, fatigue, weight loss, and night sweats (5). The cough is non-productive at first, but produces sputum at a later period (5). Advanced laryngeal TB may produce symptoms of hoarseness and hemoptysis (5). Joint and bone TB is associated with deformity, chronic pain, and disability (9). In the same retrospective study referenced above, patients with the joint and bone TB experienced pain (100%), fever (58.9%), reduced range of movement with pain (47%), bone/joint deformity (41.2%), and cold abscesses (5%) (9).

One study identified, via an exhaustive literature review, 10 extrapulmonary TB and 13 disseminated TB cases among 36 proven, probable, and possible donor-derived TB cases via solid organ transplant (SOT) (herein referred to as organ transplant) (10). Of the 10 extrapulmonary donor-derived TB cases identified in organ transplant recipients, there were 9 cases with reported affected sites and corresponding signs and symptoms (SSX):

Extremities (n=1) with SSX of painful foot; pericardium (n=1) with SSX of fever and shortness of breath; non-specified allograft (n=5) with SSX of graft failure, nausea, fever, and abdominal pain; bone marrow (n=1) with SSX of fever and sepsis; and heart (n=1) with SSX of fever, chills, and shortness of breath (10). Of the 13 disseminated TB cases, affected sites and corresponding SSX included: kidney allograft (n=1) with SSX of fever; lymph node, lung, and spleen allograft (n=1) with SSX of fever; lung allograft (n=3) with SSX of cough, fever, shortness of breath, surgical site infection; lung and BM allograft (n=3) with SSX of effusion and fever; allograft liver, spleen, and lungs (n=1) with SSX of fever and sepsis; blood (n=1) with SSX of sepsis and fever; bone marrow and kidney allograft (n=1) with SSX of fever and cough; liver allograft (n=1) with SSX of fever and should pain; and blood (n=1) with SSX categorized as "asymptomatic" (10).

Tuberculosis (TB) is a global health issue, particularly in countries of low or middle income (11). TB is the 6th primary cause of morbidity within the Philippines, with 141.4 cases reported per 100,000 individuals (12). TB contributes more deaths annually than any other infectious disease, categorized as a top 10 global cause of death annually (13). It was approximated by the World Health Organization (WHO) that 1.5 million TB-related deaths occurred in 2019 solely, and 10 million individuals contracted TB in 2017, with 1.7 million TB-related mortality cases subsequently following within this year (8, 13). Other estimates indicate that there are approximately 8 million TB cases and 3 million TB-related deaths yearly (14).

Individuals who contract Mtb and are more likely to progress to active infection and subsequent morbidity and mortality are those who are immunocompromised, including those with HIV, undergoing dialysis, or receiving organ transplants (14-16). TB is one of the most frequently recognized and reported "bacterial causes of organ donor-derived infection," (16, 17), exemplified by donor-derived transmissions reported to the OPTN between 2005 and 2009 There were 201 reported infections (106 confirmed in recipients), of which 38 were reported as bacterial (26 confirmed in recipients); of the 201 reported infections, 26 were reported as Mtb (10 confirmed in recipients) (18). Cases of transplant-associated TB are discussed in Section 4 and Section 5.

TB identified subsequent to organ or stem cell transplants primarily results from re-activation of a dormant TB infection, and "it depends on TB burden, the type of organ transplanted, level of immunosuppression and concomitant opportunistic infections" (8). Considering the risk of TB re-activation is greater in organ transplant recipients compared to the general population, the "early diagnosis and the prompt initiation of therapy" in organ transplant cases with great suspicion of TB can increase rates of survival (8).

3. POPULATIONS AT INCREASED RISK OF TUBERCULOSIS AND EXPULMONARY TUBERCULOSIS

3.1. PREVALENCE AND INCIDENCE

It is estimated that there are 10.4 million incident TB cases and 1.7 million deaths related to TB that occur each year globally (19). Approximately 1 in 4 persons globally are impacted by latent TB (6). Those with latent TB have a 5%-10% lifetime risk of developing active TB, which may be decreased by 65%-80% using preventative antimicrobial treatment; however, due to variation of incident rates across populations, 5-10% risk may not apply to many individuals (7). The WHO estimated that the worldwide latent TB prevalence was 23% in 2016, with approximately 1.7 billion individuals infected globally (20). The Centers for Disease Control and Prevention (CDC) reported that yearly TB incidence in the U.S. was under 3 cases per 100,000 individuals, while incidence in other countries, such as sub-Saharan Africa and Asia, is greater at hundreds per 100,000 individuals (19). Countries/areas that were estimated by the CDC to have incidence rates over 300 per 100,000 individuals in 2016 included Senegal, Sierra Leone, Liberia, Central African Republic, Congo, Gabon, Democratic Republic of the Congo, Angola, Zambia, Namibia, Botswana, South Africa, Mozambique, Kenya, Djibouti, Myanmar, Cambodia, Democratic People's Republic of Korea, Philippines, Indonesia, and Papua New Guinea (19). The WHO indicated that the 30 countries with the highest TB burden, defined as countries with the highest absolute number of cases (top 20 countries) and countries with the greatest number of cases per capita that are not in the top 20 countries and have a threshold of at least 10,000 cases (absolute number) per year, from 2016 to 2020 included (21):

> *Angola, Bangladesh, Brazil, Cambodia, China, Congo, Central African Republic, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Sierra Leone, South Africa, Thailand, the United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.*

The 30 countries the WHO indicated had the highest TB burden comprise 85-89% of the TB global burden (21). Of the 30 countries listed, there are 14 countries that were also listed in list of countries with the highest TB/human immunodeficiency virus (HIV) and multidrug-resistant (MDR)-TB burden; these countries included Angola, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand, and Zimbabwe (21). The CDC provided estimated proportions of cases of MDR TB cases in countries with a greater burden of MDR TB; estimations of incidence of MDR TB cases and percent of TB re-treatment in MDR cases are provided

Table *3-1* below (obtained directly from CDC resources) (19).

Table 3-1. Estimated proportion of MDR TB cases in high MDR TB burden countries, 2016 (19)

COUNTRY	% OF NEW TB CASES THAT ARE MDR	% OF RETREATMENT TB CASES THAT ARE MDR
Angola	2.6	18
Azerbaijan	13	39
Bangladesh	1.6	29
Belarus	38	72
China	7.1	24
Democratic Republic of Congo	2.2	17
Ethiopia	2.7	14
India	2.8	12
Indonesia	2.8	16
Kazakhstan	26	44
Kenya	1.3	9.4
Kyrgyzstan	27	60
Mozambique	3.7	20
Myanmar (Burma)	5.1	27
Nigeria	4.3	25
Pakistan	4.2	16
Papua New Guinea	3.4	26
Peru	6.3	24
Philippines	2.6	29
Republic of Moldova	26	56
Russia	27	65
South Africa	3.4	7.1
Tajikistan	22	45
Thailand	2.2	24
Ukraine	27	47
Uzbekistan	27	63
Vietnam	4.1	26
Zimbabwe	4.6	14

The global prevalence of latent TB was estimated through a systematic review and meta-analysis by Cohen et al. (2019), with results "based on TB incidence-stratified estimates directly derived from both IGRA and TST" (20). There were 88 studies included, of which 41 pertained to interferon gamma release assay (IGRA) and 67 pertained to tuberculin skin test (TST) (20). There was a 24.8% (95% CI 19.7–29.9%) global prevalence of latent TB based on IGRA and 21.2% (95% CI 17.9–24.4%) global prevalence of latent TB based on TST (10 mm) (20). A "strong monotonic relationship between WHO TB incidence rates and LTBI prevalence based on both IGRAs ($rs=0.706$, $p<0.0001$) and TSTs ($rs=0.697$, $p<0.0001$)" was observed (20). The inclusion of indeterminate results in the denominator yielded a global prevalence of 24.2% (95% CI 19.2–29.2%) for IGRA and "24.1% (95% CI 20.2–28.0%), 21.2% (95% CI 17.9–24.4%) and 17.4% (95% CI 14.4–20.4%)" for TST results based on "5-, 10- and 15-mm cut-offs" (20). Prevalence estimated in the meta-analysis slightly varies from the WHO estimation.

In 2016, there were approximately 6.3 million new TB cases with a prevalence of 10.4 million globally; of these cases, extrapulmonary TB consisted of 15% of notified cases, with higher rates of extrapulmonary TB demonstrated in those with immunodeficiency (11). In the U.S., the incidence of TB has decreased over time (16). Conversely, the proportion of extrapulmonary TB incidence among all TB cases has increased, as suggested by some research: Within the U.S., extrapulmonary TB cases have increased from 16% in 1993 to 21% in 2013, primarily attributed to increased HIV prevalence (4). Tuberculous ocular involvement in systemic tuberculosis has been reported (12). In individuals receiving hemodialysis, the IGRA-positive proportion for TB detection is approximately 21 – 40% (22). In one study, described in Section 3.2.1 below, the prevalence of latent TB in 425 dialysis patients from Taiwan hospitals was 25%, which was higher than the 11% prevalence observed in 63 individuals with severe chronic kidney disease (CKD) and the 11% prevalence observed in 111 dialysis-unit staff (22).

3.2. RISK FACTORS

There are various risk factors for active (extrapulmonary/pulmonary) and latent TB. **Table 3-2** below provides a summary of active and/or latent TB risk factors, with detailed information provided in the subsections below, with the exception of organ transplant-related content, which is elaborated in Section 5.

Table 3-2. Risk Factor Summary Table from Reviewed Literature

Factors	Active (P/EP)/Latent TB	Comments	Reference
Age (older)	Active (EP)	In patients undergoing dialysis, older age may be a risk factor for bone/joint EPTB.	Wu et al. (9)
	Active (EP)	Findings from multivariable analyses of EPTB patients and EPTB sites: Patients aged 45 years and older had a greater rate of bone TB.	Qian et al. (4)
	Latent	For individuals undergoing dialysis or with severe CKD, a latent TB risk factor includes old age.	Shu et al. (22)
Albumin and hemoglobin levels decreased	Active (EP)	In patients undergoing dialysis, reduced albumin and hemoglobin levels may be a risk factor for bone/joint EPTB.	Wu et al. (9)
Albumin serum level Increased	Latent	For individuals undergoing dialysis or with severe CKD, a latent TB risk factor includes high serum albumin.	Shu et al. (22)
CD4+ cell count low	Active (EP)	In patients undergoing dialysis, a low CD4+ cell count may be a risk factor for bone/joint EPTB.	Wu et al. (9)
Chest imaging indicative of active/prior TB	Latent	For individuals undergoing dialysis or with severe CKD, a latent TB risk factor includes "radiographic lesions compatible with prior TB."	Shu et al. (22)
	Unspecified	No further context provided.	Jones et al. (16)
CKD (severe)	Unspecified	Those with severe CKD have a greater "risk of TB due to their attenuated cellular immunity."	Shu et al. (22)

Factors	Active (P/EP)/Latent TB	Comments	Reference
Close contact to an individual with TB	Unspecified	No further context provided.	Jones et al. (16)
Dialysis recipient	Latent	Based on study results, prevalence was greater in those undergoing dialysis.	Shu et al. (22)
	Unspecified (Active (EP) implied)	The "risk of TB in patients undergoing hemodialysis and peritoneal dialysis is 3- to 25-fold higher than that in the general population." In multiple publications, "the bones and joints are identified as the third most frequent sites of" EPTB.	Wu et al. (9)
Employment in prior institutional settings with greater TB rates	Unspecified	No further context provided.	Jones et al. (16)
End-stage renal disease (ESRD)	Active (EP)	Findings from multivariable analyses of EPTB patients.	Qian et al. (4)
Female sex	Active (EP)	Findings from multivariable analyses of EPTB patients demonstrated female patients were at greater risk for EPTB. However, the study assessed risk for PTB, EPTB only, and EPTB with PTB involvement; of the exclusively EPTB individuals, 55.4% were male.	Qian et al. (4)
Hispanic ethnicity	Active (EP)	The study assessed risk for PTB, EPTB only, and EPTB with PTB involvement; of the exclusively EPTB individuals, 46.6% were male.	Qian et al. (4)
History of TB confirmed through interferon-gamma assay or TST	Unspecified	No further context provided.	Jones et al. (16)
Homelessness	Unspecified	EP TB was more frequent in non-homeless, rather than the homeless. Homelessness was negatively associated with EP, especially lymphatic TB. In one study, there was a significantly greater number of homeless cases in "PTB (5.8%) than in exclusively EPTB (2.4%)."	Qian et al. (4)
Immigration (Foreign born/previous residence outside the U.S.)	Active (EP)	Study assessed risk for PTB, EPTB only, and EPTB with PTB involvement; of the exclusively EPTB individuals, 59.1% were foreign born. Findings from multivariable analyses of EPTB patients and EPTB sites: Foreign-born individuals were more likely to have pleural TB.	Qian et al. (4)
	Unspecified	Risk factor characterized by residence or birth in countries with greater rates of TB (for example, over 25 cases per every 100,000 individuals).	Jones et al. (16)
Immunocompromised patients, including those with HIV positivity	Active (EP)	Findings from multivariable analyses of EPTB patients and EPTB sites: HIV-positive individuals were more likely to have meningeal TB.	Qian et al. (4)
Pregnancy	Active	Progression from latent to active TB is greater in pregnant and post-partum women.	Jones et al. (16)
	Unspecified	Pregnant and post-partum women demonstrated incidence rate ratios of 1.4 and 1.9, respectively, compared to non-pregnant females.	WHO (23)

Factors	Active (P/EP)/Latent TB	Comments	Reference
Substance use	Active and latent	There is a greater risk of developing active or latent TB in substance users, however, there is greater prevalence in PTB compared to EPTB.	Qian et al. (4)
	Unspecified	Substance use through injections is a risk factor for TB.	Jones et al. (16)
Organ transplant recipient	Unspecified	Organ transplant patients have a 20 – 74 greater incidence of TB compared to general population.	WHO (23)
	Unspecified	Organ transplant recipients "are immunocompromised and at risk" for TB.	Jones et al. (16)

P=pulmonary; EP=extrapulmonary; PTB=pulmonary TB; EPTB=extrapulmonary TB

3.2.1. TUBERCULOSIS (ACTIVE OR LATENT UNSPECIFIED)

Geographic

While the incidence of TB has decreased over time in the U.S., TB disproportionately impacts those born outside of the U.S. and racial/ethnic minorities (16). Particularly, being born or residing in regions with greater TB rates, such as more than 25 cases per every 100,000 persons within a population, is a risk factor for TB (16). Additionally, TB prevails in high-income countries, such as the U.S., due to the immigration of individuals residing in regions with greater TB incidence (24). Individuals that recently migrated to low-incidence regions have demonstrated substantially greater rates of active TB development than the general population (24). The greatest TB incident rates occur during the first five years following immigration, although TB development may also occur at a later period (24).

Campbell et al. (2015) performed a meta-analysis to evaluate potential predictors for positive results for IGRA and TST performed on immigrant populations. The authors did not provide the countries of origin for the immigrant populations assessed in the study. There were 23 studies that were used to analyze predictors of positive TST results, of which 5 studies evaluated age, 11 evaluated gender, 5 evaluated TB incidence in country of origin, and 7 evaluated BCG vaccination. Meta-analysis results from the 23 studies found that there was a greater likelihood of TST positivity for those aged 35 years and older (odds ratio (OR) 1.59; 95 %CI 1.32–1.92), yielding age as a predictor for TST positivity. The male gender demonstrated an OR of 1.38 (95 %CI 1.20–1.58), yielding this gender as a predictor of TST positivity. Additionally, immigrants with BCG vaccinations and immigrants from regions of greater TB incidence were predictors of TST positivity with ORs of 2.38 (95 %CI 1.14–4.98) and 2.10 (95 % CI 1.54–2.88) yielded, respectively. There were 8 studies included in an analysis for positive IGRA predictors, with IGRA tests of T-SPOT.TB and QFT-GIT utilized; of the 8 studies, 1 evaluated TB incidence in country of origin and 8 evaluated gender. Male gender demonstrated a greater likelihood of IGRA positivity (OR 1.34; 95 % CI 1.08–1.66). A meta-analysis could not be performed for TB incidence in country of origin due to the inclusion of 1 study solely, however, results from the study demonstrated an OR of 17.25 (95

% CI 1.03–289.34). The authors note the results are based on statistical, not clinical, significance. (24)

Jackson et al. (2021) performed a systematic review and meta-analysis to assess the impact of migration from regions of high TB incidence on TB epidemiology in regions of low to medium TB incidence. There were 32 studies included containing 93,235 cases of TB (median sample size = 98.5; range: 6–73,945), of which 25 studies and 7 studies pertained to low TB incidence and medium TB incidence, respectively. Low incident countries included in the systematic review were Spain, Saudi Arabia, Czech Republic, Israel, United Kingdom, Italy, Guadeloupe, Switzerland, Norway, Australia, Greece, and United States. The Fischer's exact test was used to compare proportions across exposures and a meta-analysis was conducted on the primary proportion outcomes with the Metaprop command. OR was utilized for secondary outcomes using "an inverse variance statistical model with a random effects analysis model." Results from the meta-analysis were presented in forest plots using visual inspection, I^2 to assess heterogeneity, and Cochran's Q-test. Medium incident countries included in the systematic review were Iran, Turkey, Poland, and Bahrain. The range of total active TB cases was 0.02 to 0.94 for migrants from high incidence TB regions. The overall proportion of migrants with high incidence was 0.15, and the pooled proportion from the meta-analysis was 0.47. There were 5 studies containing information for sputum smear positivity. The overall sputum smear positivity proportion was 0.71 for migrants from high incident regions and 0.70 for migrants, with no differences identified between odds and low heterogeneity (I^2=0%). There were 4 studies containing data for clustered cases, with a significantly greater proportion of clustered cases for migrants from high incidence regions in comparison to non-migrants 0.42 versus 0.26, P: <0.001); "meta-analysis did not detect any significant difference between the odds ratios of exposure categories with moderate levels of heterogeneity detected." There were 5 studies of HIV co-infection, of which 2 studies with TB and HIV co-infection, which demonstrated a significantly greater overall proportion of cases for migrants (0.19) from regions of high TB incidence compared to non-migrants (0.05; p<0.001). There were no significant differences detected for HIV and TB co-infection between exposure categories through meta-analysis (OR 1.91 [0.09–41.22]). The authors concluded that there were significant differences observed in overall proportions of specific outcomes in migrants from high TB incident regions and non-migrants, however, "findings should be interpreted cautiously due to the high levels of clinical, methodological and statistical heterogeneity present among the included studies." (13)

Dialysis

Individuals with severe CKD or receiving dialysis are at greater risk for TB. Individuals with severe CKD have poorer immunity compared to those with mild to moderate CKD, thus rates of infections are greater in the severe CKD population. Active TB is 7.8 times greater in those receiving dialysis compared to the general population, and the proportion of IGRA-positive individuals is approximately 21%-41%. (22)

Immunocompromising Factors

Findings from multivariable analyses of EPTB patients and EPTB sites: HIV-positive individuals were more likely to have meningeal TB (23). Organ transplant patients have a 20 – 74 greater incidence of TB compared to general population (WHO). Organ transplant recipients "are immunocompromised and at risk" for TB (16).

General Risk Factors

Risk factors for active and latent TB development are old age and substance use. However, illicit drug use prevalence is greater in pulmonary TB than extrapulmonary TB. In a 2016 Centers for Disease Control and Prevention (CDC) report, increased TB prevalence and incidence rates were commonly detected in homeless individuals during that year and correctional facility residence during diagnosis. However, homelessness was found to be negatively associated with extrapulmonary TB, particularly for lymphatic TB, demonstrating that homeless is not a risk factor for this TB type. (4)

3.2.2. ACTIVE TUBERCULOSIS

The progression of latent TB to active TB over a median follow-up of 3.7 years was evaluated by Gupta et al. (2020) in low-transmission environments, characterized as a yearly incidence of ≤20 per 100,000 individuals. This systematic review included 26 studies consisting of 82,360 records, of which 51,697 demonstrated evidence of latent TB and 826 were diagnosed with TB; the primary analysis was performed for 80,468 cases that contained sufficient information, of which 803 were TB cases. The 2-year cumulative risk of TB incidence in those with latent TB who did not undergo preventative treatment, those with latent TB who initiated preventative treatment, and those without TB was 4.0% (95% CI, 2.6–6.3%), 0.7% (0.4–1.3%), and 0.2% (0.1–0.4%), respectively; the 5-year risk of TB incidence for each of these groups was "5.4% (3.5–8.5%), 1.1% (0.6–2.0) and 0.3% (0.2–0.5%), respectively." In the risk populations evaluated, "incidence rates among untreated people with LTBI were markedly higher in the 0–2-year interval, compared to the 2–5-year interval, but were highly heterogeneous across studies." A personalized risk model was created to detect incident TB based on individual-level factors; particularly, the model combined "a quantitative measure of T cell sensitization and clinical covariates." The "internal-external external cross-validation of the model demonstrated a random effects meta-analysis C-statistic of 0.88 (95% CI, 0.82–0.93)." Additionally, the findings demonstrated TB risk varied across those with latent TB in different risk groups. (7)

Extrapulmonary Tuberculosis

A meta-analysis of 9,160 TB cases in Texan patients by Qian et al. (2018) evaluated factors associated with extrapulmonary TB dissemination and mortality during TB treatment. TB cases included pulmonary TB, extrapulmonary TB, or concurrent extrapulmonary TB with pulmonary involvement; extrapulmonary sites included, but were not limited to, lymphatic, pleural, bone, peritoneal, genitourinary, and meningeal regions. Significantly greater risk of extrapulmonary TB was observed for female patients (OR 1.32, 95% CI: 1.19–1.46),

individuals with HIV (OR 1.77, 95% CI: 1.47–2.13), end-stage renal disease (ESRD) (OR 3.42, 95% CI: 2.39–4.88), and immunosuppression (OR 1.31, 95% CI: 1.00–1.77). ESRD was associated with majority of extrapulmonary TB types, including genitourinary and meningeal TB. Individuals aged 45 years or older demonstrated a disproportionately greater rate of bone TB (OR 1.47, 95% CI 1.04–2.08); foreign-born individuals demonstrated a greater rate of pleural TB (OR 1.77, 95% CI 1.31–2.41); and individuals with HIV demonstrated a greater rate of meningeal TB (OR 5.73, 95% CI 3.43–9.56). Individuals with a history of TB contact within 2 years (OR 0.44, 95% CI 0.35–0.55) and individuals with diabetes (OR 0.61, 95% CI 0.52–0.71) were more likely to have pulmonary TB than extrapulmonary TB. The authors concluded that risk factors for extrapulmonary TB includes individuals: aged 45 years or older, HIV-positive, and ESRD. Findings from this study affirm risk factors referenced above, but provide context specific to extrapulmonary TB development. (4)

Dialysis

A retrospective study of 17 patients (mean age 61.3 years; 10 males) who underwent dialysis and developed extrapulmonary joint and bone TB was performed by Wu et al. (2020). There were 13 patients undergoing hemodialysis and 4 patients undergoing peritoneal dialysis. Of the 17 patients, 10 had a history of intravenous iron therapy, most demonstrated low albumin levels, and 9 demonstrated low CD4+ cell count, with 6 patients demonstrating a count <300/mm^3. The authors concluded that potential risk factors for joint and bone TB in individuals undergoing dialysis included old age, low levels of hemoglobin and albumin, and low CD4+ count. Results from this study provide additional context regarding pulmonary TB specific to joint and bone sites in the sub-population of those undergoing dialysis. (9)

Disseminated Tuberculosis

Abad et al. (2018), discussed in further detail in Section 5.1, identified 17 proven, 8 probable, and 11 possible cases of reported donor-derived TB (DDTB) in organ transplant recipients. Of the identified proven, probably, and possible DDTB cases, TB types included pulmonary (n=13), extrapulmonary (n=10), and disseminated (n=13). Donors demonstrated risk factors of residence in an endemic country (n=13), travel to a location where TB is endemic (n=1), history of latent TB (n=4), active TB during procurement (n=3), and socioeconomic factors of incarceration (n=2), homelessness (n=1), and substance abuse (n=2). (10)

3.2.3. LATENT TUBERCULOSIS

Dialysis

Shu et al. (2015) conducted a cross-sectional study in northern and southern Taiwan hospitals to evaluate latent TB prevalence in 63 individuals with severe CKD, 425 individuals receiving long-term dialysis, and 111 dialysis-unit staff. Latent TB cases were characterized by a positive QFT-GIT IGRA result through testing of peripheral blood. There were greater radiographic findings indicative of prior TB in those undergoing dialysis compared to those

with severe CKD. IGRA results were positive for 11% (7/63) of those with severe CKD, 25% (106/425) of those undergoing dialysis, and 11% (12/111) of dialysis-unit staff. The greater positive QFT-GIT IGRA results were demonstrated in dialysis patients compared to those with severe CKD (p=0.015) and dialysis-unit staff (p=0.001). One-way ANOVA indicated that positive QFT-GIT response was comparable between the 3 groups (p=0.814). Multivariate logistic regression demonstrated independent predictors for latent TB in those undergoing dialysis or with severe CKD included older age (OR 1.03, 95% CI: 1.01–1.04; per year increment), serum albumin (OR 2.59, 95% C.I. 1.63–4.11, per 1 g/dl increment), dialysis (OR 2.47, 95% C.I. 1.02–5.95), and radiographic findings indicative of prior TB (OR 2.90, 95% C.I. 1.45–5.83). Latent TB rates for dialysis-unit staff was similar to rates observed in other healthcare workers. The authors concluded that individuals undergoing dialysis demonstrate high latent TB prevalence compared to dialysis-unit staff and those with severe CKD. (22)

Shu et al. (2012) performed a cross-sectional study in northern and southern Taiwan hospitals to evaluate latent TB prevalence in 303 individuals underdoing long-term hemodialysis (HD) and 124 individuals undergoing peritoneal dialysis (PD). Latent TB cases were tested using QFT-GIT IGRA on peripheral blood and ELISA to measure the "interferon-gamma level of the post-reaction supernatant," with positive QFT IGRA results characteristic of latent TB. PD patients were significantly less likely to demonstrate pulmonary lesions through chest radiography (18%) when compared to HD patients (37%; p<0.001). QFT results were positive for 19% (24/124) for PD and 22% (67/303) for HD (p=0.528). Based on univariate analysis, individuals with positive QFT IGRA results were more likely to have a TB history and were older compared to those with negative results. Based on multivariate logistic regression, latent TB independent predictors included older age (OR 1.034, 95% C.I. 1.013–1.056, per year increment), current smoker (OR 6.467, 95% C.I. 1.985–21.066), and TB history (OR 6.467, 95% C.I. 1.985–21.066). The prevalence of latent TB was 57.1% in those with a TB history; 29.6% in current smokers; and 30% in those over the age of 80 years old, which was a greater prevalence compared to the <15% in those under 50 years old. The authors concluded that PD and HD patients demonstrated comparable latent TB prevalence rates, and prevalence within the dialysis patients assessed was greater for current smokers, elder patients, and those with a history of TB. (15)

Sester et al. (2004) performed a study on hemodialysis patients to evaluate the T-cell response to purified protein derivate (PPD) for Mtb and assess "whether its direct quantitation from whole blood could represent an alternative approach to the skin test in anergic and/or immunocompromised patients." There were 127 individuals undergoing hemodialysis included and 218 immunocompetent controls consisting of 107 healthcare workers, 59 immunocompetent individuals admitted to a German hospital, and 52 healthy blood donors. Results demonstrated PPD-specific CD4 T cells >0.05% in 30.8% (16/52) of blood donors, 48.6% (52/107) of healthcare workers, and 53.5% (68/127) of hemodialysis patients. TST results >5 mm were demonstrated in 91.7% (11/12) of healthcare workers,

82.6% (19/23) of control patients, and 51.4% (18/35) of hemodialysis patients, with a significantly lower rate of positive TST observed for hemodialysis patients (p=0.007). The authors concluded that "unlike the skin test, measurement of PPD reactivity by in vitro quantitation of PPD-specific T cells was unaffected by uremia-associated immunosuppression," and "ESAT-6–specific T cells could moreover allow distinction of latent *M. tuberculosis* infection from BCG-induced reactivity to PPD." (14)

4. MTB TRANSMISSION IN THE SETTING OF HUMAN TISSUE TRANSPLANTS

History, publications, and/or experience with Mtb transmission through human tissue are discussed in detail in the subsections below. In addition to the review of clinical literature presented in the sections below, the NOTIFY library[1] was searched for recipient *Mycobacterium tuberculosis* infection (Harm to a Recipient => Infection => Bacterial => Mycobacterium) associated with tissue products. The Notify Library, which is co-sponsored by the WHO and the Italian National Transplant Centre (CNT), is a publicly accessible database of adverse outcomes associated with the use of medical products of human origin (MPHO), collected and analyzed by dedicated editorial groups of international experts, regulators, and clinicians. The data is identified primarily by literature review but may also include case reports from regulatory or professional vigilance programs. Details regarding the NOTIFY Library search results are provided in Appendix B: NOTIFY Library Search Results. There were 24 records identified in the NOTIFY Library search, including 2 associated with tissue transplants. The records described cases of bone and heart-valve transmission that were also identified in the clinical literature summarized in the subsections below.

4.1. REPORTED CASES OF MTB TRANISSMISSION VIA TISSUE TRANSPLANT

Reported cases of TB following tissue transplants described in the literature are summarized below. Types of tissue transplants discussed below include bone, heart valves, and corneal tissue transplants.

4.1.1. BONE

In the 1950s, the banking of ribs removed during thoracoplasties for pulmonary TB, and subsequent application in orthopedic procedures, became frequent. The ribs were frozen at "- 15 degrees Centigrade to -20 degrees Centigrade in a solution containing penicillin and streptomycin," however, this did not prevent TB transmission in recipients. James (1953) reported 4 cases of TB transmitted through bone in orthopedic procedures; patients

[1] https://www.notifylibrary.org/notifylibrary/search/incident

presented with TB abscesses and following the "removal of the infected bone chips and curettage, the wounds have healed without further incident." One patient underwent "a first and second stage spine fusion for scoliosis." In the 2 months following the first age, the patient presented with pleurisy and fever for 3 weeks; biopsy of the enlarged axillary gland demonstrated TB, and confirmation of TB was obtained through by smear and culture of the wound. One patient underwent "one-stage fusion for scoliosis" and presented with 2 small sinuses in the weeks following operation, then curettage 4 months following the procedure. The caseous material within the sinuses tested positive for TB through histological evaluation and culture. A third patient underwent "first stage fusion for scoliosis." This patient presented with haematoma, which was drained and 10 weeks later, an enlarged axillary gland was observed. Presence of acid-fast bacilli was detected within the wound. A fourth patient underwent "one-stage fusion of eight vertebrae." The patient presented with a "wound," and a small sinus was detected 3 months following the procedure. At 6 months post-operation, the patient underwent sequestectomy and "granulations were removed and two small bone chips which were lying loose were picked out." A portion of the granulation demonstrated typical TB, although there were no general symptoms observed within the patient. (2)

4.1.2. HEART VALVES

While heart valves were historically tested due to concerns regarding Mtb transmission, "such tests are not done on other tissues donated for transplantation," as reported by Warwick et al, that cited a personal communication by Scott Brubaker (then Chief Policy Officer of the AATB) (25). There were three publications that documented transmission of Mtb through heart valve allografts.

Khanna et al. (1981) reported on 165 patients that underwent aortic valve replacements with antibiotic-treated homograft, of which one case of miliary TB was reported that developed 8 months after the procedure due to "a cold abscess in relation to the donor valve." In the six months to seven years follow-up, this patient died due to TB. (1)

Anyanwu et al. (1976) reported 7 cases of miliary TB and subsequent death in a majority of the cases following the performance of homograft valve replacements in the five years following August 1969. One case began demonstrated symptoms, including pyrexia, rigors, headache, and pleural effusion, three weeks post-operation; following death, acid-fast bacilli was detected in the liver, lungs, spleen, suprarenals, and kidneys, and blood cultures obtained from the patient and inoculated into animal subjects caused development of TB. A second case presented to the hospital with dyspnoea, pyrexia, and confusion post-operation and deceased 5 days later; following death, miliary tubercles with AFB was found—through histological evaluation—in the liver, kidneys, lungs, and spleen. A third case presented post-operatively with diarrhea, anorexia, and lethargy, followed by later symptoms of pyrexia and chest radiographs of right lower lobe consolidation, suggesting tuberculosis; following death, histological evaluation of the lungs demonstrated partly organized emboli, patchy

bronchopneumonia, scattered miliary tubercles and AFB. A fourth case demonstrated presented with jaundice, lethargy, drowsiness, and an enlarged spleen and liver post-operation; following death, histological evaluation found "miliary tubercles with acid-fast bacilli in the liver and scanty acid-fast bacilli in a vegetation from the homograft valve," and blood collected prior to death revealed Mtb. A fifth case demonstrated dyspnoea at rest, pyrexia, dehydration, enlarged liver, and peripheral oedema 5 weeks post-operation; lung biopsy detected Mtb and treatment was initiated, however, the patient died 77 days post-operation with tubercle bacilli found in urine samples obtained at the time of the lung biopsy, AFB observed in the lung, and miliary TB in other organs. A sixth case presented with rigors, pyrexia, and night sweats 6 weeks post-operation; radiograph 61 days post-operation found widespread miliary opacities within the lungs, lung biopsy found tubercles, and culture demonstrated Mtb. This prompted treatment and patient remained hemodynamically stable. A seventh case presented with intermittent pyrexia, malaise, and salt-losing nephropathy 11 weeks post-operation; a culture demonstrated Mtb and the patient was diagnosed with miliary TB and successfully underwent antituberculosis chemotherapy. (26)

Warwick et al. (2008) conducted a survey of 22 heart valve banks to determine whether donor evaluation practices provided beneficial information regarding MTB and other non-TB mycobacteria. Data for 38,13 donors was obtained. Of the 22 banks, 10 banks provided information regarding testing analytes, which included heart-valve-associated tissue, myocardium, and saphenous vein; 15 banks performed AFB staining on 27,840 donors; 18 banks employed automated and culture systems on 32,289 donors. None of the 22 banks reported mycobacteria transmission to recipients from donors. While there were no donors that tested positive for Mtb through culture or AFB tests, there were 2 potential donors that were diagnosed with TB based on clinical manifestations and were subsequently rejected for donation: One potential donor was a male born in Algeria with a history of pulmonary disease suggesting TB and one was "diagnosed macroscopically at organ explantation and autopsy." (25)

4.1.3. CORNEAL TISSUE

Currently, there are no documented cases of Mtb transmission through corneal tissue donors, however, corneal tissue transplants are considered contraindicated when donors are TB-positive. The detection of Mtb using PCR and culture in donors' corneas was evaluated in a prospective, cross-sectional Philippines study by Catedral et al. (2010). Donors were categorized as TB-positive or TB-negative; TB-positive donors were defined by active TB and/or receiving TB treatment at the time of death, as well as confirmed pulmonary TB through autopsy, whereas TB-negative donors were defined by no TB history and/or treatment and lack of confirmation of pulmonary TB through autopsy. Corneas included in the study were obtained from donors with complete medical data for TB, and assessed as being TB-positive, thus contraindicated for transplantation; additionally,

corneas were obtained from "donors from medicolegal cases whose autopsy revealed pulmonary" TB.

There were 12 TB-negative donors and 13 TB-positive donors. Of the 12 TB-negative donors, 10 were positive for TB using PCR and 0 positive using smear and culture. Of the 13 TB-positive donors, there were 6 positive using PCR and 0 positive using smear and culture. There were significantly more positive results detected using PCR for those with TB-negative donors compared to TB-positive donors. However, the authors noted that growth of TB bacilli was not detected, and inferred that cornea tissue contained DNA fragments without live tubercle bacilli, likely resulting from being inactivated from being placed in McCarey-Kauffman solution or insufficiency to grow in Lowenstein-Jensen agar. The authors speculated that the TB-negative corneas were positive via PCR because the original determination of being TB-negative was made through history, which may have been insufficient, and the donor may have had subclinical TB. The authors concluded that although PCR detected TB, TB transmission through cornea tissue is low considering the PCR-positive samples contained TB bacilli that was not growing. (12)

4.1.4. STEM CELLS

A national survey reported an increase in TB cases for recipients of hematopoietic stem cell transplants (HSCT) in Spain. There were significantly greater rates of new cases for active TB in recipients of allogeneic transplants, compared to autologous transplants. Authors of a systematic review reported that these findings are "consistent with the hypothesis that hematopoietic stem cells may represent a niche for MTB" in latent TB infection. (6)

In a systematic review and meta-analysis by Mamishi et al., active TB prevalence following stem cell transplantation procedures, including stem cell transplant (SCT) and HSCT, in recipients was evaluated using data from 60 studies (1,524 patients, of which 1,025 were male; median age range: 24.2 ± 7.4 to 57 ± 8.2 years old). TB types included active TB, pulmonary TB, extrapulmonary TB, disseminated TB, and military TB. Active TB pooled prevalence following transplant was 2%, with prevalence varying per transplant type: 1% for SCT and 2% for hematopoietic stem cell transplant. The prevalence of pulmonary TB following stem cell transplantation procedures based on transplant type was 80% for SCT and 85% for HSCT. The prevalence of extrapulmonary TB based on transplant type was 20% for SCT and 15% for HSCT. (8)

5. MTB TRANSMISSION IN THE SETTING OF ORGAN TRANSPLANT

TB is an infection that transplant recipients may experience following transplantation (8). Transplant recipients have a greater risk of developing active TB due to immunosuppression (23); the infection may be acquired from the transplant donor, the transplant recipient (untreated or unrecognized latent TB re-activation), or others from within communities

(17). Rates of TB in transplant recipients range from 1%–15% and thus 20–74 times greater compared to the overall population, and when transmitted, demonstrates a mortality rate as high as 30% (27, 28).

The World Health Organization noted, based on systematic review findings, that individuals undergoing organ transplantation are immunosuppressed and have a significantly greater risk of developing TB (23). The World Health Organization found, based on one study, that TB incidence is "20 – 74 times higher in organ transplant patients compared with the general population" (23). The pooled prevalence of latent TB in organ transplant candidates using IGRA in various countries, based on a systematic review and meta-analysis, was 18% in the United States (U.S.), 19% in Iran, 23% in Switzerland, 29% in Canada, 33% in Korea, 40% in Spain, and 53% in Turkey; rates based on TST were 4% in Switzerland, 7% in the U.S., 14% in Korea, 17% in Canada, 19% in Iran, 32% in Spain, and 40% in Turkey (28). Risk factors of solid organ donor TB transmission includes residence in an endemic country, travel to a location where TB is endemic, history of latent TB, active TB during procurement, and socioeconomic factors of incarceration, homelessness, and substance abuse (10). However, the rate of TB in organ transplant recipients is determined through TB burden within a region and organ transplant type (28). Furthermore, the transmission of TB through donors is exceedingly rare due to organ protocols regarding organ donor evaluation (27). The unintended transmission of communicable disease from a donor to recipient in organ transplants is estimated to be under 1% for all transplants (10). However, unexpected TB may still occur in the present, particularly due to not performing donor testing or false negative test results prior to donation (29). Additionally, there is high mortality and morbidity associated with organ transplants "from TB-positive donors to recipients with pre-existing" TB (12, 16).

A systematic review and meta-analysis was performed by Rahimifard et al. (2018) on 40 articles to evaluate latent TB prevalence in organ transplant candidates. Of the 40 studies, 5 assessed TST, 7 assessed IGRAs, and 28 assessed IGRAs and TSTs. The pooled prevalence of latent TB using TST was 21% (17%–24%, 95% CI) with a random effects model; when positive TST cut-off was 10 mm pooled prevalence was 21% (16%–26%, 95% CI) and when the cut-off was 5 mm pooled prevalence was 20% (15%–25%); there were no differences observed in latent TB prevalence between TST cutoffs of ≥5mm or ≥10mm induration. The pooled prevalence of latent TB using TST based on transplant type with a random effects model was 24% (14%–33%, 95% CI) for liver, 22% (18%–26%) for lung, 21% (16%–27%, 95% CI) for renal, and 14% (9%–19%) for HSCT. The pooled prevalence of latent TB using IGRA was 26% (23%–30%, 95% CI) with the random effects model. The pooled TB prevalence for T-SPOT and QFT IGRAs was 30% (20%–39%) and 25% (21%–28%, 95% CI), respectively. The pooled prevalence of latent TB using IGRA based on transplant type with a random effects model was 31% (25%–37%, 95% CI) for renal, 25% (17%–33%, 95% CI) for liver, and 13% (10%–16%) for HCT transplants. The pooled TB prevalence following transplantation was 2%, however, the rate was greater for renal recipients at 4% (2%–7%,

95% CI) and lower in liver recipients at 1% (0%–2%, 95% CI). Subgroup meta-analysis results found a latent TB prevalence based on IGRA results of 31% in renal transplant candidates, 25% in liver transplant candidates, and 13% in HCT transplant candidates, with significant differences observed ($p<0.001$). Results also demonstrated that mean/median age impact latent TB prevalence, as the prevalence was significantly greater in the subgroup under 50 years older compared to the prevalence in the subgroup aged 50 years and older. The authors concluded that there was "fair overall agreement between IGRAs and TST in patients requiring liver and HCT transplantation, while a superiority of IGRAs over TST in patients requiring renal transplantation was seen." (28)

In a systematic review and meta-analysis by Mamishi et al., active TB prevalence following organ transplantation procedures in recipients was evaluated using data from 60 studies (1,524 patients, of which 1,025 were male; median age range: 24.2 ± 7.4 to 57 ± 8.2 years old). TB types included active TB, pulmonary TB, extrapulmonary TB, disseminated TB, and miliary TB. Active TB pooled prevalence following transplant was 2%, with prevalence varying per transplant type: 3% for renal, 4% for lung, 3% for heart, and 1% for liver. The prevalence of pulmonary TB based on transplant type was 57% for renal and 64% for liver. The prevalence of extrapulmonary TB based on transplant type was 50% for heart, 30% for renal, and 18% for liver; however, renal transplantation was performed at the greatest frequency compared to other transplants for patients with extrapulmonary TB. The prevalence of disseminated TB based on transplant type was 19% for renal and 16% for liver. Individuals with miliary TB only received renal transplants for transplant type. (8)

History, publications, and/or experience with Mtb transmission through organ transplants are discussed in greater detail in the subsections below. In addition to the review of clinical literature presented in the sections below, the NOTIFY library2 was searched for recipient Mycobacterium tuberculosis infection (Harm to a Recipient => Infection => Bacterial => Mycobacterium) associated with organ products. The Notify Library, which is co-sponsored by the WHO and the Italian National Transplant Centre (CNT), is a publicly accessible database of adverse outcomes associated with the use of medical products of human origin (MPHO), collected and analyzed by dedicated editorial groups of international experts, regulators, and clinicians. The data is identified primarily by literature review but may also include case reports from regulatory or professional vigilance programs. Details regarding the NOTIFY Library search results are provided in Appendix B: NOTIFY Library Search Results. There were 24 records identified in the NOTIFY Library search, including 2 associated with tissue transplants. Proven or potential cases of TB transmission through lung, liver, kidney, and heart transplants were reported in the NOTIFY Library.

[2] https://www.notifylibrary.org/notifylibrary/search/incident

5.1. REPORTED MTB TRANSMISSION VIA SOLID ORGAN TRANSPLANT

As described above, Mtb transmission through organ transplants may occur, although rare (10, 27).

A literature review of MEDLINE, OVID, and EMBASE through December 2016 was performed by Abad et al. (2018) to identify cases of reported DDTB in organ transplant recipients. There were 17 proven, 8 probable, and 11 possible DDTB cases identified. Proven cases were defined by identical or clonal isolates within the donor and recipient identified by molecular analysis; probable cases were defined by suspected transmission and detection of TB in various recipients of 1 donor, or if there was more than one clinical or epidemiological characteristic shared between the recipient and donor. Possible cases were defined by a suspected transmission and a donor demonstrating TB risk factors. Of the identified proven, probably, and possible DDTB cases, TB types included pulmonary (n=13), extrapulmonary (n=10), and disseminated (n=13). Donors demonstrated risk factors of residence in an endemic country (n=13), travel to a location where TB is endemic (n=1), history of latent TB (n=4), active TB during procurement (n=3), and socioeconomic factors of incarceration (n=2), homelessness (n=1), and substance abuse (n=2). In 24 of 36 of the total identified DDTB transmission cases donors were screened and reported to be negative for TB. (10)

Edathodu et al. (2010) reported 3 cases of donor-transmitted TB from a single donor. Following mortality, the donor's 2 kidneys and liver underwent procurement for transplantation. One recipient received 1 of the donor's kidneys and 8 weeks post-implantation presented with fever. A repeat chest x-ray demonstrated bilateral diffuse infiltrates 6 days following the initial x-ray. Acid-fast bacilli were detected in the sputum and bronchoalveolar lavage, and DNA amplification using BD ProbeTec ET DTB, a direct detection assay, confirmed presence of *M. tuberculosis*. Bone marrow biopsy findings demonstrated multiple granulomata containing acid-fast bacilli. Presence of *M. tuberculosis* was detected by InnoLiPA Mycobacteria and biochemical testing and isolated from bone marrow, sputum, and BAL. This patient underwent treatment and morbidities were reported. There was a second recipient that received the donor's liver. In the 3 months following transplantation, the recipient presented with a fever. Acid-fast bacillus was detected from abdominal wound discharge and MRI and US demonstrated various small hepatic abscesses, of which 1 was aspirated. The acid-fast bacillus stain demonstrated positive results, with *M. tuberculosis* later developing. The patient underwent treatment and no morbidities were reported. The third recipient received 1 of the donor's kidneys. Immediately following transplantation, the patient experienced acute tubular necrosis and underwent treatment with positive results; however, 3 weeks post-transplantation, the patient presented with a fever. The patient received a bone marrow biopsy, and died shortly after. Results from the bone marrow transplant demonstrated "necrotic changes secondary to granulomatous changes," as well as positive findings from acid-fast bacillus staining. Although presence of *M. tuberculosis* was not confirmed in the third case, as was in the others,

the authors noted there was sufficient circumstantial evidence to conclude TB contraction from the donor. (27)

Jones et al. (2020) reported 4 cases diagnosed in early 2018 of donor-transmitted TB through organ transplant. The donor was a born in a country where TB was endemic and displayed negative TSTs annually. In the 8 weeks following the donor giving birth, the individual presented with fever and headache and sought medical care. Following death, chest x-ray demonstrated small pleural effusion and the donor's death was attributed to anoxia and pulmonary embolism. There were no TB risk factors identified and TB testing or autopsy was not performed. The authors noted that the lack of identification of risk factors was likely due to multiple events, including multiple hospital admissions across various medical systems, which may have caused an incomplete transfer of medical data; imaging reports were transferred between medical systems, but the images were unavailable to be reviewed by hospitals; fever was suppressed by steroids, reducing clinical detection of an infection; and providers were unaware of a TB outbreak in the donor's community. The donor's lungs, kidneys, liver, and heart were transplanted in 4 individuals. The lung was transplanted into a female, and 50 days following the procedure, a mycobacterial culture, isolated *M. tuberculosis* in the "bronchoalveolar lavage sample from the sixth post-transplant bronchoscopy performed 14 days after transplantation." This patient completed treatment without adverse events. A female liver-kidney recipient presented with fever 2 weeks post-transplantation. A chest CT demonstrated various nodules, implicating infectious bronchiolitis. PCR using bronchoalveolar lavage and urine samples yielded positive results for *M. tuberculosis*, which was isolated from both samples. The patient completed treatment 20 months following transplantation. A male kidney recipient presented with a fever 5 weeks following transplantation. A bone marrow biopsy demonstrated non-specific lymphoid aggregates, however, no acid-fast bacilli was detected with stains. Following notification of other recipients' TB diagnoses, a urine AFB stain was conducted, yielding negative results; a second urine sample was obtained and centrifuged and Mtb was detected using PCR and AFB smear. However, 3 sputum AFB smears were negative, as were mycobacterial culture using bone marrow, sputum, and urine. The patient was treated without adverse events. A male heart recipient developed no TB symptoms, however, following notification of the other cases, the patient was evaluated for TB using chest CT and PCR with endomyocardial biopsy samples, with no TB detected. IGRA was indeterminate. The patient was treated for TB irrespective of absence of symptoms and detection in tests and experienced no adverse events during treatment. (16)

There were 10 cases of potential Mtb transmission from latently infected donors to recipients summarized in a systematic review by Mayito et al. (2019); cases were summarized from articles published from 1996 – 2017. Case 1 involved two recipients with pulmonary TB and identical isolates following receipt of a lung from a donor who demonstrated normal chest radiograph and had no prior history of TB. Case 2 involved two recipients with matching isolates for "active TB (renal TB at 14 months posttransplant in

kidney recipient, TB osteomyelitis at 12 months posttransplant in liver recipient)" following receipt of a kidney and liver from a donor with no history of TB and normal chest radiograph. Case 3 involved a recipient with multi-drug resistant TB (MDRTB) 7 weeks post-transplantation (recipient negative prior to transplant and had no exposure to MDR-TB) who received a lung from a donor who recently emigrated from China with no history of TB, normal chest x-ray, negative results for AFB smear and culture. Case 4 involved a recipient with pulmonary and pericardial TB following transplant (no exposure to TB known) from a donor with a normal chest radiograph during donation, but had a history of a prior PPD 24 mm without chemoprophylaxis and emigrated from Peru 11 years prior. Case 5 involved a recipient with pulmonary TB (indo-oceanic lineage isolate) who received a lung from Vietnamese-born donor with no positive TST, no history of TB, and a normal CT chest scan. Case 6 involved a lung recipient with pulmonary TB (2 months following transplantation) with an isolate that matched a strain from an outbreak located near the donor's residence; the donor had a remote history of incarceration, died in an accident, and demonstrated a normal chest radiograph and bronchoscopy. Case 7 involved a lung recipient with pulmonary TB (4 months following transplantation with Manila-family-associated spoligotype) who did not travel outside of the U.S.; the donor traveled to the Philippines prior and demonstrated a normal chest radiograph and "normal bronchoscopy and BAL culture negative for TB ante-mortem." Case 8 was a lung recipient with pulmonary TB (11 weeks following transplantation) with isolates that matched the index case the donor was exposed to; the donor was "diagnosed with latent TB 5 years before death after exposure to index case with isoniazid-resistant TB" and received insufficient treatment. Case 9 involved a lung recipient with pulmonary Tb (6 weeks following transplantation) with no known exposure to TB or history of TB; the donor did not have TST results available, but demonstrated no symptoms of active TB, no indicators of previous TB through CT chest, and negative lung biopsy culture and PCR for Mtb. Case 10 involved a liver recipient with hepatic TB (6 months following transplantation with a Manila family isolate); the donor was from the Philippines and demonstrated normal chest radiograph and abdominal ultrasound. (6)

Reports of probable and proven unanticipated, donor-derived infections were systematically reviewed in 119 studies (54 studies reported non-viral infection and 65 studies reporting viral infection) published from 1948 – June 2017 comprised of 116 patients (21 males; median age of 45 years) with viral infections and 91 patients (50 males; median age 45 years old) with non-viral cases following kidney transplant. Of the total 91 patients with probable and proven non-viral, donor-derived infection, the most common infection was due to *M. tuberculosis* contraction observed in 10 patients (4.8% of all pathogens). For *M. tuberculosis*, the median duration from transplant procedure to disease onset was 1.4 months, the median time to diagnosis was 1.3 months, and the median follow-up period was 9.5 months. By the end of the follow-up period, 2 of 10 (20%) individuals with donor-derived *M. tuberculosis* were deceased. (29)

6. TUBERCULOSIS SCREENING

6.1. RISK FACTORS

The World Health Organization provided the following guidelines for clinical TB screenings in those with various risk factors:

- "Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care." (23)
    - conditional recommendation, with "very low certainty of evidence" (23)
- "Systematic screening for TB disease should be conducted in prisons and penitentiary Institutions." (23)
    - strong recommendation, with "very low certainty of evidence" (23)
- "Household contacts and other close contacts of individuals with TB disease should be systematically screened for TB disease." (23)
    - strong recommendation, with "moderate certainty of evidence" (23)
- "Among individuals younger than 15 years who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both." (23)
    - strong recommendation, with "moderate to low certainty of evidence for test accuracy" (23)

6.2. DIALYSIS

Based on results from one study, authors recommended that amongst individuals with CKD, latent TB screenings should be prioritized in individuals undergoing dialysis, rather than individuals with severe CKD not undergoing dialysis, due to the increased risk of TB demonstrated in dialysis patients (22).

6.3. HIV

The World Health Organization provided the following guidelines for TB screenings in the HIV-targeted population:

- "People living with HIV should be systematically screened for TB disease at each visit to a health facility." (23)
    - strong recommendation, with "very low certainty of evidence" (23)

- "Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient." (23)
    - strong recommendation, with "low certainty of evidence for test accuracy" (23)

According to the American Public Health Association, screening for active TB (pulmonary or extrapulmonary) is performed on HIV-positive individuals, particularly, symptomatic TB is assessed at clinical check-ups based on the four symptoms of weight loss, cough, night sweats, and fever. HIV-positive individuals that demonstrate one of the four symptoms through clinical history or examination, including chest radiography or Xpert MTB/RIF, should be further assessed for active TB (pulmonary or extrapulmonary). If HIV-positive individuals test positive for TB through IGRA or TST, then treatment for latent TB should be provided. (5)

6.4. GEOGRAPHIC

Research has demonstrated substantial variation in international TB (active and latent) screening procedures, and approximately half of the countries with low TB incidence do not have a latent TB screening program implemented (24).

The World Health Organization provided the following guidelines for TB screenings based on region-specific TB prevalence:

- "Systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher." (23)
    - Conditional recommendation, with "low certainty of evidence" (23)

6.5. DONORS

6.5.1. ORGAN TRANSPLANT

This section provides a review of a variety of recommendations from the literature and guidelines regarding organ transplant screening. Some recommendations included classifying organ transplant donors into risk categories (high, moderate, and low) based on risk factors, such as previous residence in countries with greater TB incidence rates (16). The American Society of Transplantation recommended that donation deferral is considered for organ donors with confirmed or suspected active TB infection (16).

A 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society, noted that "transplant candidates should be screened for latent" TB. Screening protocols for transplant recipients prior to transplantation commonly includes acquiring a medical history of possible previous

exposure or latent TB treatment, chest radiography, and TST, although utilization of IGRAs has increased. In TB endemic regions, organ transplant centers may provide a screening model for organ recipients and donors, however, there is limited data regarding the utilization of new diagnostic methods for TB screenings in the donor population. Present screening and diagnostics are focused on the detection of latent TB, however, the aforementioned consensus conference report notes that it may be more essential "that screening protocols identify donors with unrecognized active TB." (17)

The following excerpt was obtained from the aforementioned 2012 consensus conference report, and contains recommendations and data to improve the screening of TB in **all** organ transplant donors (17):

> *1. Reasonable efforts must be made to rule out active TB in the donor with any identified historical or epidemiologic risk factors. For suspected or confirmed cases of active TB, donation should be deferred except in dire circumstances*
>
> *2. All SOT donors (living and deceased) should have a careful epidemiologic and personal medical history, physical and a chest radiograph*
>
> *3. TST and IGRA test results should be cautiously interpreted taking into consideration the epidemiologic history and chest radiograph findings. A negative result on an immunological test such as TST or IGRA does not rule out active TB*
>
> *4. For lung donors, bronchoscopy specimens should be obtained for mycobacterial testing for TB and atypical mycobacteria (AFB smear and culture at a minimum) prior to donation*
>
> *5. Molecular methods for mycobacterial culture and species identification are preferred to standard culture if available, due to the shorter turn-around time*
>
> *6. There is insufficient evidence to recommend IGRA testing of all SOT donors at this time. Further research into the utility of IGRAs in donors is needed. IGRAs have potential utility for identification of increased TB risk deceased donors (moderate or high risk)*
>
> *7. Donation need not be deferred for the diagnosis of latent TB in any SOT donor including lung donors*
>
> *8. Urinalysis with microscopy, genitourinary imaging and urine AFB smear and culture should be considered for all organ donors in intermediate- and high-risk countries. This is particularly important for kidney donors*

The following excerpt was obtained from the aforementioned 2012 consensus conference report, and contains recommendations and data to improve the screening of TB in **deceased** organ transplant donors (17):

> *1. In deceased donors of solid organs other than lungs, who have an abnormal chest radiograph suspicious for active TB, specimens should be collected for AFB smear and culture, and specimens should be sent for nucleic acid amplification testing [NAAT] (34,35). The results of these tests can be used to guide further investigations and treatment in the recipients. Teams may have limited information when deciding whether to proceed to transplant*

2. There is insufficient evidence to recommend routine IGRA testing of deceased donors. However, if IGRA testing is pursued, the following considerations should be taken into account

a. IGRA results are not generally available for 24 h. Therefore, the decision to utilize the organs must be a clinical decision

b. IGRAs have relatively high rates of indeterminate results in different subpopulations (0–16%) (23). Repeat testing of a donor is generally not feasible. Therefore, interpretation of these results must be done cautiously as it has possible therapeutic implications for the recipient(s)

c. If an IGRA is positive or indeterminate and the deceased donor of any organ except lung is from an area of low incidence for TB but otherwise in a high risk group for TB, clinical history and chest imaging should be carefully reviewed for correlation. This should precede donation if the positive result is known prior to procurement. Regardless, the IGRA testing results alone should not influence suitability for donation, but may be used to guide follow up assessments or TB therapy in the recipient

d. Literature suggests that cell-mediated immunity is depressed following head injury. Therefore, persons with head injury may not respond to mitogen. This situation has not been specifically studied with IGRAs

e. There is minimal published information regarding the performance characteristics of IGRAs in infants and young children

The following excerpt was obtained from the aforementioned 2012 consensus conference report, and contains recommendations and data to improve the screening of TB in **living** organ transplant donors (17):

1. When active TB is found in the donor, clinicians caring for the recipient must be rapidly informed in order for the recipient to be managed promptly; in cases involving 'swaps' of organs, the transplant centers and/or procurement organizations involved must notify the recipient centers as soon as possible

2. Living donors with a positive TST or IGRA should be offered treatment for latent TB prior to donation or as per local or national guidelines. As completion of this treatment may delay the transplant and adversely impact the recipient, expert opinion was that each situation should be individualized, but the prophylaxis need not be completed before the transplant occurs. There are no data on optimal duration of LTBI therapy in this setting

Cases that exemplify the failure to prevent TB transmission through donors, despite performance of TB screenings, are reported in the literature. Edathodu et al. (2010), also discussed in Section 5.1, presented 3 cases of donor-transmitted TB from a single organ donor (donor of 2 kidneys and the liver). Although the donor was screened for latent TB through a chest X-ray and TST upon entering Saudi Arabia, and demonstrated negative results for acid-fast bacilli stain, culture, and Mtb DNA using cerebrospinal fluid, TB went undetected and was transmitted to three individuals, causing death in one. The authors from this study suggested that (27):

1) Organs from patients who die of unknown infectious causes should not be harvested for transplantation. 2) To facilitate prompt treatment of possible donor-related infections, and to report any significant developments in the recipients, there should be rapid communication among the teams responsible for organ harvesting and transplantation. 3) In countries endemic for TB, tissue from the organs being transplanted should be sent for AFB culture along with DNA probe assay and histology, to allow early or pre-emptive treatment of the recipient.

Jones et al. (2020), also discussed in Section 5.1, reported 4 cases of donor-transmitted TB within the U.S. from a donor who was born outside of the U.S. (16). Similar to the latter recommendation above, the authors also noted the significance of testing for TB in all organ donors from regions with greater endemic rates of TB (16). Prior to organ donation, interviews with the next of kin were conducted through questionnaires, which included questions regarding TB infection (such as previous TB confirmed by test and residence with an individual with active TB within the past 12 months before death); TB risk factors were not detected, a TB test was not utilized, and donor autopsy was not conducted. The authors elaborated that TB, active or latent, is not easily identified through a review of the donor's medical history (exemplified by the donor screening that occurred and failed to detect TB prior to transplantation), thus it is essential that donors of high risk are assessed for risk factors and undergo supplemental laboratory screening (16). Evaluations of chest imaging anomalies should include TB testing with a bronchoscopy sample using NAAT, AFB smear, and mycobacterial culture; however, AFB results wouldn't be received prior to transplantation but could provide information to treat recipients – this does not apply to tissue transplantation (16).

One systematic review and meta-analysis found greater active TB prevalence rates using x-ray and culture, and noted that the "result could be expected because culture is the gold standard method" (8). Therefore, the authors recommended following transplantation that TB diagnostic tests are performed regularly, including mycobacterial cultures and chest x-ray as an additional test (8). TST testing demonstrates low efficacy, however, it may serve as a first diagnostic test to detect the presence of Mtb for transplant recipients (8).

6.5.2. TISSUE TRANSPLANT

Within the literature, there were various recommendations regarding TB screening methods for tissue donors. It was reported that the screening of heart value donors is based on evidence and consider factors that increase the risk of TB (25). The selection of heart valve donors with low TB risk was reported as sufficient in decreasing the risk of TB transmission in heart value transplantation (25). Conversely, screening through AFB microscopy provided no benefit to heart valve safety, and was recommended for discontinuation by one publication (25).

7. TUBERCULOSIS DIAGNOSIS

7.1. CLINICAL

Suspected TB cases should be diagnosed through a complete diagnostic assessment, including the performance of a chest radiograph (5). Latent TB may be identified through tuberculosis skin tests (TSTs) or blood tests employing IGRAs (5).

The diagnosis of latent TB in populations of increased susceptibility, such as those with severe CKD and undergoing dialysis, is often delayed due to common extrapulmonary manifestations (22). Early detection of TB is essential for the immediate isolation and subsequent treatment of those infected and those who were exposed to the infected individual (30). Detailed discussions of TB risk factors and TB detection are provided in Sections 3 and 8, respectively.

7.2. SOLID ORGAN TRANSPLANT DONOR

The following excerpt was obtained from the 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society, and contains recommendations and data to improve the diagnosis of TB in organ transplantation (17):

> *1. Organ donors can be divided into low, moderate and high-risk categories for risk of TB infection or LTBI based on detailed history and prior countries of residence/exposure. It should be noted that some donors thought to have LTBI may actually have undiagnosed active TB at the time they become an organ donor. Individuals with active TB will likely pose a greater risk for transmission; therefore, it is especially critical to identify these patients prior to donation.*
>
> *2. Risk stratification based on donor social and medical history may be predictive of TB infection (either LTBI or unrecognized active TB) in donors and hence possible risk of TB transmission to organ recipients.*
>
> *3. Diagnosis of LTBI and assessment of risk for transmission in organ donors optimally should be based on objective medical data such as prior historical results of TST, IGRA and CXRs.*
>
> *4. The presence of TB disease in individuals currently residing in low risk countries is closely correlated with the donor's prior countries of origin and residence*
>
> *5. Epidemiologic data can be used to target diagnostic evaluation of donors and recipients and formulate management algorithms. It therefore may be useful to include this information when evaluating donors.*
>
> *6. It is currently unknown how recipient history modifies the impact of donor epidemiologic risk factors on the probability of transmission of TB through transplantation. Factors such as recipient immunogenetics may confound donor risk stratification when evaluating transplant outcomes*

Risk stratification of TB using medical and social history of organ donors "may be predictive of TB infection (either LTBI or unrecognized active TB) in donors and hence possible risk of

TB transmission to organ recipients" (17). Risk stratification of TB can be based on medical and social risk factors such as country of origin and type of organ transplant. Factors that may confound the risk stratification of TB epidemiology include (17):

- *Donor exposure timing and the changing incidence of TB in geographic locales.*
- *Different TB reactivation risk based on the organ transplanted and the choice of immunosuppressives.*
- *The impact of prior TB exposure and genetic factors in the recipient.*

7.3. TISSUE DONOR

There was no information provided regarding the diagnosis of TB in tissue transplantation. However, in regards to tissue sampling in clinical diagnosis, the CDC reports that such sampling typically occurs following the failure of other TB tests to provide a definitive diagnosis (31). Details regarding the performance of tests that utilize tissue to detect TB are discussed in Section 8 below.

8. DETECTION OF TUBERCULOSIS

This section contains information from the literature and guidelines pertaining to the reported performance of various TB diagnostic tests, including, but not limited to, the direct detection of TB in tissue. **Table 8-1** below provides a summary of TB tests utilized or discussed within the literature reviewed; information in each table row, such as whether the tests were performed on the deceased or living for active (pulmonary or extrapulmonary) or latent TB, reflect the methods performed or discussed within a specific literature reference. An elaborate review of the TB tests, with comparisons of benefits and risks, can be found detailed in the subsections below. All tests were reported to be used on tissue, tissue donors, or were unspecified, with the exception of T-SPOT.TB and Quantiferon-TB Gold IGRAs, which were employed on organ transplant donors.

Table 8-1. Tuberculosis Test Summary Table from Reviewed Literature and Guidelines

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
Histological Examination	Unspecified	Deceased	Active (EP)	Of seven cases of miliary TB following homograft valve replacements: post-mortem histological examination discovered acid-fast bacilli in spleen, lungs, liver, suprarenals, and kidneys in one case; post-mortem histological examination of the lungs and homograft valve	Anyanwu et al. (1976) (26)

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
				demonstrated acid-fast bacilli in a second case; and post-mortem histological examination of the liver and homograft valve detected acid-fast bacilli in a third patient.	
IGRA	Quantiferon (QFT)	Living	Unspecified	TST and IGRAs were compared for TB detection in immigrant populations, finding that TST demonstrated significantly higher positive rates.	Campbell et al. (24)
	QuantiFERON-Gold In-Tube (QFT-GIT)			TST and IGRAs were compared for TB detection in immigrant populations, finding that TST demonstrated significantly higher positive rates.	
	Quantiferon-TB Gold (QFT-G)	Living or deceased		Guidance provided in 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society. Due to the publication type, the data obtained regarding IGRA use on living/deceased was general. The authors noted, "There are no data yet on the clinical utility or test performance of IGRAs in the deceased donor population, or similar populations such as critical care unit patients or patients with head injury. It is unknown whether brain death may impact the performance of this assay."	Morris et al. (17)
		Living		TST and IGRAs were compared for TB detection in immigrant populations, finding that TST demonstrated significantly higher positive rates.	Campbell et al. (24)
	T-SPOT.TB	Living or deceased		Guidance provided in 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society. Due to the publication type, the data obtained regarding IGRA use on living/deceased was general. The authors noted, "There are no data yet on the clinical utility or test performance of IGRAs in the deceased donor population, or	Morris et al. (17)

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
				similar populations such as critical care unit patients or patients with head injury. It is unknown whether brain death may impact the performance of this assay."	
		Living		TST and IGRAs were compared for TB detection in immigrant populations, finding that TST demonstrated significantly higher positive rates.	Campbell et al. (24)
Imaging	Chest x-ray/ radiograph	Living	Latent	Chest x-ray accompanied with TST was performed upon the individual's arrival to Saudi Arabia to test for latent TB; this individual was later an organ transplant donor that transmitted TB to 3 recipients.	Edathou et al. (27)
			Active (EP)	Of seven cases of miliary TB following homograft valve replacements: suspicions of TB arose based on chest radiograph performed prior to patient's death; and TB was suspected in one case (living subject) performed following radiograph performance.	Anyanwu et al. (26)
Microscopy and culture	Solid (Lowenstein-Jensen) medium and liquid Mycobacteria Growth Indicator Tube (MGIT; BD Biosciences, Sparks MD) medium	Living	Active (P/EP)	AFB microscopy and culture utilized with respiratory and non-respiratory clinical specimens	Somily et al. (30)
	"(i) smear microscopy for acid-fast organisms (Ziehl-Neelsen and/or auramine-rhodamine stain) and (ii) mycobacterial culture in solid (Löwenstein-Jensen) and liquid media (Bactec MGIT 960; Becton Dickinson, Towson, MD)."		Active (EP)	Smear microscopy and culture utilized with extrapulmonary samples, collected from adult patients.	Perez-Risco et al. (11)
	Direct smear and/or culture	Unspecified	Active (P)	Direct smear and culture was performed on rib marrow removed from individuals with pulmonary TB, finding no acid-fast bacilli. The tissue was subsequently used for bone grafting on other patients, resulting in TB transmission.	James (2)

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
		Living/Deceased	Active (EP)	Of seven cases of miliary TB following homograft valve replacements: Case one: Blood cultures obtained prior to death were incubated, centrifuged, and injected into guinea pigs following the patient's death, with Mtb detected in the animals' spleens. Case two: Post-mortem spleen culture grew Mtb. Case three: Blood culture acquired prior to death was evaluated post-mortem, demonstrating Mtb growth. Case five: Biopsy and culture of the left lung obtained in living patient; following death, acid-fast bacilli was detected in the brain and lymph nodes, and a blood and urine culture obtained prior to death was examined post-mortem, detecting TB. Case six: Lung biopsy and culture obtained from living patient, with Mtb growth. Case seven: Urine culture obtained from living patient, with Mtb growth.	Anyanwu et al. (26)
Mycobacterial identification	BIO-LINE SD Ag MPT64 TB test (Standard Diagnostics, Yongin, South Korea)	Living	Active (EP)	Extrapulmonary samples were collected from adult patients.	Perez-Risco et al. (11)
	DNA AccuProbe (Gen-Probe Inc., San Diego, CA)			Extrapulmonary samples were collected from adult patients.	
	Genotype Mycobacterium CM/MTBC (Hain Lifescience, Nehren, Germany)			Extrapulmonary samples were collected from adult patients.	
PCR	Abbott Real time MTB assay and Abbott m2000rt real-time PCR instrument	Living	Active (EP)	Analyzed extrapulmonary specimens (non-sterile fluid, sterile fluid, lymph node acquired post-operatively, fine needle aspiration, non-lymph node tissue, abscess aspirate) were obtained in routine diagnosis following suspicion of TB. Lymph node specimen included open biopsy and fine needle biopsy; tissue biopsy	Borras et al. (32)

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
				specimen included skin, pleural, mediastinal, intervertebral disc, bone, colonic, liver, supraclavicular, and synovial; abscess aspirates specimen included liver, bone, muscle, and brain; sterile fluid specimen included pleural, bone marrow, cerebrospinal, peritoneal, synovial, pericardial, and blood; non-sterile fluid specimen included urine, gastric aspirate, and seminal.	
	BD ProbeTec ET MBTC direct detection assay (DTB)		Active (P/EP)	Respiratory and non-respiratory clinical specimens	Somily et al. (30)
	COBAS Taqman MTB (Roche Diagnostics)	Unspecified	Active (EP)	Targets "sequences within either the IS6110 or the 16S rRNA genes."	Borras et al. (32)
	Nested-PCR system	Living	Unspecified	Specimens obtained from bovine lesions and human sputum samples.	Araujo et al. (33)
	Taq polymerase (Invitrogen Life Technologies, Tokyo, Japan)	Deceased	Active (P/EP)	Corneas from PTB-positive patients were tested using PCR.	Catedral et al. (12)
	Taqman assays	Unspecified	Active (EP)	Targets "sequences within either the IS6110 or the 16S rRNA genes."	Borras et al. (32)
	Unspecified	Deceased	Latent	PCR is employed in modern necropsy research to detect Mtb DNA within spleen, lung, kidney, liver, and adipose tissue.	Mayito et al. (6)
	Xpert MTB/RIF (Cepheid)	Unspecified	Active (P/EP)	Utilized for PTB and EPTB, but demonstrates low sensitivity for EPTB.	Borras et al. (32)
		Living	Active (P/EP)	Used for diagnosis in children and adults.	American Public Health Association (5)
	Xpert MTB/RIF Ultra (GX-Ultra; Cepheid) assay			Developed due to the limitations of the Xpert MTB/RIF (Cepheid) in EPTB sensitivity; demonstrates greater sensitivity in detecting Mtb complex DNA when low bacillary loads are present. In the study itself, Xpert MTB/RIF (Cepheid) was performed on smear-negative EP samples.	Perez-Risco et al. (11)
TST	TST	Living	Unspecified	TST and IGRAs were compared for TB detection in immigrant populations, finding that TST	Campbell et al. (24)

Test Type	Specific Test/Test Description	Living/Deceased	Active (P/EP)/Latent TB	Notes	Reference
				demonstrated significantly higher positive rates.	
			Latent	TST accompanied with chest x-ray was performed upon the individual's arrival to Saudi Arabia to test for latent TB; this individual was later an organ transplant donor that transmitted TB to 3 recipients.	Edathou et al. (27)
				Testing performed on specific immunocompromised population--those undergoing hemodialysis.	Sester et al. (14)
Whole blood testing	T-cell response to PPD	Living	Latent	Testing performed on specific immunocompromised population--those undergoing hemodialysis.	Sester et al. (14)

P=pulmonary; EP=extrapulmonary; PTB=pulmonary TB; EPTB=extrapulmonary TB

8.1. TUBERCULOSIS TESTING

8.1.1. LIVING SUBJECTS

The 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society, reported it was feasible to perform TST in living organ transplant donors, but not feasible to perform on deceased organ transplant donors (17). It is infeasible to perform TST in the deceased because of "the delay in development of a reaction," (17); in the living, TST is widely utilized for Mtb detection in those without disease (14). Various cut-offs have been suggested for characterizing positive reactions to TST, such as a cut-off of ≥15 mm applicable to those who are immunocompetent and ≥10 mm for those who are mildly immunocompromised (14). While TSTs are cost-effective and demonstrate high sensitivity in detection of latent TB, TST demonstrates low specificity for those with bacillus Calmette-Guerin (BCG) vaccinations and those who are immunocompromised and at high risk for TB (14, 24).

Microscopy and cultures are also performed on living individuals, with one study testing for TB using extrapulmonary samples were collected from adult patients (11), and another study testing for TB using Respiratory and non-respiratory clinical specimens (30).

8.1.2. OTHER TESTING CONSIDERATIONS

Geographic

There are challenges in identifying true specificity and sensitivity of TB tests in immigrant populations, attributable to research assessing low-risk populations for specificity

approximation and "active TB as a surrogate to determine sensitivity" (24). In literature by Campbell et al. (2015) it was found that TSTs demonstrated significantly higher positive rates compared to IGRAs (OR 1.46; 95% CI: 1.07 – 2.01) for TB detection in the immigrant population (24). It was recommended that the utilization of TST as a standard test in immigration populations should be reevaluated, as "BCG vaccination is likely the culprit for the inflated number of positive TSTs as there is no significant difference between test specificity in unvaccinated populations and test sensitivity is not significantly different between the TST and versions of the" QuantiFERON (QFT) (24). The authors elaborated that various countries perform dual testing on those with increased risk of false positives for TST, thus, IGRAs may be time- and cost-effective (24).

In another publication, there were 3 organ transplant recipients that contracted TB post-transplantation, as reported by Edathou et al. (2010); these cases demonstrated the failure of the TST testing method, as well as other diagnostic methods (chest x-ray) to detect TB in the donor, including TST (27).

Dialysis

Sester et al. (2004), also discussed in Section 3.2.3 performed a study on hemodialysis patients to evaluate the T-cell response to PPD for Mtb and assess "whether its direct quantitation from whole blood could represent an alternative approach to the skin test in anergic and/or immunocompromised patients." There were 127 individuals undergoing hemodialysis included and 218 immunocompetent controls consisting of 107 healthcare words, 59 immunocompetent individuals admitted toa German hospital, and 52 healthy blood donors. Reactivity to the PPD was determined using Mendel-Mantoux and an 5 mm induration, and "early secretory antigenic target-6 (ESAT-6), a protein expressed in *mycobacterium tuberculosis* but absent from *M. bovis bacillus Calmette-Guerin* (BCG) vaccine strains," was "flow cytometrically quantified from whole blood" and compared to TST. Results demonstrated PPD-specific CD4 T cells >0.05% in 30.8% (16/52) of blood donors, 48.6% (52/107) of healthcare workers, and 53.5% (68/127) of hemodialysis patients. TST results >5 mm were demonstrated in 91.7% (11/12) of healthcare workers, 82.6% (19/23) of control patients, and 51.4% (18/35) of hemodialysis patients, with a significantly lower rate of positive TST observed for hemodialysis patients (p=0.007). Individuals with reactive in vitro PPD results, approximately 50% demonstrated T cells specific to ESAT-6. The authors concluded that (14):

> *Unlike the skin test, measurement of PPD reactivity by in vitro quantitation of PPD-specific T cells was unaffected by uremia-associated immunosuppression. This whole-blood assay may thus be a valuable alternative to skin testing, and detection of ESAT-6–specific T cells could moreover allow distinction of latent M. tuberculosis infection from BCG-induced reactivity to PPD.*

8.1.3. ALL SUBJECTS (LIVING OR DECEASED)

IGRAs do not demonstrate the decreased specificity observed in TST and use "highly specific antigens derived from *Mycobacterium tuberculosis*, which are absent in all strains of Bacillus Calmette-Guerin (BCG) and most environmental mycobacteria" (24). IGRAs offer the advantage of being performed within a single visit, however, IGRAs are more expensive and have less long-term data to support application in latent TB diagnosis (24). Specific IGRAs include, but are not limited to, T-SPOT.TB and QuantiFERON-Gold In-Tube (QFT-GIT), which will demonstrate positive results approximately 2-6 weeks following exposure (5). QFT manufacturer instructions specify that interferon- Ɣ values of ≥0.35 IU/ml are positive, interferon- Ɣ values <0.35 IU/ml and mitogen control values ≥0.5 IU/ml are negative, and interferon- Ɣ levels <0.35 IU/ml and mitogen control values of <0.5 IU/ml are indeterminate. T-SPOT manufacturer instructions specify results are interpreted based on spot-forming units (28):

> *number of spots was scored as positive if either antigen was ≥6, and negative if it was ≤5. Tests were considered as indeterminate if SFUs in positive control were<20, or if SFUs in the negative well exceeded 10 and SFUs in both antigens wells had less than twice the number of SFUs of the negative well.*

Detection of TB in extrapulmonary TB is guided by imaging techniques, but tested through culture, microscopy, and histopathological assessment on samples from involved sites (5). Traditionally, the detection of active pulmonary TB can be assessed based on the presence of "acid-fast bacilli (AFB) in the microscopic examination of the sputum" (5). Upon collection, smear microscopy should be performed on the samples (5). Direct smear microscopy (Ziehl-Neelsen and/or auraminerhodamine stain) benefits include being quick, low in cost, and simple, however, this method demonstrates decreased sensitivity (ranging from 50% to 80%), particularly in non-respiratory samples (11, 30). Furthermore, TB smears may demonstrate false negatives in individuals positive for HIV and Sputum cultures may demonstrate false positive results due to clerical errors, such as cross-contamination and contamination of equipment (5, 8). Mycobacterial cultures are deemed the gold standard, however, diagnosis through this method can take several weeks (11, 30). New molecular diagnostic methods were developed to enhance detection and subsequent control of TB, including identification of particular lipids, DNA amplification, and serological demonstration of cell surface proteins, and microscopy (11, 30).

8.1.4. SOLID ORGAN TRANSPLANT DONORS

Whole blood assays may be utilized on deceased organ transplant donors, however, "it is important to assess whether antigen presenting cells and T cells are functional enough to produce an appropriate immune response" (17). A possible benefit of performing IGRAs on deceased organ transplant donors is (17):

> *that specific stimulation reactions are accompanied both by a negative control that allows assessment of nonspecific background reactivity, and also by a mitogen stimulus that is used*

as a positive control to assess general T cell responsiveness. This may allow for interpretable results.

There is limited evidence to support the performance of IGRAs in deceased organ transplant donors, however, if IGRA testing is performed in this population, then specific stipulations follow, as described in Section 6.5.1 above (17). The 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society, reported it is feasible to use the Quantiferon-TB Gold and T-SPOT.TB IGRAs in living or deceased donors (17).

In addition to the potential use of IGRAs in deceased organ transplant donors, described above, the 2012 consensus conference report, endorsed by the American Society of Transplantation, Canadian Society of Transplantation, and the Transplantation Society, recommends that deceased organ transplant donors that demonstrated abnormal chest radiographs should have AFB smears and cultures obtained and processed using NAAT (17). However, PCR has also been employed for TB testing on samples obtained from living patients, discussed in the study descriptions in the subsection below.

8.1.5. TISSUE DONOR

In the 1950s, the banking of ribs removed during thoracoplasties for pulmonary TB, and subsequent application in orthopedic procedures, became frequent. James (1953) described the use of direct smear and culture to examine rib marrow from 69 thoracoplasty stages (from those with pulmonary TB), with acid-fast bacilli undetected. However, TB transmission did occur through the tissue transplantation, deeming rib marrow from those with pulmonary TB unsuitable for bone graft. (2)

The detection of Mtb using PCR and culture in donors' corneas was evaluated in a prospective, cross-sectional Philippines study by Catedral et al. (2010). Donors were categorized as TB-positive or TB-negative; TB-positive donors were defined by active TB and/or receiving TB treatment at the time of death, as well as confirmed pulmonary TB through autopsy, whereas TB-negative donors were defined by no TB history and/or treatment and lack of confirmation of pulmonary TB through autopsy. Corneas included in the study were obtained from donors with complete medical data for TB, and assessed as being TB-positive, thus contraindicated for transplantation; additionally, corneas were obtained from "donors from medicolegal cases whose autopsy revealed pulmonary" TB. (12)

8.2. DIRECT DETECTION OF TUBERCULOSIS IN TISSUE

While culture is considered the gold standard for TB diagnosis, PCR is a rapid and sensitive method to detect Mtb in individuals without systemic manifestations of TB, and is a preferred testing method for rapid identification of Mtb in tissue samples (12, 30). Evidence

of Mtb within Ghon foci, in addition to macroscopically normal tissue, introduced the use of PCR in modern necropsy research to detect Mtb DNA in various cell types in the spleen, lung, kidney, liver, and adipose tissue (6). Real-time PCR assays are beneficial in the diagnosis of extrapulmonary TB, especially for cases, such as abdominal, meningitis, or osteoarticular TB, in which culture and smear tests are primarily negative (32). In-house PCR may serve to detect extrapulmonary TB in body fluid samples, demonstrating a sensitivity of 61% and specificity of 75% compared to various reference standards, including culture, histopathology, and acid-fast bacilli staining; however, detection in tissue is not as effective using this method due to the formalin or fixative within tissue samples (12).

Types of real-time PCR assays that have been used for extrapulmonary TB detection include the COBAS Taqman MTB (Roche Diagnostics), the Abbott Real Time MTB assay, the Xpert MTB/RIF (Cepheid), or Taqman assays created within laboratories (32). COBAS Taqman MTB (Roche Diagnostics), the Xpert MTB/RIF (Cepheid), or Taqman assays created within laboratories target 16S or IS6110 rRNA gene sequences (32). The Xpert MTB/RIF can identify rifampin (RIF) resistance caused by rpoB gene mutation, and is recommended by the WHO for rapid diagnosis of pulmonary and extrapulmonary TB (5, 11). This assay has been beneficial for the detection of pulmonary TB, however, the low bacillary load impacts assay sensitivity for extrapulmonary samples (11). Due to these limitations, the Xpert MTB/RIF Ultra (GX-Ultra; Cepheid) assay was developed and demonstrates greater sensitivity in detecting Mtb complex DNA when low bacillary loads are present (11). This assay differs from its predecessor in that there are 2 multicopy targets (IS1081 and IS6110 insertion sequences) and total capacity of 50 microliters, compared to 25 microliters (11). The Abott Real Time MTB assay identifies 8 Mtb complex species, including *M. tuberculosis*, *M. bovis, M. africanum, M. bovis BCG, M. canetti, M. caprae, M. pinnipedii*, and *M. microti*, through "amplification of both the insertion sequence !S6110 and the protein antigen B (PAB) gene" (32). The manufacturer for the Abbott Real Time MTB assay characterizes positive specimens by PCR cycle thresholds equal to or less than 40 (32).

Araújo et al. published a study in which a nested-PCR system was used to detect Mtb complex directly from bovine tissue homogenates from lesions of infected cattle. Though the authors noted that "one of the problems with detecting *M. tuberculosis* complex directly from lesions that are compatible with tuberculosis is that tissues generally exhibit strong fibrosis and calcification, which decrease the access to the mycobacterial DNA," clinical specificity of 100% and clinical sensitivity of 76.7% was achieved. In addition to culture samples obtained from cattle, the DNA from 170 sputum samples from humans with *M. tuberculosis* were isolated. For the 170 human samples, 100% were positive using the nested PCR for Mtb complex. The nested-PCR system involved a first-step of conventional PCR followed by a second-step of real-time PCR, and resulted in a higher sensitivity than real-time or conventional PCR alone. The authors concluded that their method provided rapid detection of Mtb in tissue samples, but large-scale validation was lacking. (33)

Borras et al. (2020) performed a retrospective study to evaluate the performance of culture, AFB-smear microscopy, and Mtb complex PCR in extrapulmonary samples for cases of suspected TB. There were 566 samples evaluated, of which 278 were sterile fluids, 147 were non-sterile fluids, 44 were lymph node samples collected after surgery, 25 were fine needle aspiration, 63 were non-lymph node tissue biopsies (35 skin, 6 pleural, 3 mediastinal, 2 intervertebral disc, 4 bone, 9 colonic, 1 liver, 1 supraclavicular, 2 synovial), and 9 were abscess aspirates. PCR was performed using the Abbott Real Time MTB assay. Samples were processed within 24 hours after being collected. Auramine-thiazine red staining using non-concentrated samples was used for AFB-smear microscopy. All samples were "digested and decontaminated with 2% N-acetyl-l-cysteine-sodium hydroxide, neutralized with phosphate buffer (67 mM; pH 6.8), followed by centrifugation at 3000 × g for 20 min." Tissue specimen and specimens obtained from biopsies were minced and disaggregated before decontamination. Then (32):

> *Sediments were resuspended in approximately 3 ml of phosphate buffer irrespective of the quantity of original specimens available for the analyses and used for inoculation onto Löwenstein-Jensen (LJ) slant tubes (0.5 ml) and Bactec MGIT 960 vials (0.2 ml) (Becton, Dickinson and Sparks, MD, USA), which were then incubated at 37□C for 3months and 8 weeks with continuous monitoring, respectively.*

Positive and negative PCR results from Borras et al. (2020) for lymph nodes, tissue biopsy, and abscess aspirates can be found in **Table 8-2**; positive and negative PCR results for sterile and non-sterile fluids can be found in **Table 8-3**. Borras et al. (2020) reported 25 confirmed cases of extrapulmonary TB: 11 samples from 11 patients (1 urine; 4 pleural fluids; 1 gastric aspirate; 3 non-lymph node tissue biopsies with a positive result for pleural, colonic, and supraclavicular; and 2 lymph node samples collected following surgery) demonstrated positive results for Mtb complex (10 included *Mycobacterium tuberculosis* and 1 included Mycobacterium bovis) through PCR and culture; 6 samples from 6 patients (2 gastric fluid, 2 urine, 1 pleural fluid, and 1 muscle abscess) demonstrated positive results for Mtb complex (5 included *Mycobacterium tuberculosis* and 1 Mycobacterium bovis) through culture, but not PCR; 11 samples from 8 patients (2 pleural fluid, 4 lymph node samples from fine needle aspiration, 2 lymph node samples following surgery, 2 cerebrospinal fluid, and 1 gastric aspirate) demonstrated positive results for Mtb complex through PCR, but not culture, and 1 (cerebrospinal fluid) was determined to be a false negative. There were 534 samples that tested negative for Mtb through PCR, culture, and AFB microscopy. Non-tuberculous Mycobacteria was isolated from 4 samples—2 Mycobacterium chimera, 1 Mycobacterium gordonae, and 1 Mycobacterium celatum—and demonstrated negative results through PCR. There were 2 samples from 2 patients that demonstrated positive results through AFB-smear microscopy, PCR, and culture. There was moderate agreement (96%; Cohen's k: 0.549; p = 0.0001) between PCR and culture. The Abbott PCR assay demonstrated a 77.7% sensitivity, 99.5% specificity, 95.4% PPV, and 98.8% NPV, whereas the mycobacterial culture demonstrated a 62.9% sensitivity, 100% specificity, 100% PPV, and 97.9% NPV. Based on sample type, the PCR assay demonstrated sensitivities of 88% for sterile fluids (primarily

pleural exudates), 42% for non-sterile fluids, and 100% for lymph nodes, whereas culture demonstrated sensitivities of 44% for sterile fluids (primarily pleural exudates), 85% for non-sterile fluids, and 25% for lymph nodes. The authors concluded, within the limitations of the study, that the Abbott PCR assay may be a feasible diagnostic option in the diagnosis of extrapulmonary TB in low-prevalence populations. (32)

Table 8-2. Borras et al. (2020) PCR Results for Lymph Nodes, Tissue Biopsy, and Abscess Aspirates Specimen (32)

Specimen type	No. of specimens	Positive *Mycobacterium tuberculosis* complex culture result		Negative *Mycobacterium tuberculosis* complex culture result	
		Positive PCR	Negative PCR	Positive PCR	Negative PCR
Lymph nodes	69	2	0	6	61
Open biopsy	44	2	0	2	40
Puncture (fine needle biopsy)	25	0	0	4	21
Tissue biopsy	63	3	0	0	60
Skin	35	1	0	0	34
Pleural	6	0	0	0	6
Mediastinal	3	0	0	0	3
Intervertebral disc	2	0	0	0	2
Bone	4	0	0	0	4
Colonic	9	1	0	0	8
Liver	1	0	0	0	1
Supraclavicular	1	1	0	0	0
Synovial	2	0	0	0	2
Abscess aspirates	9	0	1	0	8
Liver	2	0	0	0	2
Bone	3	0	0	0	3
Muscle	2	0	1	0	1
Brain	2	0	0	0	2

Table 8-3 Borras et al. (2020) PCR Results for Sterile and Non-sterile Fluid Specimen (32)

Specimen type	No. of specimens	Positive *Mycobacterium tuberculosis* complex culture result		Negative *Mycobacterium tuberculosis* complex culture result	
		Positive PCR	Negative PCR	Positive PCR	Negative PCR
Sterile fluids	278	4	1	4	269
Pleural	131	4	1	2	125
Bone marrow	38	0	0	0	38
Cerebrospinal	66	0	0	2	65
Peritoneal	14	0	0	0	14
Sinovial	16	0	0	0	16
Pericardial	11	0	0	0	11
Blood	3	0	0	0	3
Non-sterile fluids	147	2	4	1	140
Urine	123	1	2	0	120
Gastric aspirate	23	1	2	1	19
Seminal	1	0	0	0	1

One study evaluated GX-Ultra's ability to detect Mtb compex in smear-negative extrapulmonary TB samples. There were 168 smear-negative extrapulmonary samples obtained from 148 patients that were processed using smear microscopy and mycobacterial cultures (in liquid and solid media) at the time of collection. Detection of mycobacteria was

performed with the Genotype Mycobacterium CM/MTBC (Hain Lifescience, Nehren, Germany), BIO-LINE SD Ag MPT64 TB test (Standard Diagnostics, Yongin, South Korea), and DNA AccuProbe (Gen-Probe Inc., San Diego, CA). Of the 168 samples, 108 tested positive for Mtb complex through culture, including 3 Mycobacterium bovis bacillus Calmette-Guérin. An additional 60 clinical samples were included to evaluate assay specificity, of which 40 were negative through culture and 20 were positive through culture, with the latter including 18 various species of Mtb. Testing results from GX-Ultra found that there was DNA for Mtb complex identified in 82 smear-negative extrapulmonary TB samples that were Mtb complex positive, demonstrating a sensitivity of 75.9% (95% CI, range: 66.6 – 83.4%). When assessing assay results with respect to bacillary load ("the time to positivity of cultures in days for extrapulmonary samples in liquid media"), there were 15, 19, 29, and 19 positive results for medium, low, very low, and trace, respectively. There were significant differences observed when trace samples were compared to medium ($p = 0.003$) and low ($p=0.04$) categories, "and when comparing the samples in the not-detected category with those in the medium category ($P = 0.005$)." There were 2 samples containing mutations associated to RIF resistance and demonstrated resistance to multiple drugs. For the additional 60 clinical samples used to evaluate the assay, GX-Ultra demonstrated a 100% specificity. The effect of duration of freezing samples was evaluated, with results indicating that GX-Ultra yielded positive results for 16 samples (80%) of those stored from 2013 to 2017, 6 samples (85.7%) of those stored from 2008 to 2012, 36 samples (75%) of those stored from 2003 to 2007, and 24 samples (72.7%) or those stored from 1999 to 2002; there were no significant differences in positivity rates observed between groups ($p>0.05$). GX-Ultra demonstrated the following sensitivities for each sample type: "94.1% in lymph nodes, 93.7% in nonsterile fluids, 86.6% in tissue specimens, 80% in stool material, 64.7% in abscess aspirates, and 60.5% in sterile fluids." There was 100% specificity observed for all clinical sample categories evaluated. Sensitivity and specificity based on various sub-types of the clinical sample categories can be found in **Error! Reference source not found.** below, excerpted from Risco et al. (2018). The authors concluded that GX-Ultra demonstrated high rates of specificity and sensitivity in the identification of Mtb DNA in smear-negative extrapulmonary samples, which are not advantageous in detecting Mtb when there is low bacillary load; thus, this test may be beneficial in the rapid diagnosis of extrapulmonary TB. (11)

Table 8-4 Perez-Risco et al. (2018) GX-Ulta Ultra Clinical Sample Sensitivity and Specificity Rates

Clinical sample	Total no. of samples	Samples MTUBC culture positive		Sensitivity (%)	Samples MTUBC culture negative		Specificity (%)
		GXU+[a]	GXU−[b]		GXU+	GXU−	
Sterile fluids	44			60.5			100
Pleural fluid	24	10	11	47.6	0	3	
Cerebrospinal fluid	4	3	0	100	0	1	
Joint fluid	9	7	1	87.5	0	1	
Ascitic fluid	3	1	2	33.3	0	0	
Pericardial fluid	4	2	1	66.6	0	1	
Nonsterile fluids	29			93.7			100
Gastric aspirate	5	3	1	75	0	1	
Urine	24	12	0	100	0	12	
Lymph nodes	25	16	1	94.1	0	8	100
Abscess aspirates	20			64.7			100
Cervical abscess	6	4	1	80	0	1	
Skin abscess	6	2	2	50	0	2	
Paravertebral abscess	3	2	1	66.6	0	0	
Osteitis pus	5	3	2	60	0	0	
Tissues	24			86.6			100
Skin biopsy	8	2	0	100	0	6	
Intervertebral disc biopsy	2	2	0	100	0	0	
Bone biopsy	4	2	0	100	0	2	
Pleural biopsy	2	2	0	100	0	0	
Rectal biopsy	1	0	1	0	0	0	
Costal cartilage biopsy	1	1	0	100	0	0	
Liver biopsy	1	1	0	100	0	0	
Cervical tissue	1	1	0	100	0	0	
Mediastinal tissue	1	0	1	0	0	0	
Synovial tissue	3	2	0	100	0	1	
Joint biopsy	18	0	0		0	18	
Stool	8	4	1	80	0	3	100
Total	168	82	26	75.9	0	60	100

[a]GXU+, positive results from GeneXpert MTB/RIF Ultra.
[b]GXU−, negative results from GeneXpert MTB/RIF Ultra.

BD ProbeTec ET is a semi-automated real-time molecular assay that amplifies specific Mtb DNA using particular primers and probes that are tagged using fluorescence. Somily et al. (2017) performed a prospective study to evaluate the ability of BD ProbeTec ET, microscopy, and culture to detect Mtb complex in 266 samples (118 respiratory and 148 non-respiratory samples, of which 49 samples were obtained from differing tissues and 99 were obtained from sterile body fluid sites) from individuals with TB. For BD ProbeTec ET, the metric other than acceleration (MOTA) values and Internal Amplification Control (IAC) was used to determine presence of Mtb complex DNA: MOTA values greater than 3,400 indicated positive results; MOTA and IAC values less than 3,400 and more than 5,000, respectively, indicated negative results; and MOTA and IAC values less than 3,400 and 5,000, respectively, were read as sample inhibition. Confirmation of TB diagnosis using BD ProbeTec ET occurred in 3-4 hours, which was substantially shorter in duration compared to culture, which typically takes 6-8 weeks. Results found that of the 266 samples, 88 (33%) were positive through culture, of which 39 (of 118) were respiratory samples, 29 (of 99) were sterile fluid body site samples, and 20 (of 49) were tissue samples. Of the culture-positive samples, DBT detected Mtb complex in 38 of 39 respiratory samples, 20 of 29 fluid samples, and 5 of 20 tissue

samples (total detection in 63 of 88 samples). Of the culture-negative samples, DBT detected Mtb complex in 3 of 79 respiratory samples, 5 of 70 fluid samples, and 3 of 29 tissue samples (total detection in 11 of 178 samples). DTB sensitivity, specificity, PPV, and NPV in respiratory samples was 97%, 96%, 93%, and 99%, respectively; in fluid samples, sensitivity, specificity, PPV, and NPV was 80%, 88%, 69%, and 93%, respectively; in tissue samples, sensitivity, specificity, PPV, and NPV was 25%, 90%, 63%, and 63%, respectively. Of the 88 culture-positive samples, there were 50 positive results through AFB smear microscopy, of which 33 were respiratory samples, 15 were fluid samples, and 2 were tissue samples. DTB sensitivity among AFB smear-positive samples was 100% in respiratory samples, 85.7% in fluid samples, and 100% in tissue samples; among AFB-smear-negative samples, DTB sensitivity was 86% in respiratory samples, 53% in fluid samples, and 16.6% in tissue samples. The authors noted that DTB performance was greater than culture performance for Mtb complex rapid detection in respiratory samples, however, DTB performance did not compare to culture in extra-pulmonary samples, particularly tissue. (30)

Anyanwu et al. (1976) reported 7 cases of miliary TB and subsequent death in majority of the cases following the performance of homograft valve replacements in the five years following August 1969. Miliary TB was detected in one case through post-mortem histological examination that discovered acid-fast bacilli in spleen, lungs, liver, suprarenals, and kidneys; blood cultures prior to death were incubated, centrifuged, and injected into guinea pigs following the patient's death, with Mtb detected in the animals' spleens. In the second case, there were suspicions of TB based on chest radiograph performed prior to the patient's death; following death, histological examination of the lungs and homograft valve demonstrated acid-fast bacilli, and a spleen culture grew Mtb. A third case demonstrated acid-fast bacilli in a post-mortem histological examination of the liver and homograft valve, and a blood culture acquired prior to death was evaluated post-mortem, demonstrating Mtb growth. A fifth case demonstrated TB through a biopsy and culture of the left lung obtained while the patient was living; following death, acid-fast bacilli was detected in the brain and lymph nodes, and a blood and urine culture obtained prior to death was examined post-mortem, demonstrating Mtb and tubercle bacilli. TB was suspected in a sixth case following the performance of a radiograph, which prompted a lung biopsy and culture that grew Mtb; this patient underwent treatment and remained in satisfactory condition. Mtb was detected in seventh case through a urine culture; this patient underwent treatment and remained in satisfactory condition. (26)

9. CONCLUSIONS

TB is a global health issue, with significant morbidity and mortality. Identified risk factors for active pulmonary and extrapulmonary TB included previous residence or birth in regions with greater TB rates; older age; close contact with TB; history of TB confirmed through interferon-gamma assay or TST; chest imaging indicative of active TB; substance use with

injections; previous employment in institutional settings with greater TB rates; homelessness; correctional facility residence; being a transplant recipient; being immunocompromised, including HIV positivity; undergoing hemodialysis; severe CKD, and ESRD.

Literature findings demonstrated that the transmission of TB through human tissue was uncommon, but clearly possible. There were 12 proven cases of TB transmission to recipients through donor tissue identified in 3 publications. Two publications, one published in 1981 and one published in 1976, reported a total of 8 cases of miliary TB following heart valve allografts. One publication, published in 1953, reported 4 cases of TB transmitted through bone, however, the clinical knowledge and processes may be outdated and not reflect current practices. Particular tissue types have the potential to transmit Mtb to recipients from donors, but most transmissions are documented from organ transplants (34). However, the unintended transmission of disease from a donor to recipient in organ transplants is estimated to be under 1% for all transplants (10).

The identification of TB source (donor or latent infection) in recipients may be challenging. Diagnostic tests reported in the literature for TB testing of the living (exclusively) included TST and chest x-ray, while diagnostic tests reported in the literature for TB testing in living and deceased subjects, including organ transplant and tissue donors, included AFB microscopy and culture, PCR, NAAT, IGRA, and in vitro quantitation of PPD-specific T cells. TB diagnostic tests reported for use in the literature for organ transplant donors included IGRA (Quantiferon-TB Gold and T-SPOT.TB IGRAs reported as feasible in a consensus report), while all other tests used tissue samples or did not specify.

TST, which may be performed in living subjects (including living organ transplant donors), demonstrates low specificity for those with bacillus Calmette-Guerin (BCG) vaccinations and those who are immunocompromised and at high risk for TB (14, 24). Whole blood assays may be utilized on deceased organ transplant donors, however, antigens and T cells must be assessed as functional prior to assay performance. IGRAs, which may be used to detect TB in the living or deceased (although there is limited evidence for the latter), do not demonstrate decreased specificity for those with BCG vaccinations and use "highly specific antigens derived from *Mycobacterium tuberculosis*, which are absent in all strains of Bacillus Calmette-Guerin (BCG) and most environmental mycobacteria" (24). The testing method of in vitro quantitation of PPD-specific T cells using whole blood was performed on a specific immunocompromised population (those undergoing hemodialysis), and suggested as a potential alternative to the latent TB test of TST. Culture is considered the gold standard for TB diagnosis, but PCR is a rapid and sensitive method to detect Mtb in individuals without systemic manifestations of TB, and is a preferred testing method for rapid identification of Mtb in tissue samples (12, 30). PCR assay was suggested as feasible diagnostic option in the diagnosis of extrapulmonary TB in low-prevalence populations, demonstrating greater or comparable sensitivity and specificity compared to AFB-smear microscopy and culture. It is recommended that deceased organ transplant donors that demonstrate abnormal chest

radiographs should have AFB smears and cultures obtained and processed using NAAT (17), but the literature demonstrated that PCR has also been employed for TB testing on tissue samples obtained from living patients. Other studies employed molecular testing techniques for the direct detection of tuberculosis in tissue, demonstrating similar results for extrapulmonary TB testing. GX-Ultra demonstrated high rates of specificity and sensitivity in the identification of Mtb DNA in smear-negative extrapulmonary samples. BD ProbeTec ET demonstrated greater performance than culture for Mtb complex in respiratory samples, but not culture in extrapulmonary samples, particularly tissue.

10. BIBLIOGRAPHY

1. Khanna S, Ross J, Monro J. Homograft aortic valve replacement: seven years' experience with antibiotic-treated valves. Thorax. 1981;36(5):330-7.
2. James JI. Tuberculosis transmitted by banked bone. The Journal of bone and joint surgery British volume. 1953;35 B(4):578.
3. Malinis M, LaHoz R, Vece G, Tlusty S, Aslam S, Bag R, et al., editors. Donor Derived Tuberculosis in Solid Organ Transplantation in the United States: 10 Years of UNOS Ad Hoc Disease Transmission Advisory Committee Experience. AMERICAN JOURNAL OF TRANSPLANTATION; 2019: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
4. Qian X, Nguyen DT, Lyu J, Albers AE, Bi X, Graviss EA. Risk factors for extrapulmonary dissemination of tuberculosis and associated mortality during treatment for extrapulmonary tuberculosis article. Emerging Microbes and Infections. 2018;7(1).
5. American Public Health Association. Control of Communicable Diseases Manual. 20th ed. Heymann DL, editor: APHA Press; 2015.
6. Mayito J, Andia I, Belay M, Jolliffe DA, Kateete DP, Reece ST, et al. Anatomic and cellular niches for mycobacterium tuberculosis in latent tuberculosis infection. Journal of Infectious Diseases. 2019;219(5):685-94.
7. Gupta RK, Calderwood CJ, Yavlinsky A, Krutikov M, Quartagno M, Aichelburg MC, et al. Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings. Nature Medicine. 2020;26(12):1941-9.
8. Mamishi S, Pourakbari B, Moradzadeh M, van Leeuwen WB, Mahmoudi S. Prevalence of active tuberculosis infection in transplant recipients: A systematic review and meta-analysis. Microbial Pathogenesis. 2020;139.
9. Wu X, Liu J, Wang G, Wu F. Bone and joint tuberculosis in patients undergoing dialysis: clinical features, risk factors, and outcomes in 17 patients. Journal of International Medical Research. 2020;48(8).
10. Abad CLR, Razonable RR. Donor derived Mycobacterium tuberculosis infection after solid-organ transplantation: A comprehensive review. Transplant infectious disease : an official journal of the Transplantation Society. 2018;20(5):e12971.
11. Perez-Risco D, Rodriguez-Temporal D, Valledor-Sanchez I, Alcaide F. Evaluation of the Xpert MTB/RIF Ultra Assay for Direct Detection of Mycobacterium tuberculosis Complex in Smear-Negative Extrapulmonary Samples. J Clin Microbiol. 2018;56(9).
12. Catedral EJ, Santos RE, Padilla MD, Fajardo-Ang C. Detection of Mycobacterium tuberculosis in corneas from donors with active tuberculosis disease through polymerase chain reaction and culture. The British journal of ophthalmology. 2010;94(7):894-7.
13. Jackson S, Kabir Z, Comiskey C. Effects of migration on tuberculosis epidemiological indicators in low and medium tuberculosis incidence countries: A systematic review. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021;23.
14. Sester M, Sester U, Clauer P, Heine G, Mack U, Moll T, et al. Tuberculin skin testing underestimates a high prevalence of latent tuberculosis infection in hemodialysis patients. Kidney International. 2004;65(5):1826-34.
15. Shu CC, Wu VC, Yang FJ, Pan SC, Lai TS, Wang JY, et al. Predictors and prevalence of latent tuberculosis infection in patients receiving long-term hemodialysis and peritoneal dialysis. PLoS ONE. 2012;7(8).

16. Jones JM, Vikram HR, Lauzardo M, Hill A, Jones J, Haley C, et al. Tuberculosis transmission across three states: The story of a solid organ donor born in an endemic country, 2018. Transplant Infectious Disease. 2020;22(6).
17. Morris M, Daly J, Blumberg E, Kumar D, Sester M, Schluger N, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. Wiley Online Library; 2012.
18. Ison M, Nalesnik M. An update on donor-derived disease transmission in organ transplantation. American Journal of Transplantation. 2011;11(6):1123-30.
19. LoBue NDGaPA. Chapter 4: Travel-Related Infectious Diseases: Centers for Disease Control and Prevention; 2019 [Available from: https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/tuberculosis.
20. Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: A systematic review and meta-analysis. European Respiratory Journal. 2019;54(3).
21. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era: Summary: World Health Organization,; n.d. [Available from: https://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020summary.pdf?ua=1#:~:text=The%2030%20TB%20HBCs%20(those,%2C%20Russian%20Federation%2C%20Sierra%20Leone%2C.
22. Shu CC, Hsu CL, Lee CY, Wang JY, Wu VC, Yang FJ, et al. Comparison of the prevalence of latent tuberculosis infection among non-dialysis patients with severe chronic kidney disease, patients receiving dialysis, and the dialysis-unit staff a cross-sectional study. PLoS ONE. 2015;10(4).
23. Organization WH. WHO consolidated guidelines on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Web annex A: methods and expert panels. 2021.
24. Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, et al. Latent Tuberculosis Infection Screening in Immigrants to Low-Incidence Countries: A Meta-Analysis. Molecular Diagnosis and Therapy. 2015.
25. Warwick RM, Magee JG, Leeming JP, Graham JC, Hannan MM, Chadwick M, et al. Mycobacteria and allograft heart valve banking: an international survey. Journal of Hospital Infection. 2008;68(3):255-61.
26. Anyanwu C, Nassau E, Yacoub M. Miliary tuberculosis following homograft valve replacement. Thorax. 1976;31(1):101-6.
27. Edathodu J, Alrajhi A, Halim M, Althawadi S. Multi-recipient donor-transmitted tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(11):1493-5.
28. Rahimifard N, Mahmoudi S, Mamishi S, Pourakbari B. Prevalence of latent tuberculosis infection in transplant candidates: A systematic review and meta-analysis. Microbial Pathogenesis. 2018;125:401-10.
29. Shingde R, Habachou LI, Calisa V, Craig JC, Tong A, Chen SC, et al. Unexpected donor-derived infectious transmissions by kidney transplantation: A systematic review. Transplant infectious disease : an official journal of the Transplantation Society. 2018;20(2):e12851.
30. Somily AM, Habib HA, Sarwar MS, Al-Beeshi NZ, Alohali RM, Shakoor ZA. Performance of the BD ProbeTec ET direct detection assay for the analysis of Mycobacterium tuberculosis in respiratory and non-respiratory clinical specimens. Journal of Taibah University Medical Sciences. 2017;12(4):364-8.
31. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases. 2017;64(2):e1-e33.

32. Borrás R, Martínez V, Vinuesa V, Torres I, Orta N, Clari M, et al. Field performance of the Abbott RealTime MTB assay for the diagnosis of extrapulmonary tuberculosis in a low-prevalence setting. Enfermedades infecciosas y microbiologia clinica (English ed). 2020;38(5):206-11.
33. Araújo CP, Osório AL, Jorge KS, Ramos CA, Souza Filho AF, Vidal CE, et al. Direct detection of Mycobacterium tuberculosis complex in bovine and bubaline tissues through nested-PCR. Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology]. 2014;45(2):633-40.
34. Eastlund TED, Strong DM. Infectious disease transmission through tissue transplantation. 2004. p. 51-131.

11. APPENDIX A: LITERATURE SEARCH METHODOLOGY

Three references included in a preliminary literature review by the AATB Physicians Council Panel on Mtb were included in this report (1, 26, 34).

Nerac performed searches to identify additional pertinent references using the following keywords:

Topic	Keywords
History of Mtb transmission through human tissue and organ transplant, including corneal:	tuberculosis; transmission; tissue, organ, sperm, egg, oocyte, placenta, embryo, bone, "heart valve", ligament, tendon, musculoskeletal, nerve, skin, vein, artery, cornea, corneal, lung, kidney, heart,
Incidence, prevalence, and risk factors for TB and extrapulmonary TB, including the risks of unrecognized TB among individuals who are immunosuppressed and/or undergoing chronic hemodialysis):	tuberculosis; prevalence, incidence, "risk factors"; "systematic review", "meta-analysis" - limits applied (title, previous 10 years) tuberculosis; prevalence, incidence, "risk factors"; immunosuppressed, hemodialysis - limits applied (title/abstract) "extrapulmonary tuberculosis"; prevalence, incidence, "risk factors" - limits applied (title)
Detection of TB infection with a focus on direct detection of TB in tissue:	tuberculosis; 'direct detection'; tissue

Resources included Embase, PubMed, and Google Scholar.

The above Nerac searches resulted in the identification and selection of 23 additional references for review and inclusion. Additionally, a relevant textbook (5), 2 manually-selected guideline publications (23, 31), 2 other AATB-requested publications (17, 18), and 2 online resources (19, 21) were reviewed and included by Nerac to provide additional information.

12. APPENDIX B: NOTIFY LIBRARY SEARCH RESULTS

Table 12-1 NOTIFY Library Search Results: Mycobacterium Tuberculosis Infection

Record number	MPHO type	Time to detection	Alerting signal, symptoms, evidence of occurrence	Estimated frequency	Demonstration of imputability	Imputability grade	References
Tissue Products							
21	Tissues => Musculoskeletal => Bone	2 weeks - 6 months	Four cases of tuberculosis (TB) transmitted by use of frozen rib allografts in scoliosis surgery. Ribs obtained from patients with active tuberculosis (TB) during thoracoplasty. Ribs stored frozen in penicillin and streptomycin. Case 1: 2 weeks-wound dehiscence, 4 months: fever, pleurisy, tuberculous lymphadenopathy, disseminated tuberculosis (TB); Case 2: "weeks" later wound sinus drainage. 4 months: caseous tuberculosis (TB) wound infection; Case 3: chronic wound drainage since surgery, at 10 weeks enlarged nodes and wound grew tuberculosis (TB); Case 4: at 3 months, chronic wound drainage with sinus. At 6 months, tuberculosis (TB) found in non-healed wound, bone non-union. No systemic symptoms.	Only 4 cases observed despite many cases using bone from same type of donor in past year.	Certain. Ribs removed at thoracoplasty for pulmonary tuberculosis and stored in bone banks. Recipients developed localised TB, demonstrated by positive smear, culture and histology of axillary lymphonode and caseous material.	3 Definite/ Certain/ Proven	James, J.I. Tuberculosis transmitted by banked bone. J Bone Joint Surg Br. 1953; 35-B(4):578

439	Tissues => Cardiovascular => Heart valves	8 months	Fever; rigors; headache; pleural effusion; hepatosplenomegaly; anorexia; systolic murmur; heart failure; pneumonia	N/A	The majority of the valves came from donors having Coroners' post mortems with a high incidence of TB (Crompton (1974 personal communication in Anyanwu) with 0.2-0.3% of Coroners cases estimated to have had TB. One case attributed to donor valve cold abscess.	Not reported	Anyanwu, C.H.; Nassau, E.; Yacoub, M. Miliary tuberculosis following homograft valve replacement. Thorax. 1976; 31(1):101 – 6 Khanna, S.K.; Ross, J.K.; Monro, J.L. Homograft aortic valve replacement: seven years; experience with antibiotic-treated valves. Thorax. 1981; 36(5):330 - 7
Organs							
1934	Organs => Multiple types or not specified	The time to detection of MTb depended on the type of infection, with reactivation representing the most common form followed by donor-derived transmission. With reactivation, the median time to clinical presentation	In terms of the type of MTB manifestation, pulmonary MTB was the most common presentation (54.2%) followed by extrapulmonary MTB (29.84%) and disseminated MTB (15.96%) The most common presenting symptom was fever (86%). In terms of organ specific data: 1. Kidney recipients - pulmonary MTB most common (53.94%) compared to 32.06% with extrapulmonary MTB (the urinary tract was most	The frequency given here relates to cases of Mycobacterium tuberculosum in organ transplant recipients as a whole and is not specific to donor-derived transmissions. The most common cause of post-organ transplant Mycobacterium tuberculosis	All cases were based on positive cultures or PCR of body fluid or tissue specimens, or if acid-fast bacilli or caseating granulomas were seen in the presence of compatible clinical presentation. In the cases of donor-derived MTB, cases were based on identical isolates of the donor and recipient (proven), probable if they	Not Assessable	Abad, C.L.R.; Razonable, R.R. Mycobacterium tuberculosis after solid organ transplantation : A review of more than 2000 cases. 2018; 32(6):e13259

		for pulmonary MTB was 22.5 months based on cohort data. However, when case reports were compiled, the median time to presentation was 17.5 months. The onset of MTB occurred beyond the first year post-transplant overall (41%), but 40% occurred within 12 months post-transplant. Organ breakdown: 1. In kidney recipients, the time to clinical presentation for pulmonary TB was 33 months, 28.5 months with extrapulmonary TB and 18 months with disseminated MTB. 2. In liver recipients - presentation of pulmonary MTB at 4	common - 23.45%) and 14% with disseminated TB. 1/3 of patients with disseminated MTB had lung involvement. 2. Liver recipients - pulmonary MTB and extrapulmonary MTB were equivalent (36.51%, central nervous system involvement was most common at 29.17% followed by liver allograft) and disseminated MTB at 26.91%, pulmonary involvement most common at 82.35% followed by liver allograft 47%, other sites included CNS, lymph node, pleura, genitourinary, peritoneum, skin, bone marrow, spine and axilla). 3. Heart transplant recipients - limited data available (only 22 of 77 heart recipients), Fever was reported in 60% of cases with lung involvement in all but one case of disseminated MTB. Abnormal chest x-rays were found in 9 patients with pulmonary and disseminated MTB. Of note, one patient with pulmonary TB had a negative chest-ray. 4. Lung transplant recipients - pulmonary MTB was the most common presentation (78.95%), two cases with disseminated MTB presented with lung involvement, then two cases of extrapulmonary, one with	infection is reactivation. Of the 2,082 cases reported between 1998-2016, 82.56% were kidney recipients, 12.15% were liver recipients and only 77 heart, 25 lung and 8 kidney-pancreas recipients. The overall incidence of TB among organ transplant recipients was 2.37% which is several fold higher than the general population. Of interest, extrapulmonary TB occurred in 29.84% of cases while disseminated MTB was seen in 15.96%, while multidrug resistant MTB was rare. In terms of individual organ transplants, the incidence of MTB in kidney transplant recipients was 1.69%, liver transplant recipients 1.33%, heart recipients	shared the same clinical and epidemiological features or possible if only epidemiological criteria were met.		

		months, extrapulmonary TB at 9 months (most commonly central nervous system) and disseminated MTB at 48 months. The median time to pulmonary MTB was 8 months, extrapulmonary TB was 18 months and disseminated MTB was 23 months. 3. In heart recipients - presentation of pulmonary MTB was 54.44% followed by disseminated disease (27.7%) and extrapulmonary disease (18.18%). 4. In lung recipients - disseminated MTB presented at 53 months while pulmonary MTB presented at 3 months, no data available	a cardiac abscess and one with a lymph node. Fever present in 50% of cases, and most patients had abnormal chest-rays.	1.46%, kidney-pancreas recipients 1.25% and lung recipients 0.96%. The highest TB incidences were reported from Asia and Europe, followed by the United States.			

		for extrapulmonary MTB. The median time for identification of donor-derived transmission was 3 months post-transplant (range 0.2 - 29 months).					
1807	Organs => Lung	Three months	Donor: Organ donor. The adult organ donor was admitted to hospital following a motor vehicle crash. A chest computed tomography (CT) scan on admission revealed diffuse nodular infiltrates consistent with pulmonary contusions, but also raised suspicion for TB. A TST was negative and IGRA was indeterminate. Endotracheal aspirate and bronchoalveolar lavage were negative for acid-fast bacilli (AFB) by smear and culture. NAAT was not performed. The donor had immigrated to the United States approximately 8 years earlier and had been incarcerated several times; he had a positive TST 2 years before death but had never received a diagnosis of TB disease. Bilateral lung recipient: the recipient developed a persistent cough and fatigue 3 months post transplant.	The frequency of donor derived Mycobacterium tuberculosis infection associated with history of Latent Mycobacterium Tuberculosis Infection (LTBI) in the absence of known active TB is unknown; the rate of transmission from a donor with active MTB infection is thought to be around 30%; In this report, there were four recipients (lungs, heart, liver, kidneys), with one transmission (bilateral lung recipient).	The organ donor was epidemiologically linked after death to an ongoing TB outbreak in the community, with the infecting strains being all of of the same genotype. Spoligotyping (a polymerase chain reaction [PCR]–based method) and analysis of 24-locus variable-number tandem repeat of mycobacterial interspersed repetitive units (VNTR-MIRU) (a PCR method that analyses specific regions of the genome) were performed, with matching profiles. Subsequent whole-genome sequencing and phylogenetic analysis also confirmed genetic relatedness of the	2 Probable	Santoro-Lopes, G.; Subramanian, A.K.; Molina, I.; Aguado, J.M.; Rabagliatti, R.; Len, O. Tuberculosis Recommendations for Solid Organ Transplant Recipients and Donors. 2018; (2S Suppl 2). Kay, A.; Barry, P.M.; Annambhotla, P.; Greene, C.; Cilnis, M.; Chin-Hong, P.; Arger, N.; McNitt, L.; Neidlinger, N.; Shah, N.; Basavaraju, S.V.; Kuehnert, M.; Shaw, T. Solid Organ Transplant-Transmitted

			Chest CT revealed bilateral pleural and pericardial effusions. Cultures from effusions and sputum yielded M. tuberculosis. The US born recipient had minimal foreign travel and no epidemiologic links to other TB cases. Pre-transplant TST and IGRA were negative. Initially, the recipient's TB was thought not to be donor-derived because of the organ donor's negative pre donation TB evaluation. The recipient responded well to TB treatment. Three other recipients of 2 kidneys, liver and heart did not develop MTB infection.		strains, which were very uncommonly seen in the USA.		Tuberculosis Linked to a Community Outbreak - California, 2015. 2017; 66(30):1 Subramanian, A.K.; Morris, M.I.; Practice, A.S.T. Infectious Mycobacterium tuberculosis infections in solid organ transplantation . 2013; 13 Suppl 4:8 Ruijter, B.N.; van Wijngaarden, A.K.S.; van Hoek, B.; Mensen, M.; van Soolingen, D.; Arend, S.M. Donor-derived tuberculosis via orthotopic liver transplantation . 2017; 75(9):5 Hernández-Hernández, E.; Alberú, J.; González-Michaca, L.; del Valle, B.; Quiroz-Mejía,

							R.A.; Baizabal-Olarte, R.; Correa-Rotter, R.; Sifuentes-Osornio, J. Screening for tuberculosis in the study of the living renal donor in a developing country. 2006; 81(2) Aguado, J.M.; Torre-Cisneros, J.; Fortún, J.; Benito, N.; Meije, Y.; Doblas, A.; Muñoz, P. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. 2009; 48(9):76 Subramanian, A.K.;

							Theodoropoulos, N.M.; Practice, A.S.T. Infectious Mycobacterium tuberculosis Infections in Solid Organ Transplantation: Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. 2019:e13513
1309	Organs => Lung	2 - 5 months	Case 1: Five months after lung transplant, the recipient developed 2 weeks of malaise followed by acute shortness of breath and bilateral pulmonary infiltrates with a nodule and patchy infiltrate. Case 2: Two months after lung transplant, the asymptomatic patient had a BAL showing AFB and culture grew M. tuberculosis with a new right upper lobe pulmonary nodule and atelectasis that cavitated the next month. Case 3: Three months after bilateral lung transplant, a routine BAL showed growth of pan-sensitive M. tuberculosis. The patient was asymptomatic. At four	N/A	Three lung recipients were TST-negative prior to transplant but developed active TB; whereas, none of the three organ donors had evidence of TB. Each of the three patient's TB isolates were identical with TB found in the country where two donors had lived (case 1 and 3), or identical to that found in a TB outbreak near where the donor had lived and had been imprisoned (case 2). This is indirect evidence of acquiring TB from the organ	1 Possible	Mortensen, E.; Hellinger, W.; Keller, C.; Cowan, L.; Shaw, T.; Hwang, S.; Pegues, D.; Ahmedov, S.; Salfinger, M.; Bower, W. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention.

			months postop BAL showed 4+ AFB and a new right upper lobe pulmonary nodule.		donors. This data does not exclude community acquisition by the recipient.		Transpl Infect Dis. 2014; 16(1):67 - 75
1308	Organs => Lung	90 days	A 58 year-old man with COPD underwent bilateral lung transplantation. No anti-TB prophylaxis was given. 90 days after lung transplant, the recipient developed persistent cough and a new pulmonary infiltrate. Bronchoalveolar lavage (BAL) sample grew pan-susceptible M. tuberculosis.	N/A	The recipient had no known TB exposure and family contacts were well and tested negative for latent TB. The donor was a 42 year-old Vietnamese man who had emigrated to USA and died of acute intracranial hemorrhage. The donor had no history of TB or positive TB skin testing. Ante-mortem CT scan of the donor's chest showed no pulmonary infiltrates or granulomas. The genotype of the recipient's TB isolate did not match any TB isolates previously reported in Ohio where the recipient resided.The spacer oligonucleotide typing (spoligotype) of the recipient's TB isolate matched the spoligotype of thirty TB cases of Indo-oceanic lineage previously reported in the USA, 29 of	1 Possible	Kumar, D.; Budev, M.; Koval, C.; Hellinger, W.; Gordon, S.; Tomford, J. Donor-Derived Tuberculosis (TB) Infection in Lung Transplant Despite Following Recommended Algorithm. Am J Transplant. 2013; 13(8):2225 - 2226

					which were among persons born in Vietnam or Cambodia. This is indirect evidence of TB transmission from the lung donor to the recipient. The two kidney recipients received isoniazid prophylaxis and did not develop M. tuberculosis infection. The liver recipient did not receive anti-TB prophylaxis and did not develop M. tuberculosis infection.		
1020	Organs => Lung	6 days	MULTIORGAN DONOR: 40-year-old male from a high tuberculosis (TB) incidence country. He had been diagnosed with TB 10 years earlier. His family stated he had received adequate treatment and was asymptomatic. Cause of death: stroke, no autopsy was performed. Chest X ray normal. Biopsy PCR from apical lung lesions was reported positive for M.tuberculosis 6 days after organ retrieval. The involved transplant centers were notified. RECIPIENTS: DOUBLE LUNG: 59 -years. Gender not stated, previous TST negative. Because of graft TB, the patient received	Multiorgan donor, TB transmission occurred only in the recipient of the double lung transplant (TB positive graft). Of the other four recipients (liver, left kidney/pancreas, right kidney and heart), three were treated with isoniazid prophylaxis without infection transmission (intervention without disease transmission, IWDT).	Pulmonary TB confirmed by positive M. tuberculosis PCR.	3 Definite/ Certain/ Proven	Coll, E.; Torre-Cisneros, J.; Calvo, R.; Garrido, G.; Matesanz, R. Incidence of Tuberculosis in Deceased-Organ Donors and Transmission Risk to Recipients in Spain. Transplantation. 2013; 96(2):205 - 210

			treatment with isoniazid, ethambutol, moxifloxacin and pyrazinamide for 18 months. Alive with functioning graft after a 14-month follow-up period. HEART: 46 years, gender not stated, TST not performed, received isoniazid prophylaxis for 12 months, no TB during a 12-month follow up period. PANCREAS & LEFT KIDNEY: 36 years, gender not stated, negative TST, received isoniazid prophylaxis for 3 months, died at 3 months due to abdominal sepsis. No TB transmission documented. RIGHT KIDNEY: TST positive, no isoniazid prophylaxis was given, no TB during a 15-month follow up period. LIVER: Negative TST, received isoniazid prophylaxis for 12 months, no TB during a 14-month follow up period.				
442	Organs => Lung	1 day	A respiratory specimen obtained from the lung recipient 1 day after transplantation grew Mycobacterium tuberculosis.	N/A	Donor chest radiograph had a previously unnoticed pulmonary opacity that was present on post-transplant recipient chest radiographs and computed tomographs. The recipient's isolate was molecularly distinct from others at her	3 Definite/ Certain/ Proven	Winthrop, K.L.; Kubak, B.M.; Pegues, D.A.; Hufana, C.; Costamagna, P.; Desmond, E.; Sanders, C.; Shen, P.; Flores-Ibarra, L.; Osborne, E.; Bruckner, D.; Flood, J. Transmission of

					hospital and in the state database, but was identical to two isolates from Guatemala (donor´s country)		mycobacterium tuberculosis via lung transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2004; 4(9):1529 - 33
441	Organs => Lung	3 - 5 months	Pulmonary tuberculosis in the graft. One of the recipients died and in other pulmonary resection was needed to cure a multi-drug-resistant TB. In the fourth case a MDR-strain was cured with a second-line drugs-based therapy	N/A	One donor with documented untreated LTBI	3 Definite/ Certain/ Proven	Ison, M.G.; Hager, J.; Blumberg, E.; Burdick, J.; Carney, K.; Cutler, J.; DiMaio, J.M.; Hasz, R.; Kuehnert, M.J.; Ortiz-Rios, E.; Teperman, L.; Nalesnik, M. Donor-Derived Disease Transmission Events in the United States: Data Reviewed by the OPTN/UNOS Disease Transmission Advisory Committee.

							American Journal of Transplantation. 2009; 9(8):1929 – 1935 Shitrit, D.; Bendayan, D.; Saute, M.; Kramer, M.R. Multidrug resistant tuberculosis following lung transplantation : treatment with pulmonary resection. Thorax. 2004; 59(1):79 - 80
1311	Organs => Liver	2 months	DONOR: 11-month-old male from a high tuberculosis (TB) incidence country. Cause of death: Dandy Walker syndrome with cerebral infarction. TB was not suspected during the donation process and autopsy was not performed. Chest X ray normal. RECIPIENTS: LIVER: a 4-year-old recipient without history or background of TB developed liver TB (Mycobacterium tuberculosis isolated in gastric fluid), gender not stated. TST not performed, received TB treatment, alive. KIDNEY: a double kidney transplant in a 49 year-old	100% transmission occurred in both liver and kidney recipients	Not reported	2 Probable	Coll, E.; Torre-Cisneros, J.; Calvo, R.; Garrido, G.; Matesanz, R. Incidence of Tuberculosis in Deceased-Organ Donors and Transmission Risk to Recipients in Spain. Transplantation. 2013; 96(2):205 - 210

			TST negative recipient developed positive PPD skin test. The recipient was treated with isoniazid for 9 months, alive.				
2011	Organs => Liver	The liver recipient time to detection posttransplant was two months, based on the exposure history of the anesthesiologist. The kidney recipient time to detection was not listed, although time of death was one year posttransplant.	This case report describes occupational exposure to a renal transplant recipient with undiagnosed INH-resistant, donor derived Mycobacterium tuberculosis who underwent intubation by an anesthesiologist for repair of a wound infection 2 months post transplant. 6 months following the intubation exposure, the anesthesiologist developed active pulmonary MTB with recurrent pleural effusions requiring multiple drainage procedures and anti-MTB therapy; the renal transplant recipient was diagnosed with MTB infection of the wound, graft, urinary tract and lungs. The second kidney recipient dies 1 year post transplant but cause was not disclosed in the paper. The liver recipient from the same donor died from MTB approximately one year post transplant, although the timing of diagnosis was not reported. The donor was a 67 year old immigrant from Russia with history of active MTB 40 years earlier requiring pneumonectomy. Possibly with INH-resistant MTB (INH was developed in	Donor-derived TB is reported to account for <5% of TB in solid organ transplants, but the source of Mycobacterium tuberculosis MTB) infection is infrequently determined (Mortensen 2014). The rate of transmission from a donor with active MTB infection is thought to be around 30%; no data exists for donor with latent MTB infection (LTBI)	Method to demonstrate imputability was the DNA fingerprinting of the liver and kidney recipients as well as anesthesiologist, which was identical.	3 Definite/ Certain/ Proven	Morris, M.I.; Daly, J.S.; Blumberg, E.; Kumar, D.; Sester, M.; Schluger, N.; Kim, S.H.; Schwartz, B.S.; Ison, M.G.; Humar, A.; Singh, N.; Michaels, M.; Orlowski, J.P.; Delmonico, F.; Pruett, T.; John, G.T.; Kotton, C.N. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. 2012; 12(9):88 Freytag, I.; Bucher, J.; Schoenberg, M.; Stangl, M.; Schelling, G. Donor-derived tuberculosis in an anesthetist after short-

			1952 - unknown drug therapy although may have received INH at the time of the donor's diagnosis). While the case report focused on the occupational exposure of the anesthesiologist, another important issue is the donor derived infection despite presumptive treatment with pneumonectomy and unclear drug therapy history.				term exposure : An old demon transplanted from the past to the present. 2016; 65(5) Clemente, W.T.; Pierrotti, L.C.; Abdala, E.; Morris, M.I.; Azevedo, L.S.; López-Vélez, R.; Cuenca-Estrella, M.; Torre-Cisneros, J.; Petersen, E.; Camargo, L.F.A.; Wright, A.J.; Beeching, N.J.; Vilela, E.G.; Santoro-Lopes, G.; Len, O.; Stucchi, R.S.B.; Manuel, O.; Faria, L.C.; Leblebicioglu, H.; Huprikar, S.; Molina, I.; Mourão, P.H.O.; Kotton, C.N.; Aguado, J.M.; Transplantation, working group. Recommendations for Management of Endemic Diseases and Travel Medicine in Solid-Organ

							Transplant Recipients and Donors: Latin America. 2018; 102(2):193
1831	Organs => Kidney	The liver recipient time to detection posttransplant was two months, based on the exposure history of the anesthesiologist. The kidney recipient time to detection was not listed, although time of death was one year posttransplant.	This case report describes occupational exposure to a renal transplant recipient with undiagnosed INH-resistant, donor derived Mycobacterium tuberculosis who underwent intubation by an anesthesiologist for repair of a wound infection 2 months post transplant. 6 months following the intubation exposure, the anesthesiologist developed active pulmonary MTB with recurrent pleural effusions requiring multiple drainage procedures and anti-MTB therapy; the renal transplant recipient was diagnosed with MTB infection of the wound, graft, urinary tract and lungs. The second kidney recipient dies 1 year post transplant but cause was not disclosed in the paper. The liver recipient from the same donor died from MTB approximately one year post transplant, although the timing of diagnosis was not reported. The donor was a 67 year old immigrant from Russia with history of active MTB 40 years earlier requiring pneumonectomy. Possibly with INH-resistant MTB (INH was developed in	Donor-derived TB is reported to account for <5% of TB in solid organ transplants, but the source of Mycobacterium tuberculosis MTB) infection is infrequently determined (Mortensen 2014). The rate of transmission from a donor with active MTB infection is thought to be around 30%; no data exists for donor with latent MTB infection (LTBI)	Method to demonstrate imputability was the DNA fingerprinting of the liver and kidney recipients as well as anesthesiologist, which was identical.	3 Definite/ Certain/ Proven	Morris, M.I.; Daly, J.S.; Blumberg, E.; Kumar, D.; Sester, M.; Schluger, N.; Kim, S.H.; Schwartz, B.S.; Ison, M.G.; Humar, A.; Singh, N.; Michaels, M.; Orlowski, J.P.; Delmonico, F.; Pruett, T.; John, G.T.; Kotton, C.N. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. 2012; 12(9):88 Freytag, I.; Bucher, J.; Schoenberg, M.; Stangl, M.; Schelling, G. Donor-derived tuberculosis in an anesthetist after short-

			1952 - unknown drug therapy although may have received INH at the time of the donor's diagnosis). While the case report focused on the occupational exposure of the anesthesiologist, another important issue is the donor derived infection despite presumptive treatment with pneumonectomy and unclear drug therapy history.				term exposure : An old demon transplanted from the past to the present. 2016; 65(5) Clemente, W.T.; Pierrotti, L.C.; Abdala, E.; Morris, M.I.; Azevedo, L.S.; López-Vélez, R.; Cuenca-Estrella, M.; Torre-Cisneros, J.; Petersen, E.; Camargo, L.F.A.; Wright, A.J.; Beeching, N.J.; Vilela, E.G.; Santoro-Lopes, G.; Len, O.; Stucchi, R.S.B.; Manuel, O.; Faria, L.C.; Leblebicioglu, H.; Huprikar, S.; Molina, I.; Mourão, P.H.O.; Kotton, C.N.; Aguado, J.M.; Transplantation, working group. Recommendations for Management of Endemic Diseases and Travel Medicine in Solid-Organ

							Transplant Recipients and Donors: Latin America. 2018; 102(2):193
1310	Organs => Kidney	2 months	DONOR: 11-month-old male from a high tuberculosis (TB) incidence country. Cause of death: Dandy Walker syndrome with cerebral infarction. TB was not suspected during the donation process and autopsy was not performed. Chest X ray normal. RECIPIENTS: LIVER: a 4-year-old recipient without history or background of TB developed liver TB (Mycobacterium tuberculosis isolated in gastric fluid), gender not stated. TST not performed, received TB treatment, alive. KIDNEY: a double kidney transplant in a 49 year-old TST negative recipient developed positive PPD skin test. The recipient was treated with isoniazid for 9 months, alive.	100% Transmission occurred in both liver and kidney recipients	The two infected recipients together with the fact that the donor's parents belonged to the Romanian community (community with high incidence of TB) are consistent with a donor-transmitted TB (probable transmission according to Disease Transmission Advisory Committee criteria).	2 Probable	Coll, E.; Torre-Cisneros, J.; Calvo, R.; Garrido, G.; Matesanz, R. Incidence of Tuberculosis in Deceased-Organ Donors and Transmission Risk to Recipients in Spain. Transplantation. 2013; 96(2):205 - 210
1021	Organs => Kidney	N/A	The recipient was diagnosed of renal TB by positivity of lymphocele fluid on staining and culture for Mycobacterium tuberculosis. A renal biopsy revealed non-caseating granulomas with positive staining for TB.	N/A	There is no information about the donor with the exception of its origin: Philippines. However we should admit the possibility of transmission because the recipient tested negative for Mantoux test and reactivation of TB or	1 Possible	Al-Nesf, M.Ali; Al-Ani, O.Isam; Al-Ani, A.AbdulRahm; Rashed, A.Hamed. Renal allograft tuberculosis with infected lymphocele transmitted from the donor.

					primary infection in the kidney is quite unusual.		Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2014; 25(2):370 - 5
476	Organs => Kidney	26 months	Fatigue and productive cough	N/A	Pleural and urinary TB (bronchial brush, sputum and urine positive for M.tubercolosis). Transmission from LRD considered "likely" because of positive PPD skin test in donor, with negative PPD and TB history in recipient.	1 Possible	Lakshiminarayan, S.; Sahn, S.A. Tuberculosis in a patient after renal transplantation. Tubercle. 1973; 54(1):72 - 6
475	Organs => Kidney	16 months	Fever, renal function decline	N/A	Transmission from LRD considered "likely" because of positive PPD skin test in donor, with negative PPD and TB history in recipient. She had positive urine culture for M.tubercolosis.	1 Possible	Lichtenstein, I.H.; MacGregor, R.R. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. Reviews of infectious diseases. 1983; 5(2):216 - 26

474	Organs => Kidney	3 months	fever and constitutional symptoms, decreased renal function.	N/A	No proven imputability. No information on the donor; recipient had a negative tuberculin test and normal chest x-ray pre-transplant; graft tuberculosis with urine culture +, possible causality.	1 Possible	Siu, Y.P.; Tong, M.K.; Leung, K.T.; Yung, C.Y. Successful kidney re-transplantation in a patient with previous allograft kidney tuberculosis. Transplant infectious disease : an official journal of the Transplantation Society. 2004; 6(3):132 - 5
473	Organs => Kidney	35 - 39 days	pleural effussion; decreasing renal function; nephritis; AFB (acid- fast bacilli) in urine	N/A	Donor: TB meningitis (CSF grew M. tubercolosis 3 weeks after procurement). Recipients of both kidneys developed TB. M. tuberculosis isolated from urine, sputum, pleural fluid,bone marrow and renal biopsy.	3 Definite/Certain /Proven	Peters, T.G.; Reiter, C.G.; Boswell, R.L. Transmission of tuberculosis by kidney transplantation. Transplantation. 1984; 38(5):514 - 6
472	Organs => Kidney	2 - 6 months	acute fever, asthenia, disorientation; miliary pneumonitis	N/A	Donor: Not known TB, but both recipients developed TB. The two mycobacterial species had the same bacteriologic characteristics and the same antibiotic sensitivity.	2 Probable	Mourad, G.; Soulillou, J.P.; Chong, G.; Pouliquen, M.; Hourmant, M.; Mion, C. Transmission of Mycobacterium tuberculosis with renal

							allografts. Nephron. 1985; 41(1):82 - 5
471	Organs => Kidney	12 - 14 months	Decline in renal function, painful and swollen foot with discharge.	N/A	Granulomatous nephritis and osteomyelitis demonstrated in biopsy, AFB (acid-fast bacilli) positive. Urine, biopsy tissue of kidney and bone with positve culture for M. tuberculosis. Recipients of liver and kidney from same donor developed TB with same strain (hemi-nested PCR of IS6110 region). No isolate from donor available for comparison.	2 Probable	Graham, J.C.; Kearns, A.M.; Magee, J.G.; El-Sheikh, M.F.; Hudson, M.; Manas, D.; Gould, F.K.; Orr, K.E.; Freeman, R. Tuberculosis transmitted through transplantation. J Infect. 2001; 43(4):251 - 4
470	Organs => Kidney	6 - 7 weeks	Fever, headache, pancytopenia, sepsis-like syndrome.	N/A	Imputability proven. Donor: Mycobacterium tuberculosis grew from CSF and spleen tissue 3 weeks after death. Recipients of both kidneys became infected: AFB (acid-fast bacilli) positive in bone marrow, TB cultured from blood, urine, liver, spleen and lungs. Recipients' TB same genotype and RFLP profile as donor's.	3 Definite/Certain /Proven	Transplantation-transmitted tuberculosis--Oklahoma and Texas, 2007. MMWR Morb Mortal Wkly Rep. 2008; 57(13):333 - 6
443	Organs => Kidney	7 weeks	not described in paper	N/A	Two probable cases. Infection was	2 Probable	Ison, M.G.; Hager, J.;

					diagnosed in the transplanted organ shortly after transplantation and typing suggests that the TB may have originated from the donor. In the second probable TB transmission, the donor was recognized, as part of a look-back investigation, to have been diagnosed but not treated for latent TB. In both cases, predonation cultures were not available in the donor.		Blumberg, E.; Burdick, J.; Carney, K.; Cutler, J.; DiMaio, J.M.; Hasz, R.; Kuehnert, M.J.; Ortiz-Rios, E.; Teperman, L.; Nalesnik, M. Donor-Derived Disease Transmission Events in the United States: Data Reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. American Journal of Transplantation. 2009; 9(8):1929 - 1935
440	Organs => Kidney	30 months	Generalized symptoms (sic), nausea, decline in renal function	N/A	Possibly donor derived. Recipient without risk factors for TB. Allograft biopsy showed granulomata; Urine culture+ for M.tuberculosis. Donor from Philippines. Other recipient did not develop TB. Authors speculate that TB is from donor origin as	1 Possible	Malone, A.; McConkey, S.; Dorman, A.; Lavin, P.; Gopthanian, D.; Conlon, P. Mycobacterium tuberculosis in a renal transplant transmitted from the donor. Irish journal of medical

					TB is endemic in Philippines		science. 2007; 176(3):233 - 5
1019	Organs => Heart	21 days	DONOR: 31-year-old male with sepsis and pneumonia. He died from intracerebral bleeding. BAL was Ziehl Nielsen negative and M.tuberculosis (MTB) PCR negative, but BAL culture turned positive for MTB 1 day after organ procurement. RECIPIENT: 62 year-old male with dilated cardiomyopathy. When the donor BAL turned positive, one day after transplantation, blood cultures (BACTEC Myco/F Lytic) and tracheal aspirates for mycobacterial cultures were obtained from the recipient, and he started treatment with prophylactic isoniazid 300 mg/day; 3 weeks later recipient's blood cultures turned positive for MTB. Respiratory samples remained negative. He started antiTB treatment with streptomycin, ethambutol and levofloxacin. The recipient died 3 months after heart transplantation (massive intracerebral bleeding). He never showed signs of active tuberculosis infection; post-mortem histological examination (brain, lung, heart,kidney, pancreas) and MTB PCR of these tissues were all negative for MTB.	N/A	Same M. tuberculosis strain in donor and recipient (according to molecular genotyping).	3 Definite/Certain /Proven	Weile, J.; Eickmeyer, H.; Dreier, J.; Liebke, M.; Fuchs, U.; Wittke, J.W.; Richter, E.; Gummert, J.; Knabbe, C.; Schulz, U. First case of Mycobacterium tuberculosis transmission by heart transplantation from donor to recipient. International journal of medical microbiology. 2013; 303(8):449 - 51