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ORIGINAL ARTICLE

Ten years of donor-derived disease: A report of the disease transmission advisory committee

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Despite clinical and laboratory screening of potential donors for transmissible disease, unexpected transmission of disease from donor to recipient remains an inherent risk of organ transplantation. The Disease Transmission Advisory Committee (DTAC) was created to review and classify reports of potential disease transmission and use this information to inform national policy and improve patient safety. From January 1, 2008 to December 31, 2017, the DTAC received 2185 reports; 335 (15%) were classified as a proven/probable donor transmission event. Infections were transmitted most commonly (67%), followed by malignancies (29%), and other disease processes (6%). Forty-six percent of recipients receiving organs from a donor that transmitted disease to at least 1 recipient developed a donor-derived disease (DDD). Sixty-seven percent of recipients developed symptoms of DDD within 30 days of transplantation, and all bacterial infections were recognized within 45 days. Graft loss or death occurred in about one third of recipients with DDD, with higher rates associated with malignancy transmission and parasitic and fungal diseases. Unexpected DDD was rare, occurring in 0.18% of all transplant recipients. These findings will help focus future efforts to recognize and prevent DDD.

Abbreviations: DTAC, Disease Transmission Advisory Committee; DTAG, Disease Transmission Advisory Group; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; DDD, donor-derived disease; DDI, donor-derived Infection; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell lymphotropic virus 1; IQR, interquartile range; IWDT, intervention without disease transmission; MRSA, methicillin-resistant *Staphylococcus aureus*; MDRO, multidrug-resistant organisms; NAT, nucleic acid test; OPTN, Organ Procurement and Transplantation Network; PDDTE, potential donor disease transmission event; VRE, vancomycin-resistant Enterococcus; WNV, West Nile virus.

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1 | INTRODUCTION

Solid organ transplantation creates a risk of donor-derived disease (DDD). Expected DDD (eg, cytomegalovirus [CMV]), is frequent and posttransplant management strategies are employed.^{1,2} Unexpected DDD transmissions occur in less than 1% of recipients.³ Infectious pathogens are most commonly involved, but malignancies and metabolic or allergic diseases may also be transmitted.³ Transmissions may result in high profile events with poor recipient outcomes that alter the public's trust in the solid organ transplant process.⁴⁻¹³

In order to improve the safety of organ transplantation, The Organ Procurement and Transplantation Network (OPTN) created the Disease Transmission Advisory Group (DTAG) in 2005, which later became the Ad Hoc Disease Transmission Advisory Committee (DTAC), an independent committee that receives reports of potential donor disease transmission events (PDDTE) and follows a standardized process to determine the likelihood of donor transmission.^{14,15} Reporting of PDDTE is required by OPTN policy 15 (Identification of Transmissible Disease), but requires vigilance and knowledge of the policy requirements by organ procurement organizations (OPOs) and transplant centers.¹⁶ The goal of the DTAC is to review these reports and use the results to improve OPTN policy and educate the transplant community to promote patient safety. With that goal in mind, this report analyzes aggregated DTAC data over the first 10 years of collection, with the object of better understanding the epidemiology and outcomes of unexpected DDD in the United States.

2 | METHODS

This study used data collected by the OPTN. This data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States submitted by the members of the OPTN and has been described elsewhere.¹⁷ The Health Resources and Services Administration (HRSA), US Department of Health and

Human Services provides oversight to the activities of the OPTN contractor.

2.1 | Reporting requirements

OPTN policy requires that, in certain circumstances, donor information learned by the OPO be reported to the OPTN as a PDDTE. Information that must be reported includes pathogens of special interest (as specified in a list maintained by the OPTN available at https://optn.transplant.hrsa.gov/media/1911/special_pathogens_list.pdf) and findings suggestive of donor malignancy learned post-transplant. Similarly, transplant programs must report a PDDTE when a recipient is suspected to have an unexpected DDD.¹⁶ Events are then reviewed by the DTAC using confidential peer review.

2.2 | DTAC classification system and changes over time

Reports of PDDTE events received by the DTAC from January 1, 2006 to December 2017 were reviewed. The DTAC categorization system matured over the initial years of the committee; thus reports from January 1, 2006 to December 31, 2007 were not fully categorized as to the probability of donor origin. Reports received beginning January 1, 2008 were classified by the committee as proven, probable, possible (and briefly in 2008 as potential), unlikely, excluded (no transmission occurred), or—if transmission may have been averted because of an intervention by the recipient center—intervention without disease transmission (IWDT). The designation “rule out” was used if information suggested that no concern for DDD existed. Details of this classification system have been described elsewhere.¹⁴ Beginning in 2012, 2 changes were made to the classification system. First, the process was standardized by the creation of a classification algorithm (Figure 1).¹⁵ Second, the committee began

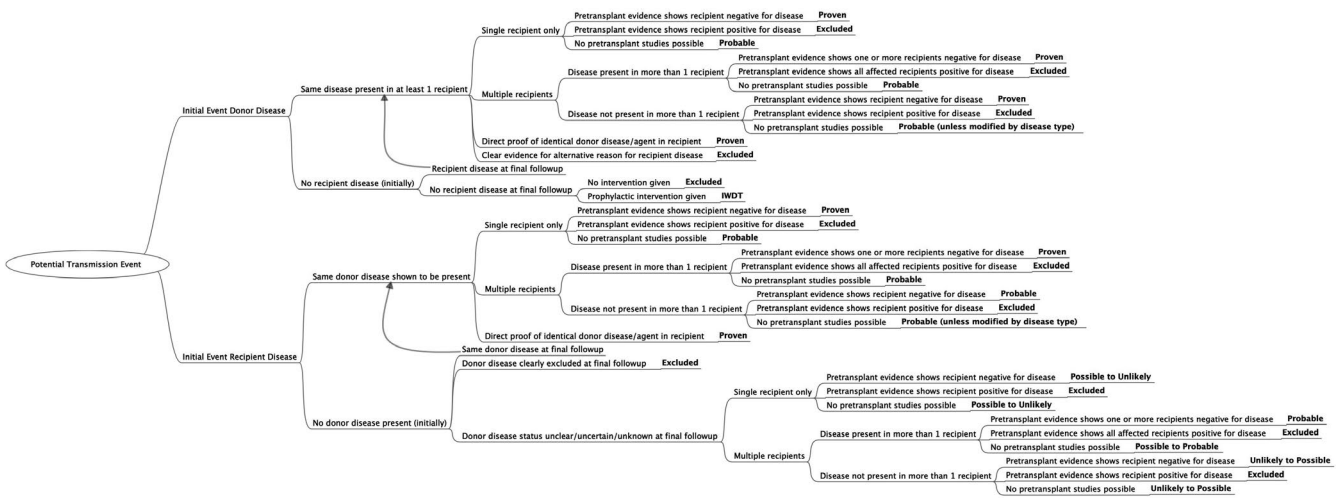


FIGURE 1 Classification scheme

individually identifying which transplanted organs from the reported donor were associated with a transmission event rather than only classifying the event by donor.

Reports involving infection were categorized as viral, bacterial, fungal, parasitic, and mycobacterial and by the organism involved. Malignancies were categorized by type: hematological, renal, liver, melanoma, lung, adenocarcinoma of unknown origin, Kaposi's sarcoma, urothelial, neuroendocrine, and other. Reports of noninfectious or nonmalignant conditions were classified separately. From 2012 - 2017, recipient deaths included deaths reported by the center for any recipient with proven/probable disease within 45 days of the PDDTE. Graft failures were any graft failure event occurring within 1 year of transplant because of a recipient with a proven/probable transmission of disease. Deaths (within 45 days of the PDDTE) at the time of graft failure were classified as deaths and were not included in the graft failure analysis.

Values were reported as median and interquartile range (IQR). The Fisher's exact or chi-square test was used to compare groups as appropriate. A P value $< .05$ was considered statistically significant. Statistical analyses were performed with Stata/MP14 (StataCorp LP, College Station, TX).

2.3 | Time to presentation substudy

The records of all recipients of any donor with at least 1 recipient with proven/probable donor-derived infection (DDI) from January 2008 through March 2012 were reviewed and a date of clinical presentation of signs or symptoms (or date of positive test results) resulting from the infection was determined by a group of 4 committee members. Based on the organism causing the DDI, each case was classified as either viral, bacterial, fungal, mycobacterial, or parasitic infection. The median time to presentation and the range were determined.

2.4 | Reports of significant public health interest

Personnel from the Centers for Disease Control and Prevention (CDC) serve as ex officio members of the OPTN DTAC and reviewed PDDTE and led investigations of reports they determined were of significant public health interest. This process between the DTAC and the CDC was formalized in 2011. CDC classified cases using the same algorithm the DTAC uses; the committee independently reviewed CDC cases and provided an independent classification used for official tabulations and reporting.

2.5 | Peer review

DTAC operates under confidential medical peer review and is required to protect the identity of individual donors and recipients; consequently, single donor reports have been aggregated when required to preserve confidentiality.

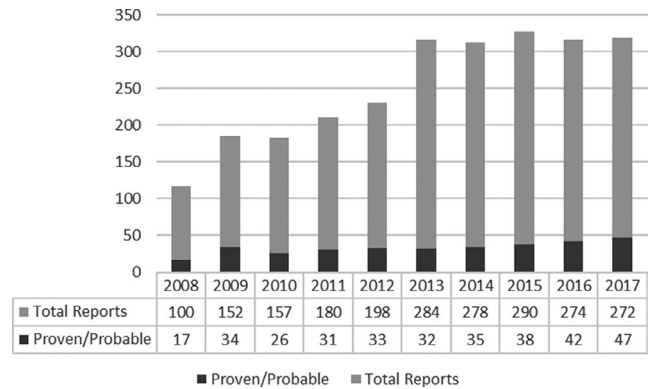


FIGURE 2 Total reports of potential donor transmission events by year

3 | RESULTS

3.1 | Classification of all PDDTE reported to DTAC 2008-2017

From January 1, 2008 to December 2017, the DTAC received 2185 PDDTE based on findings in either the donor or recipient. Most PDDTE were reported due to donor findings ($n = 1336$, 61.1%). The committee classified 335 (15%) reported PDDTEs as proven/probable DDD. Of the remaining PDDTE, 9 (0.4%) were potential (a category used only in 2008), 244 (11%) possible, 174 (8%) unlikely, 371 (17%) IWDT, 1012 (46%) excluded, 32 (1.5%) rule out, and 8 (0.4%) not further classified. Most reports involved infection (1504, 69%) followed by malignancy (581, 27%). The committee received 100 (5%) reports of noninfectious/nonmalignant disease processes. The change in report numbers over the years with the proportion that led to proven or probable cases is illustrated in Figure 2.

3.2 | Classification of proven/probable PDDTE 2008-2017

Of the 335 donors who transmitted proven or probable disease to at least 1 recipient, 244 donors transmitted infection and 70 transmitted malignancy. Other noninfectious, nonmalignant diseases were transmitted from 21 donors (Tables 1, 2, 3).

Viral (76; 31%) and bacterial (74; 30%) pathogens each accounted for just under one third of donors transmitting infections. Fungal infections occurred in 53 (22%), parasitic infections in 32 (13%), and mycobacterial (all tuberculosis) in 9 (4%). Forty-eight donors transmitted gram-negative bacteria (17 *Pseudomonas*) as compared to 14 transmitting gram-positive bacteria. Hepatitis C virus (HCV) was the leading viral pathogen with 24 reported donors transmitting unexpected HCV. Details regarding HCV transmissions (expected HCV transmissions were excluded) have been previously published.¹⁸ The 10 reports of unexpected CMV transmission reflected either human error or false negative donor serologic results. Notable pathogens reported to DTAC but without proven/probable transmission

TABLE 1 Proven and probable infection transmissions by type (by number of pathogens/syndromes in proven/probable donors) 2008-2017

Category of Infection	Pathogen	Total p/p; (percent of p/p by category)	Comment
Viral	Cytomegalovirus	10 (13)	Unexpected transmission
	Hepatitis B virus	14 (18)	
	Hepatitis C virus	24 (32)	
	Lymphocytic choriomeningitis virus	3 (4)	
	Community respiratory viruses	9 (12)	RSV, parainfluenza, rhinovirus, adenovirus
	Parvovirus	4 (5)	
	West Nile virus	5 (7)	
	Other	7 (9)	HSV (2), HTLV-2 (1), rabies (1), HHV-8 (2), EEEV (1)
	Total Viral	76 (30)	
Bacterial (1)	Gram-positive	16 (20)	
	<i>Staphylococcus aureus</i>	8 (10)	MRSA (6)
	<i>Enterococcus</i>	7 (7)	VRE (2)
	Other	1 (1)	<i>Actinomyces</i> (1)
	Gram-negative	52 (65)	
	<i>Enterobacteriaceae</i>	23 (29)	<i>E coli</i> (7), <i>Enterobacter</i> (3), <i>Klebsiella</i> (9), <i>Serratia</i> (5)
	<i>Pseudomonas</i>	17 (21)	
	Other	12 (15)	<i>Acinetobacter</i> (2), <i>Aeromonas</i> (1), <i>Burkholderia</i> (2), <i>Bacteroides</i> (2), <i>Cardiobacterium</i> (1), <i>F. tularensis</i> (1), <i>Ehrlichia</i> (2), <i>Bartonella</i> (1)
	<i>Mycoplasma</i> spp.	6 (8)	<i>Mycoplasma</i> (3), <i>Ureaplasma</i> (3)
	Other	6 (8)	Syphilis (2), HUS (1), pyelonephritis (1), sepsis (1), pneumonia (1)
	Total Bacterial	80 pathogens (32) from 74 donors	
Fungal (2)	<i>Aspergillus</i>	7 (13)	
	Mucorales	2 (4)	(one cotransmission with <i>Aspergillus</i>)
	<i>Candida</i>	13 (24)	
	Coccidioidomycosis	10 (19)	
	Histoplasmosis	7 (13)	
	<i>Cryptococcus</i>	11 (20)	
	Other	4 (7)	<i>Scopulariopsis</i> (1), <i>Trichosporon</i> (1), <i>Geotrichum</i> (1), <i>Microsporidia</i> (2)
Total Fungal	54 pathogens (22) from 53 donors		
Mycobacterial	Tuberculosis	9 (4)	
Parasitic	<i>Strongyloides</i>	13 (42)	
	Toxoplasmosis	11 (35)	
	Trypanosomiasis	3 (10)	
	<i>Balamuthia</i>	2 (6)	
	Other	2 (6)	Amoebic encephalitis (1), Schistosomiasis (1)
Total Parasite	31 (12)		
Total Infectious Agents/Syndromes		250 pathogens from 244 donors	

Note: p/p = proven or probable

6 donors with multiple bacterial pathogens

1 donor with multiple fungal pathogens

Abbreviations: RSV, respiratory syncytial virus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus 1; HHV-8, human herpes virus-8; EEEV, Eastern equine encephalitis virus; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; HUS, Hemolytic Uremic Syndrome.

TABLE 2 Proven and probable malignancy transmissions by type (by number of proven/probable donors) 2008-2017

Malignancy	Type	Total p/p; percent of malignancy	Comment
	Hematological	6 (9)	AML (1), hairy cell (1), APL (1), CLL (1), lymphoma (2)
	Renal	18 (26)	
	Melanoma	5 (7)	
	Liver/cholangiocarcinoma	10 (14)	
	Lung	10 (14)	Small cell (2)
	Adenocarcinoma	3 (10)	Unknown origin
	Kaposi sarcoma	2 (3)	
	Urothelial	2 (3)	
	Neuroendocrine	2 (3)	
	Other	12 (17)	Basaloid, medulloblastoma, colon cancer, blue cell tumor, oncocytoma, choriocarcinoma, mesothelioma, metastatic paraganglioma, small bowel cancer, squamous cell cancer, colon, unknown (1 each)
Total Malignancy		70	

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia

TABLE 3 Proven and probable nonmalignancy, noninfection transmissions by type (by number of proven/probable donors) 2008-2017

Nonmalignancy, Noninfection	Type	Total p/p; percent of other	Comment
	Peanut allergy	5 (24)	
	Amyloidosis	3 (14)	
	Hemochromatosis	3 (14)	
	Ornithine transcarbamylase deficiency	2 (10)	
	Other	8 (40)	Fabry's disease, acute disseminated encephalomyelitis, thromboangiitis obliterans, membranous nephropathy, hypertrophic cardiomyopathy, pulmonary atherosclerosis, sarcoidosis, thin basement membrane disease (1 each)
Total Other		21 (6)	

included atypical mycobacteria, prion diseases, and human T cell lymphotropic virus 1 (HTLV-1).

Kidney, lung, and liver cancers were the most common malignancies, with 18, 10, and 10 donors, respectively, transmitting to at least 1 recipient. Fifteen PDDTE involving breast cancer and 28 involving thyroid cancer were reported by either transplant centers or OPOs (eg, due to post-procurement pathologic donor finding, recipient development of tumor, or development of cancer in a living donor) with no proven/probable transmissions. Among noninfectious and nonmalignant diseases, peanut allergy was most common with 5 transmitting donors.

3.3 | Disease transmission to exposed recipients

Beginning in 2012, the committee classified the probability of transmission to each individual recipient rather than by the event as a whole. Among all reports from 2012 - 2017, 227 donors (0.25% of

90, 167 total donors) transmitted proven/probable disease to at least 1 recipient (Tables 4, 5, 6). These 227 donors donated organs to 694 recipients; 321 (46.3%) of exposed recipients developed DDD (0.16% of 201,717 total recipients).

DTAC categorized 174 donors as transmitting DDI to at least 1 of 567 exposed recipients. Of these exposed recipients, (252/567) 44% developed a proven/probable DDI. For some infectious agents, exposed lung recipients were more likely to develop DDI than recipients of other organs. Among 35 recipients exposed to respiratory viruses, infection was observed in all 9 of 9 lung recipients, compared to only 1 of 26 nonlung recipients (Fisher's exact test, $P < .001$). Mycoplasma was transmitted to 8/8 exposed lung recipients, but none of the 23 exposed nonlung recipients (Fisher's exact test, $P < .001$). Similarly, 3/4 lung recipients exposed to *Aspergillus* developed disease (found on donor cultures that were resulted post-procurement), but none of the 9 nonlung recipients were infected (Fisher's exact test, $P = .014$) (Table 5). Of the 9 recipients infected with *Toxoplasma*, 5 were not

TABLE 4 Outcomes associated with proven and probable transmission of donor-derived malignancy by organ type (2012-2017)

Malignancy Type	Total Reports	Total P/P Donors	Total Recipients from P/P Donors	Recipients with P/P Transmission ÷ Exposed Recipients					Recipients with P/P Transmission ÷ Recipients from P/P Donors	Total Transmission-Related Deaths ÷ Recipients with P/P Transmission	Recipients with P/P Transmission per 10,000 Transplanted Recipients During 2012-2017	Transmission-Related Deaths per 10,000 Transplanted Recipients During 2012-2017	
				kidney	kidney/panc	liver	heart	lung					Graft Loss
Adenocarcinoma (unknown origin)	33	3	8	1/3	0/1	3/3	1/1	0/0	40.0%	3	40.0%	0.28	0.11
Liver	14	5	7	0/2	0/0	5/5	0/0	0/0	71.4%	2	60.0%	0.28	0.17
Hematological	14	2	7	2/3	0/1	0/1	0/1	1/1	42.9%	2	33.3%	0.17	0.06
Kaposi's	12	1	5	2/2	0/0	0/1	0/1	1/1	60.0%	0	33.3%	0.17	0.06
Lung	23	4	7	2/2	0/0	3/4	0/0	1/1	85.7%	0	83.33%	0.33	0.28
Melanoma	11	2	4	2/2	0/0	2/2	0/0	0/0	100.0%	1	50.0%	0.22	0.11
Neuroendocrine	15	1	3	2/2	0/0	1/1	0/0	0/0	100.0%	0	33.3%	0.17	0.06
Other Malignancy	138	6	14	4/8	0/0	4/6	0/0	0/1	50.0%	1	42.9%	0.39	0.17
Renal	146	11	26	10/18	0/0	0/5	1/4	0/0	38.5%	2	0.0%	0.56	0.00
Urothelial	3	1	1	1/1	0/0	0/0	0/0	0/0	100.0%	1	0.0%	0.06	0.00
Total Malignancy	409	36	82	26/43	0/2	18/28	2/7	3/4	57.3%	12	38.3%	2.62	1.02

Note: P/P = proven/probable

Liver = hepatocellular and cholangiocarcinoma.

Recipients of multiorgan (other than kidney/pancreas or heart-lung) would appear under the column for each organ type they received.

The percentage "recipients with P/P transmission ÷ exposed recipients" is a count of unique donors regardless of number or types of organ received, thus the sum by organ type may be greater than the total recipients.

No pancreas alone or heart-lung.

heart recipients (2/7 exposed liver recipients, 2/12 exposed kidney recipients, and 1/3 exposed lung recipients).

In addition to these proven or probable transmissions, 98 exposed recipients were classified as IWDT. Thirty of these recipients were exposed to bacterial infection, 36 to fungal infections, 3 to tuberculosis, 22 to parasites, and 7 to viruses. Among the most common specific pathogens classified as IWDT were *Strongyloides* (14), *Toxoplasma* (8), *Coccidioides* (9), *Candida* (8), *Histoplasma* (8), and *Aspergillus* (6).

Thirty-six donors were associated with a proven/probable transmission of malignancy to at least 1 recipient; (47/82) 57% of exposed recipients developed DDD. All 5 exposed liver recipients developed liver cancer (adenocarcinoma or cholangiocarcinoma) (Table 4).

For noninfectious, nonmalignant disease processes, 17 donors transmitted disease to at least 1 recipient. These 17 donors donated organs to 45 recipients, (24/45) 53% developed proven or probable disease. Of 21 exposed recipients, 8 (38%) developed peanut allergy (4/5 liver, 3/3 lung, 1/3 kidney-pancreas, and 0/7 kidney alone) (Table 6). Peanut allergy was recognized at a median 26 days posttransplant (range 7-56).

3.4 | Graft failure in recipients with donor-derived disease

Graft failure within 1 year of transplantation occurred in (49/321) 15% of recipients with proven/probable DDD. Recipients with proven/probable donor-derived malignancy experienced a higher rate of graft failure (12/47) 26% as compared to recipients with DDI (31/252) 12% ($P = .02$), often because of graft removal after discovery of a tumor in the renal allograft. In the subcategories of infection, the highest rates were observed with fungal infection (9/48) 19% with 5 occurring in recipients with donor-derived *Cryptococcus* (Tables 4, 5, 6).

3.5 | Mortality in recipients with donor-derived disease

The total mortality within 45 days of report among the 321 recipients with proven/probable DDD from 2012-2017 was (59/321) 18%. The highest mortality rate was associated with donor-derived malignancy (18/47) 38%, specifically adenocarcinoma (7/10) 70% and liver malignancy (3/5) 60%. No deaths were associated with renal cancer (0/11). The mortality associated with proven/probable DDI was 39/252 (15%); the highest rate was associated with parasitic infections (11/32) 34%. Two deaths occurred in patients with nonmalignant and noninfectious donor-derived disease (2/22) 9% (Tables 4, 5, 6).

3.6 | Risk among all transplant recipients of donor-derived disease and of death associated with donor-derived disease

Over the period 2012-2017, the risk of unexpected DDD was calculated per 10,000 transplant recipients. The rate of proven/probable

DDD was 14.0/10,000 for infection, 2.6/10,000 for malignancy, and 1.2/10,000 for other processes. The overall risk of any DDD was 17.8/10,000 or 0.178% (Tables 4, 5, 6). During 2008-2017, of 147,661 solid organ transplantation donors, 335 transmitted proven or probable infection to at least 1 recipient for an overall rate of 23/10,000 0.23% of donors.

An organ transplant recipient faces a risk of contracting and dying with DDD (within 45 days of the report) of 2.2/10,000 for infection, 1.0/10,000 for malignancy, and 0.1/10,000 for other diseases for an overall DDD rate of 3.3/10,000. Among the subcategories of infection, the risk of a recipient contracting and dying from infection was higher for bacterial (0.83/10,000), particularly gram-negative infection (0.56/10,000) and parasitic (0.61/10,000) compared to fungal (0.39/10,000) or viral (0.33/10,000) infections. Among malignancies, the greatest overall risk was associated with adenocarcinoma (0.39/10,000).

3.7 | Living donors

A separate analysis of living donors only was performed. The committee received 87 reports involving living donors; 11 resulted in proven/probable transmission. Among infections, 4 were viral (2 HCV, 1 hepatitis B virus [HBV], and 1 herpes simplex virus [HSV]) and 2 were fungal (1 *Coccidioides*—resulting in death—1 *Histoplasma*). One living donor transmitted HIV reported to public health authorities but not the DTAC. All 4 malignancies were renal cell carcinoma. The risk of a living donor recipient acquiring a DDD was 1.8/10,000, and the mortality risk was 0.16/10,000.

3.8 | Pediatric donors

Twenty-seven pediatric donors transmitted a proven/probable disease. Twenty infections were transmitted; 9 bacterial (3 *Staphylococcus aureus*, 2 *Pseudomonas aeruginosa*, and 4 other) 5 viral (CMV, respiratory syncytial virus, and rhinovirus); 3 fungal infections (*Histoplasma* and *Zygomycetes*), and 3 parasitic (*Toxoplasma*). Seven reports were noninfectious etiologies (4 peanut allergy, 2 malignancy, and 1 acute demyelinating encephalomyelitis).

3.9 | Time to presentation of donor-derived disease

The time from transplantation to the development of symptoms/other positive tests resulting from DDI was analyzed in the recipients of 119 donors reported from January 2008 to March 2012. A determination of the date of presentation with proven or probable DDI could be made in 81 recipients of 60 donors. In the remainder, either no symptoms associated with DDI developed or insufficient information was available. The time to presentation of specific pathogens is described in Table 7. Sixty-seven

TABLE 5 Outcomes associated with proven and probable transmission of donor-derived infection by organ type (2012-2017)

Type	Recipients with Transmission ÷ Exposed Recipients													Recipients with P/P Transmission per 10,000 Transplanted Recipients During 2012-2017	Transmission-Related Deaths per 10,000 Transplanted Recipients During 2012-2017
	Total Reports	Total P/P Donors	Total Recipients from P/P Donors	kidney	pancreas	kidney/panc	liver	heart	lung	heart/lung	intestine	Recipients with P/P Transmission ÷ Recipients from P/P Donors	Graft Loss		
Viral															
CMV	32	7	25	10/13	0/0	0/0	1/5	2/4	0/3	0/0	0/0	52.0%	1	0.0%	0.00
HBV	75	12	28	7/17	0/0	0/0	10/12	0/1	0/0	0/0	0/0	53.6%	0	6.7%	0.06
HCV	85	17	52	11/24	0/0	1/1	12/14	3/6	4/7	0/0	0/0	59.6%	1	3.2%	0.06
LCMV	2	1	3	2/2	0/0	0/0	1/1	0/0	0/0	0/0	0/0	100.0%	1	33.3%	0.06
CRV	29	9	35	1/16	0/0	0/0	0/8	0/4	9/9	0/0	0/0	28.6%	2	0.0%	0.00
Parvovirus	8	3	10	4/6	0/0	0/0	0/2	0/1	0/1	0/0	0/0	40.0%	0	0.0%	0.00
WNV	19	1	5	1/2	0/0	0/0	1/1	0/1	1/1	0/0	0/0	60.0%	1	0.0%	0.00
Other	56	6	15	4/6	0/0	0/0	4/6	1/2	1/2	0/0	0/0	60.0%	1	33.3%	0.17
Total Viral	320	56	173	40/86	0/0	1/1	29/49	6/19	15/23	0/0	0/0	50.9%	7	6.8%	0.33
Bacterial															
<i>S. aureus</i>	118	7	27	2/8	0/0	0/2	3/7	0/3	5/7	0/0	0/0	37.0%	0	20.0%	0.11
<i>Enterococcus</i>	13	3	7	2/3	0/0	1/1	1/3	0/0	0/0	0/0	0/0	57.1%	0	0.0%	0.00
Other Gram-Positive	56	1	5	1/2	0/0	0/0	0/1	0/1	0/2	0/0	0/0	20.0%	0	0.0%	0.00
All Gram-Positive	187	11	39	5/13	0/0	1/3	4/11	0/4	5/9	0/0	0/0	38.5%	0	13.3%	0.11
<i>Enterobacteriaceae</i>	61	15	40	10/19	0/0	0/1	4/12	3/4	3/4	0/0	0/0	50.0%	1	30.0%	0.33
<i>Pseudomonas</i>	28	11	37	15/18	0/0	0/1	1/9	0/6	3/3	0/0	0/0	51.4%	8	10.5%	0.11
Other Gram-Negative	38	8	25	6/13	0/0	1/1	1/5	0/3	4/4	0/0	0/0	48.0%	1	16.7%	0.11
All Gram-Negative	127	34	102	31/50	0/0	1/3	6/26	3/13	10/11	0/0	0/0	50.0%	10	19.6%	0.56
<i>Mycoplasma</i> spp.	14	6	31	0/9	0/1	0/2	0/8	0/5	8/8	0/0	0/0	25.8%	1	25.0%	0.11
Other	30	6	20	3/9	0/0	0/0	2/5	0/3	2/3	0/0	0/0	35.0%	1	14.3%	0.06
Total Bacterial	358	57	192	39/81	0/1	2/8	12/50	3/25	25/31	0/0	0/0	42.2%	12	18.5%	0.84
Fungal															
<i>Aspergillus</i>	27	3	13	0/4	0/0	0/0	0/3	0/2	3/4	0/0	0/0	23.1%	0	33.3%	0.06
<i>Candida</i>	52	10	31	4/16	0/0	0/0	1/10	2/2	3/3	0/0	0/0	32.3%	1	10.0%	0.06
Coccidioidomycosis	29	6	19	1/6	0/0	0/1	3/5	0/3	3/5	0/0	0/0	36.8%	2	42.9%	0.17
Histoplasmosis	58	6	21	5/9	0/0	0/2	2/4	2/3	2/4	0/0	0/0	47.6%	1	0.0%	0.00
<i>Cryptococcus</i>	35	7	20	6/11	0/0	0/0	4/5	1/2	2/2	0/0	0/0	65.0%	5	7.7%	0.06
Other	36	3	11	2/6	0/0	0/0	1/3	1/1	2/2	0/0	0/0	45.5%	0	20.0%	0.06

(Continues)

TABLE 5 (Continued)

Type	Total Reports	Total P/P Donors	Total Recipients from P/P Donors	Recipients with Transmission ÷ Exposed Recipients										Recipients with P/P Transmission per 10,000 Transplanted Recipients During 2012-2017	Transmission-Related Deaths per 10,000 Transplanted Recipients During 2012-2017		
				kidney	pancreas	kidney/panc	liver	heart	lung	heart/lung	intestine	Recipients with P/P Transmission ÷ Recipients from P/P Donors	Graft Loss			Total Transmission-Related Deaths ÷ Recipients with P/P Transmission	
Total Fungal	237	35	115	18/52	0/0	0/3	11/30	6/13	15/20	0/0	0/0	0/0	41.7%	9	14.6%	2.67	0.39
Mycobacteria																	
Tuberculosis	63	3	12	0/4	0/0	0/1	0/3	0/2	3/3	0/0	0/0	0/0	25.0%	0	0.0%	0.17	0.00
Parasite																	
Strongyloides	52	10	29	3/12	0/0	3/3	5/9	1/3	3/3	0/1	1/1	1/1	44.8%	1	30.8%	0.72	0.22
Toxoplasmosis	18	8	30	2/12	0/1	0/1	2/7	4/6	1/3	0/0	0/0	0/0	30.0%	0	55.6%	0.50	0.28
Trypanosomiasis	7	1	5	0/2	0/1	0/0	1/1	0/0	0/1	0/0	0/0	0/0	20.0%	0	0.0%	0.06	0.00
Other	20	4	11	4/4	0/0	0/0	2/3	1/2	2/2	0/0	0/0	0/0	81.8%	2	22.2%	0.50	0.11
Total Parasite	97	23	75	9/30	0/2	3/4	10/20	6/11	6/9	0/1	1/1	1/1	42.7%	3	34.4%	1.78	0.61

Note: P/P = proven/probable

Recipients of multiorgan (other than kidney/pancreas or heart-lung) would appear under the column for each organ type they received.

The percentage "recipients with P/P transmission ÷ exposed recipients" is a count of unique donors regardless of number or types of organ received, thus the sum by organ type may be greater than the total recipients

Abbreviations: CMV, cytomegalovirus; CRV, community respiratory virus; HBV, hepatitis B virus; HCV, hepatitis C virus; LCMV, lymphocytic choriomeningitis virus; WNV, West Nile virus.

TABLE 6 Outcomes associated with proven and probable transmission of noninfectious, nonmalignant donor-derived disease by organ type (2012-2017)

Type	Total Reports	Total P/P Donors	Recipients with P/P Transmission ÷ exposed recipients							Recipients with P/P Transmission ÷ 10,000 Transplanted Recipients During 2012-2017	Transmission-Related Deaths per 10,000 Transplanted Recipients During 2012-2017		
			Total Recipients from P/P Donors	kidney	pancreas	kidney/panc	liver	heart	lung			Recipients with P/P Transmission ÷ Recipients from P/P Donors	Total Transmission-Related Deaths ÷ Recipients with P/P Transmission
Allergic	5	5	21	0/7	0/0	1/3	4/5	0/3	3/3	38.1%	3	0.446	0
Amyloidosis	4	3	7	0/3	0/0	1/1	2/3	0/0	0/0	42.9%	0	0.167	0.056
Hemochromatosis	4	2	2	0/0	0/0	0/0	2/2	0/0	0/0	100.0%	2	0.111	0
Other PDDTE	23	6	12	7/8	0/0	0/0	0/2	1/1	1/2	66.7%	0	0.446	0.056
Total Other	58	16	42	7/18	0/0	2/4	8/12	1/4	4/5	50.0%	5	1.170	0.111

Abbreviation: PDDTE, potential donor disease transmission event.

percent of recipients developed symptoms within 30 days of transplantation, and 88% within 90 days. Fungal and bacterial infection presented earliest after transplantation with median days to presentation of 14 days (range 2-45) for bacterial infection and 18 days (range 5-256) for fungal infection. No bacterial infection presented after 45 days. Viral infections presented a median of 48 days (range 11-776) after transplantation, parasitic infections 50 days (range 17-145), and mycobacterial infections 67 days (range 8-148).

3.10 | Pathogens with possible public health significance

Beginning in 2011, reports to the DTAC involving pathogens with potential public health significance were referred to the CDC. CDC led investigations on 270 reports; 65 of these resulted in proven/probable DDD. Bacterial organisms resulted in 4 cases, fungal 11, mycobacterial 3, parasitic 20, and viral 27. Notable pathogens resulting in transmission included *M. tuberculosis* (3/25), *Strongyloides* (10/32), HCV (15/52), HBV (3/25), West Nile virus (2/15), *Toxoplasma gondii* (6/11), *Coccidioides* (5/12), and *Histoplasma* (2/10).

4 | DISCUSSION

Disease transmission is an inherent risk of solid organ transplantation. In the DTAC experience, unanticipated DDD was uncommon, occurring in 0.18% of recipients, with 0.23% of donors transmitting proven or probable disease to at least 1 recipient. Although rare, DDD was associated with significant morbidity and mortality. Graft loss or death occurred in about 33% of recipients experiencing proven/probable unexpected DDD. Recipient death occurred at a higher rate in malignancy versus infection. Interestingly, renal cancer—the most common transmitted malignancy—was not associated with any deaths likely due to nephrectomy when recognized (often shortly after the time of transplantation). Of note, a previous report of the DTAC experience with renal cell carcinoma demonstrated no transmission to any recipients when the tumor was resected at the time of transplantation.¹⁹

Among infections, the mortality rate was 15% but was considerably higher for certain parasitic diseases (*Strongyloides* and *Toxoplasma gondii*) and among fungi, particularly *Coccidioides*. Delay in diagnosis likely contributes to the high mortality as these diseases may present with diffuse, difficult-to-recognize symptoms in the posttransplant period. Lack of consideration of donor exposures when evaluating recipient disease may also contribute to diagnostic delay.

Multidrug-resistant organisms (MDRO) are an emerging area of concern in transplantation. Transmissions of MDROs have been associated with poor recipient outcomes.^{13,20,21} Although DTAC data did not uniformly include antimicrobial susceptibility information, it is notable that among the 80 bacterial pathogens transmitted

TABLE 7 Time to presentation of donor-derived infection

	Median (Range)	0-30 days	31-90 days	91-180 days	> 180 days
Viral	48 days (11-776)	LCM WNV (4) RSV	CMV (3) Parvovirus WNV	Hepatitis C	Hepatitis B
Bacterial	14 days (2-45)	Assorted (23)	<i>Klebsiella</i>		
Fungal	18 days (5-256)	<i>Candida</i> (3) <i>Coccidioides</i> (6) <i>Aspergillus</i> <i>Cryptococcus</i> (4) <i>Scopulariopsis</i> <i>Zygomycetes</i> (2)	<i>Aspergillus</i> <i>Coccidioides</i> (3) Histoplasmosis		<i>Aspergillus</i>
Mycobacterial	67 days (8-148)	<i>M. tuberculosis</i> (2)	<i>M. tuberculosis</i> (2)	<i>M. tuberculosis</i> (2)	
Parasitic	50 days (70-145)	<i>Toxoplasma</i> <i>Balamuthia</i> (5)	<i>Strongyloides</i> <i>Toxoplasma</i> <i>Encephalitozoon</i> (2)	<i>Strongyloides</i> (2) <i>Toxoplasma</i> <i>Encephalitozoon</i> <i>Balamuthia</i>	

Abbreviations: CMV, cytomegalovirus; LCMV, lymphocytic choriomeningitis; RSV, respiratory syncytial virus; WNV, West Nile virus.

TABLE 8 Summary of key lessons learned

<p>Recognition of donor-derived disease Two thirds of DDI develop symptoms within 30 days of transplantation Endemic fungal, parasitic, mycobacterial may be manifest after 30 days Consider donor exposures in cases of unexpected recipient illness Although infections predominate, one third of DDD is noninfectious DDD from living donors may occur but is less common than from deceased donors</p>	<p>Trends requiring future confirmation Breast cancer and thyroid cancer were not transmitted using current screening protocols Respiratory viruses, mycoplasma, tuberculosis, aspergillus primarily transmitted to lung recipients Bacterial and candida DDI rarely noted later than 30 days posttransplant D + R- toxoplasma non-heart recipients are at high enough risk to merit prophylaxis Peanut allergy rarely transmitted to kidney recipients No proven/probable transmissions of atypical mycobacteria or prion disease DDD from malignancy (other than renal cell carcinoma) has highest mortality MDRO organisms are a common cause of bacterial DDI</p>
<p>Donor evaluation Critical evaluation to determine accuracy of listed cause of death Consideration of universal or targeted donor testing (even if results learned posttransplant as early interventions effectively prevent development of disease) <i>Strongyloides</i> <i>Coccidioides</i> <i>Cryptococcus</i> Improved mechanism for development and evaluation of donor tests</p>	<p>System improvements Improve early warning systems and global harmonization to recognize and address emerging trends Lengthen and improve follow-up to better attribute death, graft loss Active tracking of recipients of donors with findings that suggest risk Rapid ability to scale up testing as new pathogens emerge</p>
<p>Reporting Critical as profound impact on other recipients because involvement of multiple recipients common allowing for interventions; graft or death loss occurred in about one third of recipients with DDD Culture of safety: reporting does not result in penalties unless significant policy violations DTAC information benefits all in transplant community Morbidity and mortality of DDI significant and attention to OPO or UNOS DDI communications necessary</p>	

Abbreviations: DDI, donor-derived disease; DDD, donor-derived disease; MDRO, multidrug-resistant organisms; HTLV-1, human T-cell lymphotropic virus; OPO, organ procurement organization; DTAC, disease transmission advisory committee; UNOS, united network for organ sharing.

methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Acinetobacter spp.*, *Burkholderia*, and *Pseudomonas* accounted for 29/80 (36%) of transmitted bacteria.

Living donors, who can be thoroughly assessed pretransplant, were rare sources of proven/probable DDD. The overall risk of acquiring a DDD or dying of DDD was about 10-fold lower in recipients of living

compared to deceased donors. Likely, the relative ease of evaluating living donors and the increased risk among deceased donors of hospital-acquired infections accounts for this difference. Reporting discrepancies (centers less likely to report a suspected transmission since the OPO system and risk to other recipients not involved), may have resulted in an underestimation of the risk of living donor transmission.

Although the majority of DDD are either infection or malignancy, the DTAC experience includes 21 donors transmitting other disease processes. Peanut allergy was the most common, transferred from 5 recipients. Interestingly, 4 of these donors were under the age of 18. Donor-derived food allergy has been described for at least 20 years, and in 1 review of previously reported cases the vast majority (>100 cases) were reported in liver recipients, presumably because of the persistence of hematopoietic stem cells preferentially in that organ.^{22,23} In the DTAC series, lung and kidney-pancreas (but not kidney alone) also developed peanut allergy, which is consistent with previous reports.²²

Although laboratory and clinical screening of potential donors are critical components of a prevention strategy, practical considerations including asymptomatic carriage of transmissible disease and time/technical limitations on testing deceased donors mean that DDD is currently an inevitable consequence of solid organ transplantation.²⁴ Thus a high index of suspicion leading to early recognition is necessary both to treat the index case and to allow strategies to prevent transmission to other recipients of the involved donor. Our data indicate that although most bacterial and *Candida* infections occur in the first 30 days after transplantation, some infections may have extended latency periods and should be considered in evaluating recipients in whom considerable time has elapsed since transplant. Prominent among these are *M tuberculosis*, *Strongyloides*, and endemic fungi. In some cases, this may involve reviewing donor information regarding exposures to pathogens that might not otherwise be considered.

Although for many DDDs all organ recipients are at risk and a high rate of penetrance among exposed recipients has been observed (eg, HCV and *Strongyloides*),^{6,9,18} lung recipients are disproportionately at risk for certain DDI. With 1 exception, only lung recipients developed DDI with community respiratory virus, *Mycoplasma*, and *Aspergillus*.

The DTAC is not intended to provide specific treatment recommendation or conduct public health investigations. Reports to the DTAC may involve syndromes or pathogens of potential public health interest and these reports are reviewed by CDC ex officio committee members. The CDC is able to alert and advise local public health authorities and access CDC laboratory expertise. This process can be invaluable particularly for rare pathogens where local familiarity and diagnostic capability may be limited. Of interest, 40 recipients or reports investigated by the CDC were classified as IWDT. It is likely that guidance from CDC or local public health authorities prevented transmission to some of these exposed recipients.

A critical function of the DTAC system is to make sure that, when concern for DDD exists, all centers with recipients of organs from

that donor are notified. The designation IWDT is used for exposed recipients treated to prevent development of donor-derived disease. We identified 98 exposed recipients classified as IWDT from a PDDTE where at least 1 recipient developed proven/probable DDI. These exposed recipients were treated preemptively (eg, ivermectin for *Strongyloides* exposure). In these cases, the system appears to be working as intended to avoid the development of disease in exposed recipients.

Efforts intended to reduce the impact of DDD have focused on HIV, HCV, and HBV. The widespread application of donor NAT testing has reduced the time from infection to detection and reduced the risk of window period transmission.²⁵⁻²⁷ Further, given the high rates of posttransplant cure of HCV, the consequences of unexpected HCV transmission are less significant. Our data demonstrate that, among DDD, malignancy and particular categories of infection that are difficult to screen for (or for which an adequate history of exposure could not be obtained) pose a significant threat. Thus, future efforts should emphasize measures to improve the recognition and management of malignancy, fungal pathogens such as *Coccidioides*, and parasitic diseases. In addition, consideration should be given to screening tests that lead to effective posttransplant interventions that mitigate risk, without reducing organ utilization. One example would be *Strongyloides*, which can be effectively prevented with recipient treatment with ivermectin even if the result is learned post-transplant. These efforts may involve targeted (eg, Chagas disease or HTLV-1), or universal (eg, *Strongyloides* or *Coccidioides*) screening in areas of relatively higher endemicity in the donor population.²⁸⁻³⁰ Ideally, the uniform donor risk assessment interview form could be modified to trigger appropriate laboratory testing.

This report describes a multiyear effort to better understand and describe DDD, but has a number of limitations. Reporting of potential DDD is mandatory but passive (ie, there is no active case finding), and likely results in underreporting. Classification may be affected by difficulty obtaining sufficient confirmatory information. Awareness of DDD in 1 recipient may result in other recipients receiving treatment that prevents or attenuates transmission of disease. Although this is an intended benefit of the DTAC system, preemptive treatment may result in an underestimation of the penetrance of donor transmission. Further, preventative strategies (such as antimicrobial prophylaxis of heart recipients at risk for toxoplasmosis) would tend to bias results regarding the relative risk of transmission faced by recipients of different organ types. Limited information on the recipient is available, and both death and graft loss reported to the OPTN may not be attributable to DDD. On the other hand, OPTN policy requires a follow-up report 45 days following the initial report. For that reason, 45 days was chosen as the arbitrary cutoff to associated mortality with the donor-derived event. This short reporting period might underestimate the mortality associated with DDD, particularly related to malignancy events. Lastly, the DTAC categorization protocol evolved over the years, and classification of the probability of transmission to each recipient (rather than the transmission event as a whole) was not done during the entire study period.

Table 8 summarizes our view on the key lessons learned. Our report suggest that future efforts should focus on the transmission of malignancy, fungal and parasitic pathogens, and MDROs. System improvements include increasing the follow-up period to allow for better attribution of death and graft loss. In 1 improvement already in place, for malignancy reports United Network for Organ Sharing staff now reach out to transplant centers for follow-up at 2-years post report. In addition, more active tracking of recipients of donors with findings that suggest increased risk should be undertaken. Further, harmonization with other global systems that track DDD in is critical to the development of more robust data to provide “early warning” as pathogens move from continent to continent. Improved industry and regulatory attention to the rapid development and licensing of tests for donor evaluation is also needed. These improvements can assist the transplant community in crafting balanced policy and guidance that protects recipients but minimizes the discard of uninfected organs. The rapid spread of coronavirus disease 2019 (COVID-19) demonstrates the need for a flexible and adaptive system that can recognize emerging threats to the safety of recipients.

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DISCLOSURE

The authors of this manuscript have conflicts of interest as described by the *American Journal of Transplantation*. Dr Michael Ison has been a paid consultant for Viracor-Eurofins, which conducts testing of deceased donors for transmissible disease. No other author has a conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared (data collected under medical peer review).

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