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Infectious Disease Transmission in Solid Organ Transplantation: Donor Evaluation, Recipient Risk, and Outcomes of Transmission

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Abstract. In 2016, the Transplantation Society of Australia and New Zealand, with the support of the Australian Government Organ and Tissue authority, commissioned a literature review on the topic of infectious disease transmission from deceased donors to recipients of solid organ transplants. The purpose of this review was to synthesize evidence on transmission risks, diagnostic test characteristics, and recipient management to inform best-practice clinical guidelines. The final review, presented as a special supplement in Transplantation Direct, collates case reports of transmission events and other peer-reviewed literature, and summarizes current (as of June 2017) international guidelines on donor screening and recipient management. Of particular interest at the time of writing was how to maximize utilization of donors at increased risk for transmission of human immunodeficiency virus, hepatitis C virus, and hepatitis B virus, given the recent developments, including the availability of direct-acting antivirals for hepatitis C virus and improvements in donor screening technologies. The review also covers emerging risks associated with recent epidemics (eg, Zika virus) and the risk of transmission of nonendemic pathogens related to donor travel history or country of origin. Lastly, the implications for recipient consent of expanded utilization of donors at increased risk of blood-borne viral disease transmission are considered.

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The unanticipated transmission of an infectious disease from an organ donor to recipient(s) is a rare event; however, when it does occur, it is associated with significant morbidity and mortality.[1] Therefore, it is the goal of organ donation and transplantation programs to minimize such events while simultaneously maximizing opportunities for transplantation. This goal relies on (i) rational donor screening policies based on an understanding of the epidemiology of infectious diseases of interest and the performance characteristics of the tests used to diagnose them, and (ii) evidence regarding patient outcomes in the event of disease transmission, to facilitate informed decision making with regard to the risk tradeoff between accepting an organ with an increased risk of disease transmission versus remaining on the waiting list.

This literature review summarizes case reports, peer-reviewed literature, and international guidelines on the following topics:

i. donor-derived infectious disease transmission events in recipients of solid organs from deceased donors;
ii. residual risk of bloodborne virus transmission under different deceased donor scenarios;
iii. the impact on recipient outcomes of the transmission of viral, bacterial, parasitic, fungal, and other infectious diseases;
iv. diagnostic test availability, modality, and performance, and international guidelines for donor screening;
v. clinical practice strategies for minimizing transmission risk from increased-risk donors;
vi. current international recommendations with respect to recipient management posttransplant in the event of possible infectious disease transmission;
vii. vigilance and surveillance systems in organ donation and transplantation.

The potential to transmit bloodborne viruses (BBV)—human immunodeficiency virus (HIV), hepatitis C virus

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(HCV), and hepatitis B virus (HBV)—is of particular concern in the transplantation context, and HIV, HCV, and HBV are the primary focus of this review. Other pathogens that are discussed in detail include human T-lymphotropic virus-1 (HTLV-1), influenza, herpes simplex virus (HSV), *Treponema pallidum*, *Mycobacterium tuberculosis*, multidrug-resistant bacteria, *Strongyloides stercoralis*, *Toxoplasma gondii*, malaria, and transmissible spongiform encephalopathy disease.

Other pathogens of special interest that are also discussed include West Nile Virus (WNV) and Zika virus.

The review excludes:

i. detailed discussion of the biological mechanisms of disease transmission;
ii. cell and tissue donation;
iii. transmission of noninfectious diseases, such as cancers;
iv. discussion of recipient quality of life as a consequence of disease transmission;
v. discussion of experimental interventions, drugs, or diagnostic tests still in the development pipeline (including genomic approaches to pathogen identification);
vi. vascularized composite allotransplantation (VCA): given that the intended outcomes of VCA is quality of life (not

survival), much stricter donor eligibility criteria apply with regard to risk of infectious disease transmission;
vii. animal to human transmission of zoonotic disease;
viii. detailed review of protocols for adverse event reporting (biovigilance is addressed in the Australian Vigilance and Surveillance Framework for Organ Donation for Transplantation);
ix. explicit recommendations for policy and practice;
x. living donor transplantation.

Lastly, although our understanding of the microbiome contained within specific organs, particularly lung and small bowel, is growing, there are at present limited data on the impact of its transfer on recipients, and transfer of microbiota is not generally considered in donor evaluation. The transfer of the microbiome is, therefore, not addressed, with the exception of a brief discussion of current existing evidence regarding the impact on recipient outcomes of the transmission of the lung virome.

Definition of Donor-derived Infectious Disease Transmission

The majority of donor-derived infectious disease transmission events are expected: that is, the donor is known to be

TABLE 1.

Definitions of imputability for donor origin of disease transmission—United States[a1,4]

Terms	Definition
Proven	Clear evidence of the same infectious disease in the donor and at least one of the recipients. All of the following conditions must be met: • Suspected transmission event • Laboratory evidence of the suspected organism (or malignancy) in a recipient • Laboratory evidence of the same organism (or malignancy) in other recipients (if multiple recipients) • Laboratory evidence of the same organism or malignancy in the donor • If there is pretransplant laboratory evidence, it must indicate that the same recipient was negative for this organism before transplantation[b]
Probable	Strong evidence suggesting but not proving disease transmission. Both of the following 2 conditions must be met: • Suspected transmission event; and • Laboratory evidence of the suspected organism (or malignancy) in a recipient AND at least one of the following criteria must also be met: • Laboratory evidence of the same organism or malignancy in other recipients • Laboratory evidence of the same organism or malignancy in the donor If there is pretransplant laboratory evidence, it must indicate that the same recipient was negative for this organism before transplantation
Possible	Used for all situations where data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probably) and transmission cannot be formally excluded The following conditions must be met: • Suspected transmission event; and • Laboratory evidence of the suspected organism or malignancy in a single recipient, or; • Data that strongly suggest but do not prove a transmission event
Unlikely	Used for situations where it is possible that the disease in question could have been transmitted from the donor to at least one of the recipients but the available data suggests that donor origin is unlikely
Excluded	Clear evidence of an alternative, nondonor origin of disease
Intervention without documented transmission	All or some of the recipients received an intervention (ie, antimicrobial therapy, specific immunoglobulins or organ removal) and no disease was recognized in any of the recipients
Positive assay without apparent disease transmission	Used for instances in which a donor assay is positive for infection (ie, coagulase-negative Staphylococcus in perfusate culture) that is felt by the clinicians not to be clinically significant, is not treated, and not associated with disease transmission
Not assessable	When there are insufficient data available to assess imputability of the disease transmission (either from insufficient data being provided in a published document or insufficient donor and/or recipient testing)

[a] Sources are directly quoted, which is why malignancy is mentioned in this context despite not being a focus of the current review.
[b] If there were only a single recipient of organs from the donor, there would have to be clear signatures tying the donor and recipient pathogen to classify as proven (ie, molecular fingerprinting of bacteria). If this was not possible, a lower grade classification would be used.

TABLE 2.

Definitions of imputability for donor origin of infectious disease transmission—Europe[5,6]

Term	Definition
Definite/certain	Conclusive evidence beyond reasonable doubt for attribution to process or transplanted organ.
Likely/probable	The evidence is clearly in favor of attributing the adverse reaction to the process or transplanted organ.
Possible	The evidence is not clear for attributing the adverse reaction to the process or transplanted organ, or to alternative causes.
Unlikely	Evidence clearly in favor of attribution to alternative causes.
Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes—that is, there is evidence clearly in favor of attributing the adverse reaction to other causes than the process or transplanted organ.
Not assessable	Insufficient data for imputability assessment.

infected with a given pathogen (eg, cytomegalovirus [CMV] or Epstein-Barr virus [EBV]). It is expected that this pathogen will be transmitted to the recipient(s) of their organs, for whom risk mitigation strategies will be used (eg, prophylaxis and/or monitoring) to minimize the impact on graft and patient outcomes. On rare occasions, however, unexpected transmissions occur. Unexpected transmissions are defined as the transmission of a pathogen from donor to recipient, despite donor screening to rule out the presence of donor infection. Unexpected transmissions are most likely to occur if the donor has recently acquired the infection and is still in the eclipse period or serological window before detection is possible, if testing is not undertaken, if sensitive diagnostic tests are not readily available, or if the donor is infected with a rare or emergent pathogen that is not included in standard screening protocols. Unexpected transmissions may also occur due to incomplete or inaccurate donor information, or due to communication or system failures.[2] Unexpected transmissions are more likely to occur in the context of deceased donation; however, they can also occur in living donor transplantation. United States surveillance data collected from 2008 to 2013 found that 0.16% of deceased donor organ transplants and 0.01% of living donor transplants were unexpectedly complicated by donor-derived infectious disease; the rate of mortality as a consequence of this disease transmission was 22%.[3]

One of the difficulties when reviewing the evidence on unexpected donor-derived infectious disease transmission events is that attributing origin of disease to the donor is not always straightforward. For this reason, standard definitions of imputability for donor origin of infectious diseases in transplant recipients have been developed in the United States and Europe (see Table 1 and Table 2). Transmission events reported in this review refer to proven/definite and probable/likely cases unless otherwise specified.

Standardized definitions of imputability are an essential component of biovigilance—without agreed upon criteria, it is very difficult to determine which adverse events should be counted by surveillance systems. Even with standardized criteria for classifying donor-derived disease transmission, it is not always possible to definitively classify reported cases.[1] Some of the required confirmatory tests may not have been performed or appropriate specimens or cultures may not be available for retrospective testing. Pretransplant recipient blood or sera are often not available, meaning it cannot be definitively established whether the recipient had latent infection before transplantation, or cultures may not have been maintained to permit molecular fingerprinting of donor and recipient bacterial strains. It is, therefore, important that

frozen serum and other samples be maintained for every donor so that, if investigation is required, sufficient archived samples are available to prove or exclude the donor as the origin of the infectious disease transmission.[5]

Donor Risk Stratification

Donor-related infectious disease transmission risk can be conceptually divided into 2 stages: the pretransplant phase and the posttransplant phase. In the pretransplant phase, the concept of "transmission risk" refers to the theoretical probability of disease being transmitted from donor to recipient based on what is known about the donor and the pathogen(s) in question. In the pretransplant phase, risk mitigation practices consist of[1]:

   i. risk assessment of the donor based on their medical and social history, in the context of local epidemiological information;
   ii. careful physical examination of the donor and the donor organs;
  iii. laboratory screening of biological samples taken donor for evidence of infection.

In the posttransplant phase, "transmission risk" (or "potential transmission") refers to the potential for live donor cells capable of transmitting a known infectious pathogen to result in an infection in the recipient. In the posttransplant phase, risk mitigation practices consist of:

   iv. prophylaxis in the recipient (including antimicrobials, immunoglobulin and/or vaccination),
   v. additional screening of donor samples (eg, finalizing blood and urine cultures and drug sensitivity testing if these were not completed before transplant),
   vi. posttransplant monitoring of recipients,
  vii. adverse event reporting and biovigilance systems.

Risk stratification of the donor is a triage step that identifies donors who should undergo additional screening tests, and also flags when specific recipient consent may be required. In the United States, donors are dichotomized as being either at increased risk or without identified risk.[7] In Europe, a graded system specifying 5 levels of risk, originally developed for donor evaluation by the Italian National Centre for Transplantation, was used until recently (see Table 3); Europe has now also transitioned to a system of dichotomous categorization of donor risk.[8] The approach currently used in Australia similarly defines potential donors as either increased-risk or non–increased-risk.

The categorization of donors according to the degree of infectious disease risk associated with their medical and social history can be useful for several reasons. First, it identifies donors for whom more sensitive diagnostic tests may be warranted

Risk levels for potential organ donors, as defined by the Italian National Transplant Centre[8]

Category	Definition
Unacceptable risk	Includes HIV-1/2–positive donors, current neoplastic conditions with some precisely defined exceptions, present nontreatable systemic infection, and prion disease.
Increased but acceptable risk	Although the risk of infection is present, organ use is acceptable in the light of a risk-benefit assessment, for example, in cases of patients with fulminant hepatitis, liver primary nonfunction, or patients undergoing hepatectomy for trauma with organ function loss. In such cases where there is no chance of survival, the use of an organ with increased risk of transmission of infectious or neoplastic disease is justified by the clinical urgency. Appropriate prophylaxis should be administered to the recipient where possible.
Calculated risk	If the presence of a specified pathogen or the serological status of the donor (HBsAg+, anti-HCV+, or HBcAb+) is compatible with transplantation into recipients with the same disease or serological status, this is considered calculated risk. This category of risk includes donors with meningitis submitted to targeted antibiotic therapy for at least 24 hours and donors with bacteremia who have started target antibiotic therapy.
Not assessable risk	Defined as where 1 or more assessment elements are missing (eg, failure to collect an accurate medical history, unavailability of microbiology data despite well-grounded suspicion of infectious pathology) and the evaluation process does not allow an appropriate risk assessment for transmittable diseases. In such cases, tests and checks have to be performed to consider the donor as suitable and identify those conditions that represent an absolute or relative contraindication to donation (biomolecular tests, autopsy). If they cannot be performed, donor organs can only be used in case of emergency, after informed consent of the recipient.
Standard risk	When the evaluation process does not identify any risk factor for transmittable disease. However, because null risk does not exist, infectious or neoplastic pathologies can still be transmitted even if guidelines and good clinical practice are followed.

HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

(eg, nucleic acid testing [NAT]), and gives appropriate context to the interpretation of results from serological tests, which might yield false-positive or false-negative results and cannot detect very recently acquired infections where the individual is still within the serological window/eclipse phase. Second, by assigning a risk category to potential donors, this facilitates discussions with the potential recipient about the risks associated with a particular donor organ and may, therefore, simplify the consent process.

On the other hand, a "labeling effect" has been described whereby describing donors as either "standard risk" or "increased risk" may lead to higher rates of organ discard. In the United States, for example, up to 20% of organs fall under the United States Public Health Service (PHS) criteria for high risk of HIV, HBV, and HCV (labeled PHS-IR), and the utilization rate for these organs is significantly lower than for non–PHS-IR organs. This is despite the absolute risk of disease transmission being extremely low and posttransplant survival being equivalent for recipients of PHS-IR and non–PHS-IR organs.[9,10] Patients and their physicians may be reluctant to accept organs labeled with pejorative descriptors, such as "increased-risk," if they have the possibility of waiting for an organ perceived to be without risk of HIV, HBV or HCV.[11-13] Patient education and consent processes, therefore, need to provide patients with an objective understanding of the infectious disease risks associated with organ transplantation, framed in terms of the trade-off between potential risks and potential benefits involved in organ acceptance decisions.

In 2017, the Victorian and Tasmanian Renal Transplant Advisory Committee established a new waiting list for patients awaiting a deceased donor kidney transplant who have consented to receive a kidney from a donor at increased risk of HIV, HBV, and HCV (referred to as an increased viral risk (IVR) donor). IVR donors are defined as (i) having known increased risk behavior and (ii) risk behavior being within the NAT window for HIV, HBV, or HCV detection (defined as 22 days from admission to hospital) and (iii) having no evidence of active infection (negative serology/NAT). More information on the patient education and consent process to join the IVR donor waiting list is given in *Recipient Consent*.

As of November 2017, the surveillance of adverse events after organ transplantation in Australia and New Zealand was performed at the individual jurisdictional level; however, a framework for an integrated, nationwide biovigilance, and surveillance system has been developed and is in the process of being implemented (see *Vigilance and Surveillance*). The historical absence of an integrated biovigilance and surveillance system means that a central database of infectious disease transmission events occurring in Australia and New Zealand does not currently exist. Table 4 was compiled based on expert consultation and summarizes occurrences of serious adverse events involving infectious disease transmission from organ donors to recipients from 2008 onward (no cases older than 10 years were reported by any of the expert consultants and the most recent reported case occurred in 2016; no cases were reported from New Zealand). Details were obtained for a total of 18 transplants complicated by donor-derived infections between 2008 and 2016, from which there were 8 deaths (mortality rate of 44%). No 2 cases involved the same pathogen. Assuming that the list of cases in Table 4 is relatively comprehensive, then this indicates that approximately 0.18% of deceased donor organ transplants in Australia were unexpectedly complicated by donor-derived infectious disease transmission between 2008 and 2016 (18 transmission events vs approximately 10000 solid organs transplanted from deceased donors in Australia). This rate is similar to the reported rate of donor-derived infectious disease transmission in the United States of 0.16%.[3]

Current Utilization of Increased-risk Donors

In 2015, 2.7% of actual organ donors in Australia and New Zealand had drug overdose listed as a cause of death (P. Clayton, personal communication). The corresponding proportion in the United Kingdom was 0.3%, whereas in the United States, it was 9.3% (see Figure 1). Although the very large proportion of donors derived from drug overdose deaths in the United States might suggest a case for greater utilization of increased-risk donors in Australia and

TABLE 4.

Clinical characteristics and outcomes of unexpected infectious disease transmission events in Australia (published and unpublished reports) involving deceased donors

Author	Year	Pathogen	Organ transplanted	Recipient details	Clinical course/symptoms	Acute rejection	Graft lost	Death
Le Page et al[14]	2010	Influenza B virus	Kidney	14-y-old male	Severe respiratory distress and fever	Day 14	No	No
			Lung	17-y-old female	No (vaccinated and received oseltamivir prophylaxis)	No	No	No
Pilmore et al[15]	2009	HHV-6	Kidney	47-y-old male, second transplant	Severe diarrhea, liver dysfunction, pancytopenia, acute abdomen	No	No	Day 31
			Kidney	33-y-old male, combined heart/kidney transplant	Severe musculoskeletal pain, liver dysfunction, pancytopenia, thrombocytopenia	No	No	No
Jensen et al[16]	2016	*M. tuberculosis*[a]	Lung	31-y-old woman	Cough	No	No	No
Palacios et al[17]	2008	Arenavirus	Kidney	63-y-old woman	Fever, sepsis, encephalopathy, acute tubular necrosis, chest infiltrates	Yes	No	Day 36
			Liver	64-y-old woman	Fever, confusion, encephalopathy with myoclonus, chest infiltrates	No	No	Day 30
			Kidney	44-y-old woman	Fever, intraabdominal hematomas and effusion, encephalopathy	Yes	No	Day 29
Personal communication (K Wyburn)	2008/2009	HCV	Kidney[b]	28-y-old woman	—	No	No	No
Personal communication (P Clayton)	2009	Pseudomonas	Kidney	—	Fever, sepsis, cardiac arrest due to pseudomonal mycotic aneurysm in the transplant renal artery anastomosis, hypoxic brain injury	No	Yes	No
Macesic et al[18]	2017	HSV-2	Kidney/pancreas[c]	Male, 30s	Initial AMI and cardiac arrest, intermittent fever and critically ill. Declared brain dead and donated lungs and transplanted kidney	No	No	Day 9
			Liver	Female 20s	Hepatitis noted day 12 posttransplant, followed by a rash suggestive of cutaneous HSV on day 19. Subsequent resolution with antiviral therapy	No	No	No
			Heart/lungs	Female 40s	Asymptomatic	No	No	No
			Kidney	Male 40s	Asymptomatic	No	No	No
			Kidney[c]	Male 60s	Asymptomatic	No	No	No
			Lungs[c]	Female 60s	Asymptomatic	No	No	No
Rogers et al[19]	2008	*T. gondii*	Kidney	60-y-old male	Kidney dysfunction, liver dysfunction, tachypnea, hypoxia, hypotension, cardiogenic shock	No	No	Day 30
			Kidney	59-y-old female	Fever, hypotension, thrombocytopenia, liver dysfunction, multiorgan failure, cardiogenic shock	No	No	Day 32
(Personal communication A Webster & D Verran)	2015	Disseminated candidiasis	Kidney	—	—	—	Yes	Day 98

[a] Does not meet definition of proven/probable donor-derived *M. tuberculosis* as laboratory evidence of the same pathogen in the donor was not available. Instead, investigation of the donor found a history of latent tuberculosis, and contact tracing found the same strain of *M. tuberculosis* in the recipient and the index case.

[b] HCV was transmitted to the recipient of 1 kidney; however, the second potential recipient avoided transmission as results of retrospective NAT were available before the transplant surgery.

[c] The kidney-pancreas recipient of the original donation died 9 d posttransplant and his lungs and the previously transplanted kidney were retrieved and transplanted into 2 new recipients.

HHV, human herpes virus; HCV, hepatitis C virus; HSV, herpes simplex virus.

New Zealand, international practice must be interpreted in context, and benchmarking approached with caution. The high proportion of drug overdose as a cause of death in the United States donor population is a consequence of the current opioid epidemic, which has caused a 2.5-fold increase in drug-related deaths from 2000 to 2015. More than 6 of 10 drug overdose deaths in the United States were due to opioids (including opioid pain relievers and heroin) in 2014.[20] The number of organ donors in the United States with drug overdose listed as the cause of death increased 350% between 2003 and 2014 (n = 138 vs n = 625).[21]

Compared with a drug-related mortality rate in the United States population aged 15 to 64 years in 2014 of 233.8 per million population, the drug-related mortality rate in Australia in 2013 was 116.2 per million population aged 15 to 64 years; in New Zealand, it was 26.7 per million population aged 15 to 64 years.[22] In the United Kingdom, the drug-related mortality rate was 66.7 per million population
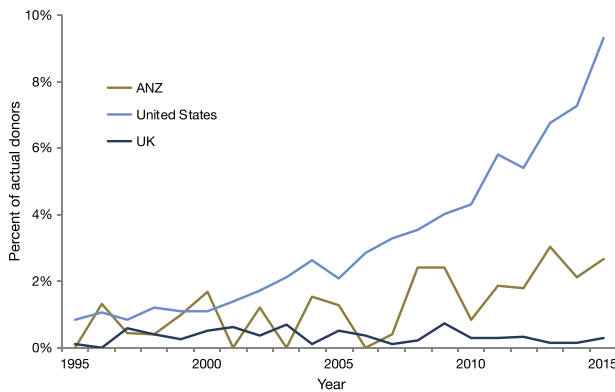
FIGURE 1. Twenty-year trends in the percentage of donors with drug overdose (intended or unintended) as a cause of death in Australia and New Zealand (ANZ) compared with the United Kingdom (UK) and United States (data sources: Australia and New Zealand Organ Donation Registry [ANZOD], Organ Procurement and Transplantation Network [OPTN], National Health Service Blood and Transplant [NHSBT]).

aged 15 to 64 years in 2014.[22] In all 3 countries, opioids were the number one drug causing death.[22] Notably, the rate of deaths due to opioids (including prescription opioids) in Australians aged 15 to 54 years has been increasing since 2007, reaching 44.7 deaths per million population (n = 564) in 2012 versus 30.4 in 2007, although rates are still far below their 1999 peak of 101.9 deat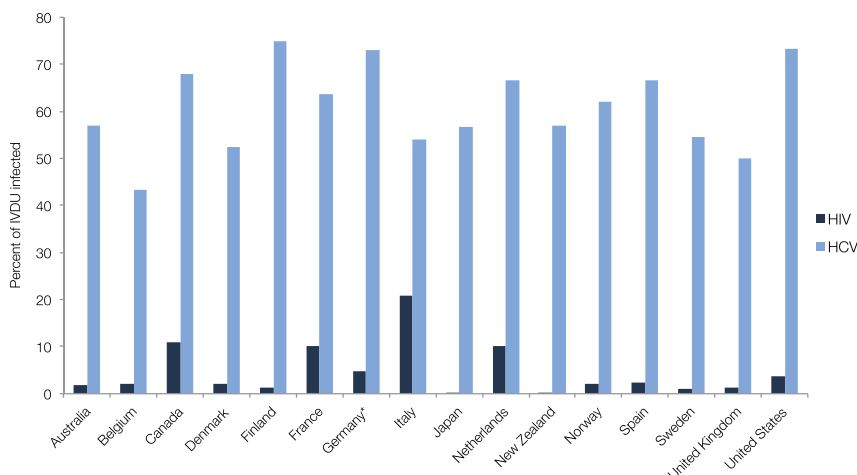hs per million population.[23,24] There has also been a spike in fatalities related to methamphetamine use in Australia: between 2009 and 2015, the annual number of methamphetamine-related deaths doubled, from around 150 to 300 per year.[25]

Also relevant when making any international comparisons with respect to utilization of increased-risk donors is the underlying prevalence of BBV in the population. Among intravenous drug user (IVDU) populations in the United States, United Kingdom, Australia, and New Zealand, the estimated prevalence of HIV in 2016 was 3.6%, 1.3 %, 1.7%, and 0.2%, respectively.[26] Estimated prevalence of HCV in IVDU populations in 2016 was 73% in the United States, 50% in the United Kingdom, 57% in Australia, and 57% in New Zealand.[22] Comparisons of BBV prevalence in the IVDU populations of selected high-income countries are shown in Figure 2.

Vigilance and Surveillance

Although cases of donor-derived disease transmission are rare, the immediate reporting and investigation of any posttransplant infection in the recipient and the notification of other recipients of organs and tissues from the same donor is imperative to prevent/minimize harm to those exposed. At the level of the transplant center/jurisdictional health service, systems must be in place to immediately notify the relevant physicians and to rapidly assess recipients of other organs or tissues from the infected donor. Ideally, centralized reporting of serious adverse events should also occur to enable monitoring of frequency and outcomes of infectious disease transmission and to facilitate continuous improvement in safety standards and practices in donation and transplant systems (involving the DonateLife agencies).

In May 2010, Resolution 63.22 of the World Health Assembly added 2 pertinent items to the World Health Organization's Guiding Principles on Transplantation:

Guiding Principle 10:

The level of safety, efficacy, and quality of human cells, tissues, and organs for transplantation, as health products of an exceptional nature, must be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported, both nationally and for exported human products.

Guiding Principle 11:

The organization and execution of donation and transplantation activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients are always protected.

This Resolution, therefore, defines an international obligation among countries with organ and tissue transplantation programs to have systems in place for quality assurance, traceability, vigilance and surveillance, and transparent reporting of adverse events. Not only is this critical to the continuing improvement of individual transplantation programs but also the more data that are available on adverse events and their outcomes, the more that all transplant programs can improve policy and practice. Serious adverse events are rare, which makes decision making complicated given a lack of prior experience or existing evidence. Greater international reporting of such events enables better decision making at the individual patient level in

FIGURE 2. Estimated prevalence of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) among people who inject drugs in selected high-income countries. HCV prevalence estimates represent mid-range estimates (source of HCV data: United Nations Office on Drugs and Crime http://unodc.org; source of HIV data: UNAIDS aidsinfo. unaids.org). *HCV estimate for Germany represents high range estimate for the year 2011. IVDU, intravenous drug users.

terms of risk mitigation and recipient management. It also improves standards of informed consent as the trade-offs between transplantation with an increase-risk organ versus nontransplantation will be better understood.

Internationally, however, centralized systems for surveillance of donor-derived infectious disease transmission events are still largely nonexistent or in developmental stages. Well-established biovigilance systems currently exist only in France, Italy, and the United States. Australia has been working toward the development of a vigilance and surveillance system since 2011, and a formal framework for this system was published in September 2016.[27] Further development and the implementation of this framework by the Vigilance and Surveillance Expert Advisory Committee are underway.

The Australian vigilance and surveillance system will operate in parallel with existing, jurisdictional clinical incident management systems, providing coordinated notification of serious adverse events and handling data collection and analysis. The clinical management and investigation of serious adverse events will remain the responsibility of the hospital and jurisdictional health authorities where the incident occurs. The objectives of the national vigilance and surveillance system are to enable centralized collection and review of information on serious adverse events, to coordinate interjurisdictional notification where appropriate, and to share de-identified information on events and outcomes internationally. The 2016 framework document outlines a governance structure, system requirements for vigilance and surveillance, performance monitoring strategies, data collection requirements, and requirements for linkages and harmonization of reporting with international vigilance and surveillance systems.[27]

INTERNATIONAL VIGILANCE AND SURVEILLANCE SYSTEMS

Europe

The European Union has implemented several pieces of legislation with relation to the quality and safety of human tissues and cells, including Directives issued in 2006 specifying technical requirements for traceability and notification of serious adverse events and reactions, and in 2010 specifying standards of quality and safety of human organs intended for transplantation. From 2009 to 2012, the Substances of Human Origin Vigilance and Surveillance project developed guidance documents for EU Member States for the establishment of effective vigilance and surveillance systems for tissues and cells for transplantation and assisted reproduction.[28] In 2011, the European Framework for the Evaluation of Organ Transplants project developed a framework for a pan-European registry of organ and transplant registries, including a set of recommendations with respect to vigilance and surveillance in organ transplantation (http://www.notifylibrary.org/content/european-framework-evaluation-organ-transplants-efretos).

The European Directorate for the Quality of Medicines & HealthCare (EDQM) makes the following recommendations with respect to vigilance and surveillance in organ transplantation[5]:

- governance structures must be defined and understood by stakeholders;
- health authorities should develop reporting procedures, standardized notification forms, surveillance methods, acceptable risk criteria, and examples of serious adverse events that must be reported;
- operating procedures must be in place defining how transplant centers are to identify, report, investigate, and communicated adverse events;
- to assist the investigation of adverse events, frozen serum and cell samples should be maintained for every donor;
- reporting should include a description of the adverse event, a root cause analysis, and a description of steps taken to resolve the problem/avoid similar events occurring in future;
- adverse events should be reported immediately, before investigation and confirmation, with all health authorities, transplant centers, and tissue establishments being alerted;
- ideally, transplant centers should have a designated vigilance coordinator;
- central coordination and oversight should be in place for center level vigilance and surveillance and quality management systems;
- regular audits should be conducted of data collection procedures and the investigation of adverse events by transplant centers;
- computerized systems for data collection and management should be established;
- data collection should be integrated with existing organ donation and transplant registries.

United Kingdom

United Kingdom Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) guidelines recommend the routine screening of recipients at 1 year posttransplant for presence of pathogens potentially transmitted from the donor.[29] Nucleic acid testing is preferred to account for the effect of immunosuppression on serological test accuracy, and ideally, samples from the recipient taken pretransplantation would be available to differentiate between preexisting and newly acquired disease. The SaBTO guidelines make the following recommendations where there is potential transmission[29]:

- it is essential that confirmatory testing, including NAT assays, be undertaken on the donor sample to confirm specificity of the serological reactivity and the likelihood of transmission;
- a risk assessment should be undertaken to identify the susceptibility of the recipient to infection and to disease;
- expert advice should be sought and appropriate postexposure prophylaxis administered to the recipient;
- prophylaxis should also be considered for close contacts of the recipient where secondary transmission is possible;
- the exposed recipient should be enrolled for follow-up;
- it is good medical practice to refer an infected donor and close contacts of any infected donor, living or deceased, to an appropriate expert.

Where recipient infection is detected and indicates potential transmission from the donor, it is then the duty of the recipient's physician to ensure that recipients of organs and tissues from the same donor are notified as soon as possible and made aware of the infection risk. The National Health Service Blood and Transplant Directorate for Organ Donation and Transplantation (ODT) has a Duty Office that is able to assist in informing the relevant clinicians. All incidents reported to the ODT Directorate are managed by the Clinical Governance Team within ODT.[30] The Clinical Governance Team forms the Clinical Governance Improvement Group, which is responsible for reviewing and monitoring serious adverse events and reactions, and aims to complete investigations

within 90 days or less. Once an incident has undergone a full review, the individual who reported the incident will be sent a summary of the outcome and any key actions or learning that is required. The central remit of the Clinical Governance Improvement Group is to (1) have oversight of all incidents, review in detail individual incidents, and ensure areas of concern are addressed, learning is shared, and practice is changed as appropriate; and (2) identify and review key themes and trends across incidents, and to develop key actions following these reviews.

Wider oversight of incidents is provided by the ODT Clinical Audit, Risk and Effectiveness Group (CARE). ODT CARE is chaired by the ODT Associate Medical Director, and its members include senior operational, nursing and medical representation, clinical governance, quality assurance and scientists.[30] The role of ODT CARE is to monitor and provide oversight of clinical complaints and legal claims, Clinical Audit, Clinical Risk Register, and the approval of clinical policies proposed by Advisory Groups. The ODT CARE group ensures that:

- clinical governance requirements are met;
- opportunities to improve practice and compliance are identified and pursued;
- areas of clinical concern are addressed and lessons learned, identified, and, where appropriate, shared and changes implemented;
- lessons learned are shared among the donation, retrieval and transplant community as appropriate;
- the regulatory requirements of the Care Quality Commission, the Human Tissue Authority and other regulatory bodies are met.

ODT CARE in turn reports to ODT Senior Management Team and the United Kingdom National Health Service Blood and Transplant (NHSBT) CARE Committee, which has oversight across NHSBT.[30]

United States

The National Organ Transplantation Act of 1984 legislated for biovigilance in organ transplantation in the United States, establishing standards for traceability and procedures for the prevention of transplantation of organs infected with HIV. Under the current system, the United States Organ Procurement and Transplant Network (OPTN) requires that all unexpected, potentially donor-derived disease transmission events be reported to the OPTN/United States United Network for Organ Sharing (UNOS), where cases are then reviewed by the Disease Transmission Advisory Committee (DTAC). Disease Transmission Advisory Committee is then responsible for (i) estimating the risk of donor-derived disease transmission, (ii) reviewing cases reported to OPTN, (iii) notifying public health agencies in the event of a suspected transmission, (iv) reporting findings to the transplant community, and (v) providing policy recommendations to the OPTN.[31] Details of the reporting requirements for posttransplant discovery of disease in donors or recipients are given in Table 5.[32] When a notification of a potential transmission event is received, a report with all patient information redacted is delivered securely to DTAC members, who are alerted of the new report. Disease Transmission Advisory Committee then engages in an email-based confidential medical peer review process. Organ procurement organizations (OPOs) are subsequently required to submit a follow-up report 45 days after the initial report with the results of their investigation into the event.[31]

Since the implementation of the OPTN mandatory reporting policy in 2005, several improvements have been made to the reporting system, including the 2012 publication of an algorithm to help the committee classify reports of potential donor transmission events as proven, probable, possible, unlikely, or excluded from further review.[3] This algorithm can be viewed at the following link: http://bit.ly/2E2eQC7.[3]

TABLE 5.

OPTN Transplant Program requirements for communicating posttransplant discovery of disease or malignancy (OPTN Policies; Policy 15: Identification of Transmissible Diseases)[32]

15.5.A Transplant Program Requirements for Posttransplant Discovery of Donor Disease or Malignancy

   (1) If the findings are from transplant program testing of the donor, then the transplant program must notify the host OPO or living donor recovery hospital of the findings

   (2) Notify the recipients under care at the transplant program, or the recipient's agents, of the risk or confirmation of transmissible disease or malignancy

   (3) Document the new information about the donor and potential risk or confirmation of transmissible disease or malignancy in the recipient's medical records

   (4) Follow the notified recipients for the development of disease or malignancy after transplant

   (5) Offer the recipients additional testing, monitoring, and treatment as appropriate, in addition to routine follow up care

15.5.B Transplant Program Requirements for Reporting Posttransplant Discovery of Recipient Disease or Malignancy

When an organ recipient is suspected to have, is confirmed positive for, or has died from a potential transmissible disease, infection or malignancy, and there is substantial concern that it could be from the transplanted organ, then the transplant program must do all of the following:

   (1) Notify host OPO or living donor recovery hospital that procured the organ without waiting for all medical documentation that may eventually become available. The transplant program must notify the host OPO or living donor recovery hospital by phone and provide documentation as soon as possible but no more than 24 hours after learning of the event

   (2) Report the event through the OPTN Improving Patient Safety Portal as soon as possible by no more than 24 hours after learning of the event

   (3) Provide additional related information or specimens if requested

15.5.C Transplant Program Requirements for Postreporting Follow-Up

If the transplant program has a recipient that is involved in an OPTN Improving Patient Safety Portal report, then the transplant program must also do all of the following:

   (1) Submit any relevant test results including cultures, infectious disease testing results, imaging studies, or autopsy results to OPTN patient safety staff2. Respond to host OPO, living donor recovery hospital, and OPTN patient safety staff requests for information regarding the recipient and communicate updated information regarding recipient condition, test results, diagnosis, and plans for treatment and follow-up

   (2) Contribute to a follow-up review of the event in partnership with OPTN patient safety staff

   (3) Provide additional related information or specimens if requested.

OPTN, Organ Procurement and Transplantation Network; OPO, organ procurement organization.

Based on DTAC reports for 2013, the most frequently reported potential transmission events involved HCV, tuberculosis, HIV, Chagas, HBV, toxoplasmosis and WNV, as well as bacterial infections. Only approximately 12% of fully evaluated reports of infectious disease transmission events in 2013 were ultimately classified as proven or probable (with ~10% classified as possible, ~33% classified as intervention without documented transmission, and 45% classified as unlikely/excluded).[3]

Overall, the estimated rate of proven/probable unexpected disease transmission events in the United States is low: from July 1, 2015, to June 30, 2016, there were 19 proven/probable infectious disease transmission events out of ~15 500 donors (9500 deceased donors), affecting 73 recipients.[33] Death in association with a proven/probable infectious disease transmission event occurred in 3 recipients in this 12-month period.[33] These numbers are likely, however, to be affected by underrecognition and underreporting of infectious disease transmission events, particularly in the case of the transmission of bacterial pathogens, which may present as transient fevers in the recipient. Infections caused by common pathogens, such as *S. aureus* may not be recognized as donor-derived, yet transmission of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) or multidrug-resistant Gram-negative rods are among the most common type of bacterial transmission event, against which standard antimicrobial prophylactic treatment in the recipient is inadequate.[1]

NOTIFY

The NOTIFY project, launched in 2010, was a joint initiative of the World Health Organization, the Italian National Transplant Center (CNT) and the EU-funded Vigilance and Surveillance of Substances of Human Origin project. From September 2010 to February 2011, global experts gathered information on documented cases of adverse outcomes in transplantation, and these cases were used as the basis for developing general principles on detection and investigation of adverse events. The NOTIFY website (www.notifylibrary.org) hosts the database of vigilance information collected by the NOTIFY Project. The NOTIFY website is managed by the Italian National Transplant Centre, a WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs, and the work of updating the database is carried out by a large group of experts, regulators, and clinicians across the globe. The NOTIFY library is intended to facilitate access to information on vigilance and surveillance derived from organ donation and transplantation programs around the world.

In February 2015, the Spanish National Transplant Organisation, ONT, and the Catalan Organisation for Transplantation signed an agreement with CNT to support the work of the NOTIFY project, contributing resources and expertise.

CHALLENGES FOR BIOVIGILANCE

One particular challenge for vigilance and surveillance systems is that the reporting of "donor-derived" transmission events is subject to substantial bias. It will not be clear in many cases whether infection is in fact donor-derived, and whether reporting occurs will depend on the interpretation of the treating physician. Whether notification occurs will then depend on the subjective evaluation of the evidence of a donor-derived transmission event. This may lead to underreporting, or delays in reporting. Where organs are distributed across multiple transplant centers, this may make it even more difficult for infection to be recognized as donor-derived. This emphasizes the importance of a centralized, integrated vigilance and surveillance system, and the need for that system to be capable of flagging multiple reports arising from the same donor in real time.[31] The longer that a system is in place the more data inputs it will have to be able to facilitate more accurate decision making in the future. Therefore, the vigilance and surveillance system needs itself to be subject to continuous performance evaluation and improvement.

Although vigilance and surveillance systems are primarily concerned with unexpected serious adverse events, data should also be collected for expected transmission events in the case of diseases where the outcome of donor to recipient transmission is incompletely understood, or in circumstances where the epidemiology of the disease is changing.[34] A topical example of this would be the transplantation of organs from donors known to be HCV-positive, given the rapidly changing treatment protocols in the event of disease transmission. The data collection goals of the system must be clearly defined and clearly understood by those responsible for reporting events.

Lastly, initial reporting processes need to be easy and quick, with full details to be submitted later. It is imperative that the notification of a potential disease transmission event is disseminated as early as possible, and that it not delayed by cumbersome form-filling requirements or system/administrative issues.

Data Sources

Major sources of information on international standards and practices included the NOTIFY Library (The Global Vigilance and Surveillance Database for Medical Products of Human Origin; www.notifylibrary.org), The European Directorate for the Quality of Medicines & Health Care Guide to the quality and safety of organs for transplantation (Sixth Edition), the SaBTO Guidance on the microbiological safety of human organs, tissues and cells used in transplantation (2011), and Transplant Infections (Fourth Edition, eds. Ljungman, P., Snydman, D. and Boeckh M.).[5,29,34,35] Epidemiological data on infectious disease notification rates and the underlying population prevalence of disease in Australia were obtained from the Communicable Disease Network Australia (CDNA) Australian National Notifiable Diseases Surveillance System and other CDNA publications, and the Annual Surveillance reports of The Kirby Institute.[36,37] Epidemiological data for New Zealand were obtained from the New Zealand Ministry of Health Institute of Environmental Science and Research Ltd Public Health Observatory, and the Ministry of Health Communicable Disease Control Manual.[38-40] International statistics on the prevalence of selected infectious diseases were obtained from the United Nations World Drug Report, AIDSinfo (UNAIDS), and the World Health Organization.[22,26]

Information on unexpected infectious disease transmission events involving deceased solid organ donors was obtained by a systematic review of the published literature. Articles

reporting on cases of donor-derived infectious disease transmission were identified using the search strategy outline in SDC Materials and Methods 1, http://links.lww.com/TXD/A152. Given the absence of biovigilence systems in most jurisdictions and a general underreporting of disease transmission events in the published literature, the reports identified likely only represent a small proportion of actual disease transmission events. In addition, establishing a true denominator for transmission events is not possible at this time, as this would require the centralized recording of donor disease status for all used donors. At this time, any information that we have on the quantitative risk of disease transmission from organ donors to recipients is based on retrospective record reviews conducted in a research context (usually based on a single center's experience). Given these limitations, reported transmission events are summarized qualitatively. The circumstances of each case, donor characteristics and serological profile, and the outcomes of the recipients are described, and similarities and differences across cases are considered.

DECEASED DONOR EVALUATION FOR INFECTIOUS DISEASE RISK

Donor Medical History and Behavioral Risk Evaluation

Infectious disease transmission risk is assessed via careful review of the potential donor's medical and social history.[41] The results of cultures and other assays to detect and diagnose infection must be interpreted in the context of the patient's full history, and the probability of false-negative results needs to be considered against the donor's background of any reported risk factors, such as IVDU or high-risk sexual contact. Close attention must also be paid to travel history: potential donors with recent travel to or previous residence in areas where they may have been exposed to endemic pathogens—*Strongyloides stercoralis*, *Schistosoma* spp., malaria, *Trypanosoma cruzi,* or endemic mycoses, for example—warrant additional screening. It is, therefore, essential that the social history is obtained from someone close to the potential donor, and an assessment should be made of how well the person knows the donor.[7] The American Association of Tissue Banks has developed guidelines for donor risk assessment interviews.[42] In Australia, the social history is captured in a nationally standardized form as part of the electronic donor record (EDR) and is completed by the Donor Coordinator (http://www.tsanz.com.au/downloads/Protocols_Appendix1.pdf).

In the event of positive test results or the existence of behavioral risk factors, decisions about whether to use a potential donor's organs need to be weighed in the context of the risk tolerance and medical status of the potential recipient(s).[7] Different thresholds for an acceptable level of risk will apply to a potential recipient for whom the transmission of an infectious disease would be a devastating outcome versus a potential recipient for whom this may be their only chance at transplantation and would otherwise die on the waiting list.

Screening for Infectious Disease in Deceased Donors: Overview

Pretransplant screening of both donors and recipients is necessary to identify any diseases/conditions that (i) preclude transplantation, or (ii) require treatment, prophylaxis, immunization, and/or monitoring. It is necessary to test for both active and latent infections in donors and recipients before initiation of immunosuppression, though the implications of a positive test will vary depending on the organ to be transplanted. Routine donor screening generally includes tests for CMV, EBV, HIV, hepatitis B (HBV), hepatitis C (HCV), syphilis (*T. pallidum*), and *Toxoplasma gondii* in the case of potential heart donors.

The goals and priorities of infectious disease screening in organ donors differ from the screening of blood donors in several important ways. First, the timeline for donor screening is restricted to less than 12 to 18 hours, whereas blood donor screening can take place 24 to 48 hours after donation and samples can be screened in batches. Second, blood donors are able to give their medical and social history via statutory declaration, whereas for deceased donors this is provided by friends or family, who may be unaware of a history of drug use or high-risk sexual contact. Thirdly, the goal of blood donor screening is to achieve zero risk of disease transmission to recipients of blood transfusions, whereas in the context of organ transplantation there is a trade-off to be made between residual risk of disease transmission and the urgency of organ transplantation.

Screening protocols in organ transplantation are, therefore, required to reduce the risk of infectious disease transmission to an acceptable level (without necessarily eliminating risk completely) while keeping turnaround time under ~12 hours. Another key consideration for screening protocols is the serological window for BBV—the period from infection to the time that the individual develops antibodies that can be detected by serological testing. During this window, a potential donor may be seronegative (and, therefore, will test negative for disease based on serological tests) but is still able to transmit infection (see Figure 3).

Figure 4 shows the serological and NAT windows for HIV, HCV and HBV. The eclipse period refers to the preramp phase and the portion of the ramp-up/exponential phase where the viral titer in peripheral blood has not yet reached levels that are detectable by NAT. Once the viral titer reaches detectable levels (5–6 days postinfection for HIV, 3–5 days for HCV, and 20–22 days for HBV), the viral load continues to increase until the plateau phase is reached, after which seroconversion occurs. NAT, therefore, significantly reduces the detection window for HIV and HCV, and to a lesser
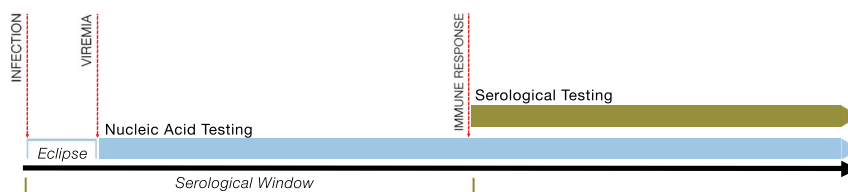
FIGURE 3. Generalized diagram of eclipse and window periods.
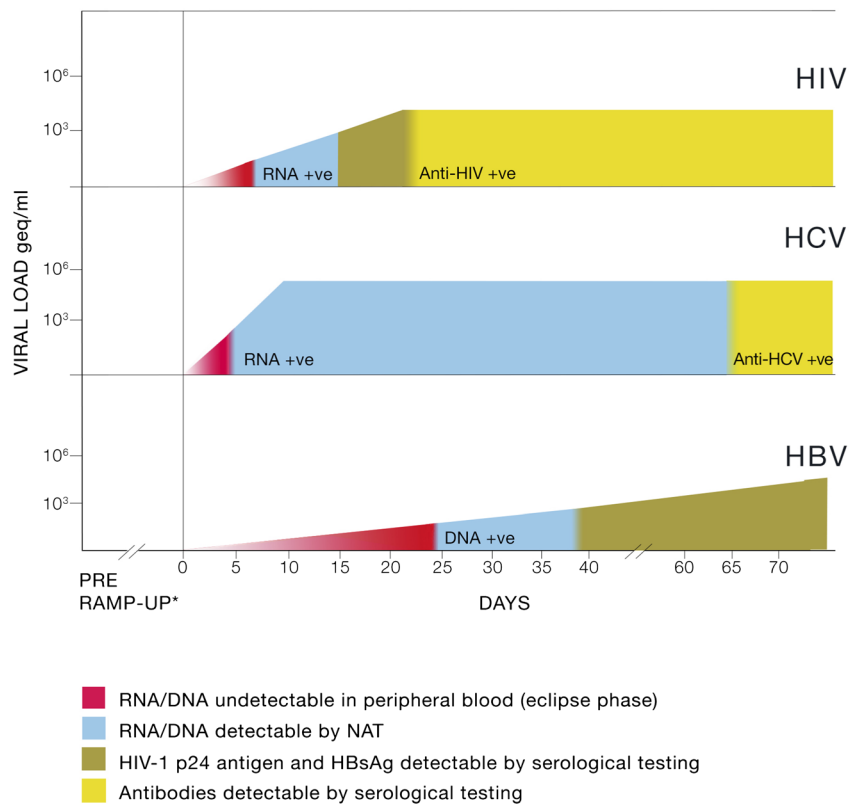
FIGURE 4. Serological and nucleic acid testing (NAT) window for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) (source: South Eastern Area Laboratory Services, New South Wales, Australia). RNA, ribonucleic acid.

extent for HBV. The serological window for HIV detection is also reduced by the combined antigen/antibody test, which identifies antibodies against HIV-1 and HIV-2 as well as the presence of HIV-1 p24 antigen, which is shed into the bloodstream at high levels shortly after infection.[43] NAT is additionally useful in the context of HCV screening, as a positive HCV-NAT distinguishes active HCV infection from an anti–HCV-positive, NAT-negative result that is indicative of a previous infection that has been cleared. The length of the serological and NAT windows for HIV, HCV and HBV are further specified in Table 6.

Although permitting earlier detection of BBV, until relatively recently the use of NAT in potential organ donors was limited by assay cost, long turnaround times, and high false-positives rates especially among average- to low-risk donors.[44] Recent development of new platforms has reduced the cost of NAT and brought turnaround times down to 4 to 6 hours, permitting repeat testing and reducing the false-positive rate. Current international donor screening guidelines, however, retain some variation in their recommendations regarding when NAT is appropriate at this time (see Table 7). UK guidelines recommend NAT testing for HIV whenever this is feasible (ie, where turnaround times and logistics permit), and require all donors to be screened using the combined anti-HIV antigen/antibody test at a minimum. European Directorate for the Quality of Medicines and Health Care guidelines also require the combined anti-HIV antigen/antibody test as a minimum requirement, but NAT is recommended only for donors at increased risk of BBV. OPTN requires the anti-HIV antibody test alone for average-risk donors, with NAT or the

combined anti-HIV antigen/antibody test required for donors identified as being at increased risk for HIV transmission. OPTN guidelines also allow for exceptions to the HIV screening requirement for organs other than kidneys when the medical urgency of the situation warrants the transplantation of an organ that has not been tested for HIV (policy 2.7.A), provided that (i) all available deceased donor medical information and social history information is provided to the transplant program, and (ii) the deceased donor is treated as having an increased risk for disease transmission in accordance with the US Public Health Services Guidelines. In this circumstance the receiving transplant hospital must obtain documented informed consent from the potential recipient (or their authorized agent) before transplantation can take place.[32]

Both OPTN and SaBTO guidelines require HCV-NAT among mandatory tests for all donors, whereas EDQM

TABLE 6.

Length of window period for selected blood borne viruses under different testing methods[44]

Pathogen	Standard serology, d	Enhanced serology (fourth-generation or combined antibody-antigen tests), d	NAT, d[a]
HIV	17–22	~7–16	5–6
HCV	~70	~40–50	3–5
HBV	35–44	Not applicable	20–22

[a] Based on Gen Probe TMA for HIV and HCV, and Roche Cobas MPX for HBV.

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; NAT, nucleic acid testing.

TABLE 7.

International protocols for infectious disease testing—mandatory testing requirements for potential deceased donors of solid organs in the United States, United Kingdom, and Europe

OPTN[a,b]	SaBTO[e]	EDQM[d]

• Anti-HIV test OR anti-HIV Ag/Ab combination test*
 • HBsAg and anti-HBc
    Anti-HCV
 • Hepatitis C ribonucleic acid (RNA) by donor screening
    or diagnostic NAT
 • Anti-CMV donor screening OR diagnostic test
 • Anti-EBV donor screening OR diagnostic test
 • Anti–*T. pallidum* donor screening or diagnostic test.
 • Anti–*T. gondii* IgG
 *For donors at increased risk for HIV, HBV and HCV transmission[e],
    either HIV RNA by donor screening, diagnostic NAT, or the HIV
    antigen/antibody (Ag/Ab) combination test is also required, unless:
 – The donor has already been tested for HIV using the HIV Ag/Ab
    combination test
 – The donor's only increased risk factor is having received hemodialysis
    in the past 12 months.
	• NAT test for HIV or anti-HIV
	    Ag/Ab combination test[f]
	 • NAT test for HCV or
	    anti-HCV[f]
	 • NAT test for HBV or
	    HBsAg and anti-HBc[f,g]
	 • Anti-HTLV1/2
	 • Anti–*T. pallidum*
	 • Anti–*T. gondii* IgG
	 • Anti-CMV
	 • Anti-EBV
		Before organ recovery:
		    • Anti-HIV Ag/Ab combination test*
		    • HBsAg AND anti-HBc*
		    • Anti-HCV*
		 As soon as possible (not necessarily before recovery and transplant):
		    • Anti–*T. pallidum* ELISA
		    • Anti–*T. gondii* IgG
		    • Anti-CMV
		    • Anti-EBV-VCA-IgG
		 *Screening should be extended to NAT for donors with an increased
		    risk of HIV, HBV or HCV infection, with the results of NAT made
		    available before organ recovery.
		 EDQM guidelines recommend that all positive serological results be
		    confirmed on a second serological test before a decision is made
		    to NOT recover the donor organs.

[a] OPTN Policies: Policy 2.9 (effective date 10 November 2016).

[b] All tests must be FDA licensed, approved or cleared for screening organ donors.

[c] Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO): Guidance on the microbiological safety of human organs, tissues and cells used in transplantation. Department of Health, United Kingdom Government. Published February 21, 2011.

[d] European Directorate for the Quality of Medicines & Health Care: Guide to the quality and safety of organs for transplantation, 6th Edition. Council of Europe, Strasbourg, 2016.

[e] As defined under the U.S. Public Health Services (PHS) Guideline.[45]

[f] NAT tests for HIV, HBV and HCV are not mandatory for organ transplantation, but their use represents good clinical practice. Turnaround time will not always permit provision of NAT results before organ transplantation, but they should still be performed to ensure the rapid identification of the recipients of potentially infectious organs. If NAT tests are either not done, or the results are not available before organ donation, combined antigen and antibody assays (rather than testing alone) are required for HIV, and should be considered for HCV.

[g] Anti-HBc screening is indicated for liver and for tissues but not for other organ donation. As other organs or tissues may be taken from the same donor, in practice the results of this test will often be available. Donors whose serum contains anti-HBc in the absence of HbsAg should be tested for anti-Hbs to confirm immunity to HBV infection. Consideration should be given to confirming the specificity of sera which exhibit anti-Hbc reactivity in the absence of other markers.

OPTN, Organ Procurement and Transplantation Network; SaBTO, Advisory Committee on the Safety of Blood, Tissues & Organs; EDQM, European Directorate for the Quality of Medicines and HealthCare; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; NAT, nucleic acid testing; HTLV1, human T-lymphotropic virus-1; ELISA, enzyme-linked immunosorbent assay; VCA, viral capsid antigen.

only recommend NAT for donors at increased risk of HCV infection and donors with an anti-HCV reactive result, to determine whether clearance of viremia exists. Historically, a positive HCV-NAT would have been a contraindication to transplantation. However, with the advent of direct-acting antiviral agents (DAAs) for HCV, this situation is rapidly changing,[46] and early trials have demonstrated successful outcomes from the transplantation of HCV-infected kidneys into HCV-negative recipients.[47] For a detailed discussion see *Donor Screening and Utilization.*

Only SaBTO guidelines recommend HBV-NAT as standard. OPTN, SaBTO and EDQM all require HBsAg and anti-HBc screening tests at a minimum. Recently, in the United States, however, there has been a significant increase in HBV-NAT use concurrent with the requirement for HCV-NAT, as most OPOs now use the triplex NAT assay (personal communication M Ison). A positive HBsAg test indicates active infection, and HBV could be transmitted by any organ or tissue in this context. A negative HBsAg test but positive anti-HBc often indicates a cleared infection, and organs from these donors may be transplanted in certain cases with appropriate HBV prophylaxis.

Recommendations for EBV and CMV screening are similar in the United States, UK and Europe. Although CMV and EBV infection are not contraindications to donation, knowing the serostatus of the donor and potential recipient is critical to the implementation of appropriate prophylaxis

or other risk reduction strategies. Donor screening should use assays with high sensitivity and specificity for anti-CMV IgG.[48] For EBV, assays testing for viral-capsid antigen IgG (VCA IgG) are preferable.[49]

Similarly, screening for *T. pallidum* is mandated for all donors by OPTN, SaBTO, and EDQM. The syphilis testing algorithm described by the US Centers for Disease Control (CDC) is as follows: an initial enzyme immunoassay (EIA) treponemal test (TP-EIA) is performed, with a positive result confirmed by a nontreponemal test such as the rapid plasma reagin (RPR) test. In the event of a negative RPR test, a second treponemal test should be performed such as the *T. pallidum* particle agglutination (TP-PA) test. If this second treponemal test is negative, then a third treponemal test should be performed, such as the fluorescent treponemal antibody (FTA-ABS). If either the second or third antibody tests are positive then a diagnosis of syphilis is made.[50] A positive TP-EIA but negative results on RPR, TP-PA, and FTA-ABS indicate a false-positive result or resolved infection. Such reverse screening approaches are associated with a lower rate of false-positive test results.[51]

OPTN, SaBTO, and EDQM additionally require testing for anti–*T. gondii* IgG as standard. Only SaBTO guidelines require testing for anti-HTLV1/2 as standard.

The TSANZ Clinical Guidelines for Organ Donation and Transplantation from Deceased Donors (April 2016) broadly outline the standard routine investigations and recommended

TABLE 8.

Policies for infectious disease screening in potential organ donors: Australia and New Zealand (see also Table 9)

TSANZ[52]	New Zealand[a]
Mandatory	Standard-risk donors
• Anti-HIV-1/2	Prospective tests
• HBsAg and anti-HBc and anti-HBs	• Anti-HIV-1/2 OR anti-HIV Ag/Ab combination test
• Anti-HCV	• HBsAg and anti-HBc and anti-HBs
Recommended	• Anti-HCV
• HIV-NAT*	• Anti-CMV
• HCV-NAT*	• Anti-HTLV 1/2
• HBV-NAT*	• Anti–T. pallidum (EIA)
• Anti-HTLV 1/2**	Retrospective tests
• Anti-CMV***	• Anti-EBV (IgG and IgM)
• Anti-EBV***	• Toxo IgG and IgM*
• Anti–T. pallidum ***	• Anti-HSV 1 (IgG) and anti-HSV 2 (IgG)*
*NAT is recommended for HIV, HCV, and HBV using PCR assays in donors at increased risk of infection, based on the definition of increased risk developed by the United States PHS[45]	• Anti-VZV (IgG)*
	Increased-risk donors
	All prospective and retrospective tests as listed above, with the addition of HIV, HCV, and HBV NAT**
**Strongly recommended for potential donors from population groups with a high prevalence of infection	*Performed for heart donors and lung donors only
***Recommended but not mandatory	**All donors who donate heart valves or skin will also have retrospective NAT completed.

[a] Personal communication J Langlands, Organ Donation New Zealand.

TSANZ, Transplantation Society of Australia and New Zealand; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NAT, nucleic acid testing; HBV, hepatitis B virus; HTLV, human T-lymphotropic virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PHS, Public Health Service; EIA, enzyme immunoassay.

investigations for deceased donors in Australia and New Zealand Table 8. Organ Donation New Zealand has their own jurisdiction-specific donor screening policy (Table 8), as do each of the Australian States and Territories (see Table 9). Jurisdiction-specific policies are generally similar to/informed by the TSANZ guidelines, though with some variations as outlined in Table 9. In all jurisdictions, all donors are required to have serological testing for anti-HIV-1/2 (or the anti HIV Ag/Ab combination test), HBsAg, anti-HBs, anti-HBc, and anti-HCV. As of July 2017, Queensland, South Australia, Tasmania, and Victoria routinely order NAT for HIV, HCV, and HBV for all solid organ donors, requiring prospective results in the case of increased-risk donors (retrospective results are acceptable for nonincreased risk-donors). In New Zealand, New South Wales, and Western Australia, urgent (prospective) NAT is required for donors with: (i) evidence of BBV (positive serology or known history), (ii) recent exposure to risk factors for BBV (past ~6 months), or (iii) where medical history is not available.

All jurisdictions stipulate mandatory prospective anti-CMV testing. NSW, Queensland, SA, and WA also require prospective anti-EBV and anti–T. pallidum testing; Tasmania and New Zealand require retrospective testing for anti-EBV. Jurisdictions are variable with regard to guidelines for HTLV-1/2 testing: NSW recommends HTLV-1/2 testing at the clinician's discretion; New Zealand, Queensland, SA, and Victoria include HTLV-1/2 among mandatory prospective tests; WA lists anti–HTLV-1/2 among additional routine tests (not strictly mandatory); Tasmania recommends retrospective testing for HTLV-1/2. Only Queensland, SA, and WA routinely test for toxoplasmosis; New Zealand includes toxoplasmosis screening among retrospective tests.

The list of possible pathogens for which potential donors might be screened is very long. Which of these pathogens to screen for depends on whether:

• The pathogen is sufficiently prevalent in the population so that screening would be useful;
• There is evidence that the pathogen in question can be transmitted by organ transplantation;
• Transmission of the pathogen would result in significant morbidity and mortality;
• A sufficiently accurate, rapid and affordable screening test exists;
• The agent has a high level of potential harm (eg, transmissible spongiform encephalopathies [TSE], WNV).

For many of the notable cases of unexpected disease transmission that have occurred in the past decade - including lymphocytic choriomeningitis virus (LCMV), arenavirus and rabies—screening would not be warranted based on the criteria above.[34] Furthermore, even when screening is performed as per guidelines, unexpected transmission events can occur. Donor screening may occur during the eclipse or window period of the disease, or screening tests can yield false-negative results (a negative assay result when the true result should be positive, due to unforeseen technical error).[53,54] In some urgent cases the risk of waiting for test results may outweigh the risk to the patient of disease transmission. Alternatively, prophylaxis or vaccination may fail, as has happened in several reported cases of posttransplant fulminant HBV associated with mutated strains of the virus that evaded recipient vaccination,[55,56] or lamivudine-resistant strains of HBV.[57] Human error may also be the reason for unexpected transmission, such as in a 2007 case of HIV transmission in Italy where the donor's HIV-positive status was incorrectly transcribed as negative on their donation record.[58]

Donor screening can never be strictly fail-safe, which is why (i) screening must be supported by vigilance and surveillance systems that are capable of responding to adverse events if and when they happen, and (ii) the informed consent of recipients is essential (not only in cases where the donor is

TABLE 9.

Jurisdictional policies for infectious disease screening in potential organ donors in Australia

New South Wales[a]	Queensland[b]	South Australia[c]	Tasmania[d]	Victoria[e]	Western Australia[f]
Mandatory • Anti–HIV-1/2 OR anti–HIV Ag/Ab combination test • HBsAg and anti-HBc and anti-HBs • Anti-HCV • Anti-CMV • Anti-EBV • Anti–T. pallidum Recommended • HIV-NAT* • HCV-NAT* • HBV-NAT* • Anti-HTLV 1/2** *Urgent NAT is ordered for potential deceased donors at increased risk of BBV[b] or in the event of a positive serology test **At the clinician's discretion If the donor has received >50% of blood volume in blood product transfusion the same is unsuitable for serology or NAT testing. A pretransfusion sample should be provided to the laboratory. If the donor is known to be infected with HCV/HBV then a specimen should be sent for NAT for HIV, HCV and HBV to confirm infection and potentially permit transplantation to HCV-positive recipients or recipients from whom risk of infection is outweighed by urgency for transplant.	Mandatory • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs • Anti-HCV • HIV-NAT* • HCV-NAT* • HBV-NAT* • Anti-CMV (IgG) • Anti-EBV (IgG) • Anti–T. pallidum (EIA) • Anti-HTLV 1/2 • Toxo IgG and IgM *NAT is routinely ordered for all solid organ donors Plasma dilution algorithm is applied as per EDR/Tissue Banks requirements to ensure a suitable specimen is available for testing. If it is determined that the potential donor is hemodiluted then a predilution blood sample MUST be sourced for the accurate testing for presence of viruses. If a suitable predilution specimen is not available, then serology may be processed using a current blood sample. The DSC must inform the organ transplant teams of this fact and medical suitability and risk assessment will be done on a case-by-case basis.	Mandatory • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs • Anti-HCV • HIV-NAT* • HCV-NAT* • HBV-NAT* • Anti-CMV (IgG) • Anti-EBV (IgG)** • Anti–T. pallidum (EIA) • Anti-HTLV 1/2 • Toxo IgG and IgM *NAT is routinely ordered for all solid organ donors **Results available the following day	Standard-risk donors Prospective tests • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs* • Anti-HCV Anti-CMV (IgG)* Retrospective tests • HIV, HCV and HBV NAT • Anti-EBV (IgG) • Anti–T. pallidum (EIA) • Anti-HTLV 1/2 Increased-risk donors Prospective tests • HIV, HCV, and HBV NAT • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs • Anti-HCV • Anti-CMV (IgG)* Retrospective tests • Anti-EBV (IgG) • Anti–T. pallidum (EIA) • Anti-HTLV 1/2 *DonateLife Tasmania does not routinely test for HBcIgM, CMV IgM, EBV IgM, EBNA, Chagas or WNV. DonateLife Tasmania does not routinely test for toxoplasmosis, but will manage this on a case-by-case basis depending on potential transmission of disease	Mandatory • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs • Anti-HCV • HIV-NAT* • HCV-NAT* • HBV-NAT* • Anti-CMV (IgG) • Anti-EBV (IgG) • Anti–T. pallidum (EIA) • Anti-HTLV 1/2 *In Victoria, the Australian Red Cross Blood Service (ARCBS) performs NAT on all organ donors, with results routinely available retrospectively. In the case of increased-risk donors, NAT must be completed prospectively. In practice, results are typically received before transplantation proceeds.	Mandatory • Anti–HIV-1/2 OR anti–HIV Ag/Ab combination test • HBsAg and anti-HBc and anti-HBs • Anti-HCV • Anti-CMV • Anti-EBV • Anti–T. pallidum Additional routine tests: • Toxo IgG • Anti-HTLV 1/2 • HSV IgG Recommended • HIV-NAT* • HCV-NAT* • HBV-NAT* *Prospective NAT is ordered (i) for potential deceased donors at increased risk of BBV, (ii) in the event of a positive serology test, or (iii) for potential donors with known HCV/HBV. Plasma dilution algorithm is applied as per EDR/Tissue Banks requirements to ensure a suitable specimen is available for testing. If a suitable specimen is not available, pathology services will advise on the validity of test results.

[a] Organ Donation and Transplantation—Managing Risks of Transmission of HIV, HCV and HBV. NSW Government Health Procedures (PD2013_029), September 2013. (http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2013_029.pdf).

[b] DonateLife Queensland Standard Operating Procedure: Collection, Transport and Processing of Donor Blood for Tissue Typing, Cross Matching, Serology, and Nucleic Acid Amplification Testing, Version 1.1 (approval date, July 2017).

[c] N Palk, DonateLife South Australia, personal communication.

[d] DonateLife Tasmania Clinical Practice Guideline.

[e] DonateLife Victoria Clinical Practice Guideline.

[f] M Smith, DonateLife Western Australia, personal communication.

HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; NAT, nucleic acid testing; HTLV, human T-lymphotropic virus; EDR, electronic donor record; BBV, bloodborne viruses.

TABLE 10.

Additional tests which might be considered for donors who have lived in areas with endemic disease[5]

Tests	Central and South America	North Africa	Sub-Saharan Africa	Indian subcontinent	Southeast Asia
HTLV-1/2 serology	Always	Always	Always	Always	Always
NAT for *Plasmodium* spp.	Central America and Amazon	No	Always	Always	Always
Stool examination[a]	Always	Always	Always	Always	Always
Urine examination[b]	No	Egypt	Always	No	No
Strongyloides stercoralis serology	Always	Always	Always	Always	Always
Schistosoma spp. serology	Caribbean, Venezuela and Brazil	Always	Always	No	Always
T. cruzi serology for screening; NAT or Strout test for exclusion of parasitemia	Always (not Caribbean)	No	No	No	No
Leishmania serology	Always	Always	Always	Always	Always
Paracoccidioides brasilliensis serology	Brazil	No	No	No	No
Histoplasma capsulatum and *Coccidioides immitis* serology	Always	No	Western Africa (Histoplasmosis)	No	No

[a] Entamoeba histolytica, *Clonorchis* spp., *Opisthorcis* spp., *Schistosoma* spp., *Strongyloides* spp.
[b] S. haematobium.
HTLV, human T-lymphotropic virus; NAT, nucleic acid testing.

considered to be at increased risk). Where donor information about behavioral risk factors is incomplete, the donor should be treated in the same way as an increased-risk donor.[45]

Another issue for donor screening is hemodilution: where the donor requires multiple blood transfusions or significant infusions of intravenous (IV) fluids before donation, hemodilution may occur such that serum antibodies and targets for PCR are at too low a concentration to be detected. OPTN guidelines state that OPOs must use nonhemodiluted blood samples for the purpose of serological screening of deceased donors wherever possible.[59] If only a hemodiluted sample is available, that donor is treated as though they are an increased-risk donor according to the US PHS Guideline (ie, HIV RNA by donor screening, diagnostic NAT, or the HIV antigen/antibody (Ag/Ab) combination test is also required in addition to the standard mandated tests). Other factors may also affect the accuracy of serological test results, such as the suppression of the donor immune response to infection as a consequence of disease or of high steroid dosage. Such factors need to be taken into account when interpreting test results.

Additional Tests for Consideration Based on Donor History

Potential donors with a history of significant travel to or residence in Africa, the Middle East, Asia or Central/South American may warrant additional screening for pathogens endemic to that area or occurring as epidemic disease. Additional tests that should be considered for donors who have lived in these geographic areas, according to European guidelines, are shown in Table 10.

In the United States, targeted *T. cruzi* screening is recommended for potential donors born in Mexico, Central America and South America.[60] Since screening assays for *T. cruzi* have a high false-positive rate and positive results require laboratory confirmation, which may not be possible within the donation timeframe but can inform posttransplant interventions.[7] United States recommendations are that kidneys and livers from potential donors testing positive for *T. cruzi* be used with the informed consent of the recipient. Given a high rate of transmission in the context of heart transplantation, however, hearts from donors infected with or screen-positive for *T. cruzi* should not be used.[60]

Donor Suitability and Recommendations for Organ Allocation

Table 11 compares published guidelines from the UK, Europe and Scandinavia with TSANZ guidelines with respect to recommendations for the utilization of organs from donors testing positive for any of the routinely screened pathogens described in *Screening for Infectious Disease in Deceased Donors: Overview*. It should be noted that the recommendations described in the table correspond to the most recently published versions of jurisdictional guidelines as of November 2017, but do not reflect more recent changes in policy and practice. Practices with respect to HCV-positive donors in particular are rapidly evolving as a result of the introduction of DAAs able to effectively treat infection in the event of disease transmission (see *Recipient Management*). With an increasing number of individuals being successfully treated for HCV infection, there will also be a need for revised guidelines to consider donors with a history of treated HCV.

VIRAL INFECTIONS IN THE DECEASED DONOR

HIV, Hepatitis C and Hepatitis B

Epidemiology

The estimated prevalence of HIV in the Australian population 15 years or older in 2016 was 0.13%[37]; in New Zealand estimated HIV prevalence in 2016 was 0.08%.[62] Rates of HIV infection in Australia and New Zealand are relatively low by international standards: estimated HIV prevalence in the overall UK population in 2015 was 0.16%, and in the United States population 13 years or older it was 0.4%.[63,64] Comparing HIV prevalence among high-risk groups, estimated rates of HIV among IVDU in Australia and New Zealand are very low compared to other high-income countries (1.7% and 0.2% respectively see Figure 5). In contrast, the estimated prevalence of HIV among men who have sex with men (MSM) in Australia is relatively high (18.3%); in New Zealand the estimated prevalence of HIV among MSM is lower at 6.5%.[26]

HCV prevalence is similar in Australia and New Zealand, with an estimated viremic prevalence of approximately 1.0% in the adult populations of both countries in 2015.[37] Figure 6 compares viremic prevalence of HCV in 2015 across

TABLE 11.

Current (November 2017) international recommendations for donor suitability and organ allocation based on the results of infectious disease screening

Test results	TSANZ[52]	SaBTO[29]	EDQM[5]	Scandiatransplant[61]
Anti-HIV+ and/or HIV-NAT+	Excluded from organ donation for HIV-negative recipients. May be considered for HIV-positive recipients (though no such transplant has yet taken place in Australia).	Excluded from organ donation, except under exceptional circumstances for HIV-positive recipients.[a]	Excluded from organ donation for HIV-negative recipients. They may be offered, under careful surveillance, to select HIV-positive recipients under a specially designed protocol.	Excluded from organ donation.
Anti-HCV+ and HCV-NAT+	HCV-NAT positive donors may be accepted for HCV-NAT positive recipients or in exceptional circumstances after specialist advice and with HCV treatment posttransplant.	Excluded from organ donation for HCV-negative recipients, may be accepted for recipients who are anti-HCV positive or HCV-NAT positive.[b]	HCV-NAT-positive donors may be accepted for HCV-NAT positive recipients or in extreme cases.	Organs are usually not accepted for HCV-negative recipients; may be accepted for HCV NAT-positive recipients.
Anti-HCV+ and HCV-NAT−	Anti-HCV positive, HCV-NAT−negative donors may be accepted for HCV-negative recipients after specialist advice.	Excluded from organ donation for HCV-negative recipients, may be accepted for recipients who are anti-HCV positive or HCV-NAT positive.[b]	May be used for HCV-negative recipients under a specially designed study protocol.	Organs are usually not accepted for HCV-negative recipients; may be accepted for HCV NAT-positive recipients.
Anti-HBsAg +	HBsAg-positive donors can be considered for HBsAg-positive recipients, or in exceptional circumstances after specialist advice.	Generally excluded from organ donation; organs may be given to HBsAg-positive recipients or recipients who are immune to HBV in urgent cases.	Generally excluded from organ donation; organs may be given to HBsAg-positive recipients or recipients who are immune to HBV.	Generally excluded from organ donation; nonliver organs may be given to HBsAg-positive recipients in urgent cases.
Anti-HBcAb +	HBcAb-positive donors may be accepted with caution after specialist advice.	Anti-HBsAb titer <100 IU/L: Nonliver organs accepted. Detection of anti-HBcAb without detection of anti-HBsAb is considered a relative contraindication to liver donation. Anti-HBsAb titer >100 IU/L: Donation is permitted with the potential exception of livers. A negative HBV-NAT result would be further evidence of suitability.	Organs accepted for HBsAg-positive/vaccinated recipients, and may also be used in other recipients with the use of prophylaxis and with lifelong monitoring.	Livers usually will not accepted but can be used in emergency situations and for HBsAg-positive/vaccinated recipients. Nonliver organs can be used for all recipients if the donor is also anti-HBsAb-positive. If the donor is anti-HBsAb-negative, recipients without HBV markers should receive a single dose of HBIG before revascularization, and short term antiviral treatment may be considered.
Anti-HBsAb+	Interpreted in the context of anti-HBcAb reactivity—see above.	See above.	—	Interpreted in the context of anti-HBcAb reactivity—see above.
Anti-CMV+	All organs accepted.	All organs accepted.	All organs accepted. Recipients require suitable prophylaxis and/or virological monitoring.	All organs accepted.
Anti-EBV +	All organs accepted.	All organs accepted. Match recipient status if possible, especially in children.	All organs accepted. Proper follow-up and surveillance is important, especially in children.	All organs accepted.
Anti−T. pallidum +	All organs accepted. Recipients require prophylaxis and special follow-up.	All organs accepted. Recipients require prophylaxis and special follow-up.	—	All organs accepted. Recipients require prophylaxis and special follow-up.
Anti-HTLV-1/2 +	Approach is unclear. If transplantation goes ahead, recipients are monitored for signs of infection and disease development.	Excluded from organ donation.[c]	Donor anti-HTLV-I/II-positive to recipient-negative transplants are not permitted.	Excluded from organ donation.[c]
Antitoxoplasma IgG +	All organs accepted. Recipients may be monitored for signs of infection and disease development.	All organs accepted. Toxoplasma prophylaxis should be considered for heart recipients.	—	All organs accepted. Toxoplasma prophylaxis should be considered for heart and/or lung recipients.

[a] In exceptional circumstances a life-preserving donation from an infected donor may be permitted for use in a recipient who is also infected with HIV. In addition, in exceptional circumstances a life-preserving donation from a donor whose serum is repeatedly reactive for anti-HIV may be released for clinical use provided the antibody reactivity is shown to be nonspecific in confirmatory testing and HIV-1 RNA is undetectable.

[b] In exceptional circumstances, a life-preserving donation from a donor whose serum is repeatedly reactive for anti-HCV may be released for clinical use provided HCV-RNA is undetectable. This does not exclude infectivity, and expert advice should be sought regarding recipient management.

[c] HTLV-1/2 testing is only performed if donor is from a geographical area with a higher prevalence of HTLV-1/2 infections.

[d] The immunosuppression associated with organ transplantation significantly increases the risk of disease by accelerating presentation of HTLV-related illness. The use of donations from and HTLV-infected donor in a recipient who will require immunosuppression should be avoided.

HIV, human immunodeficiency virus; NAT, nucleic acid testing; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HTLV, human T-lymphotropic virus.
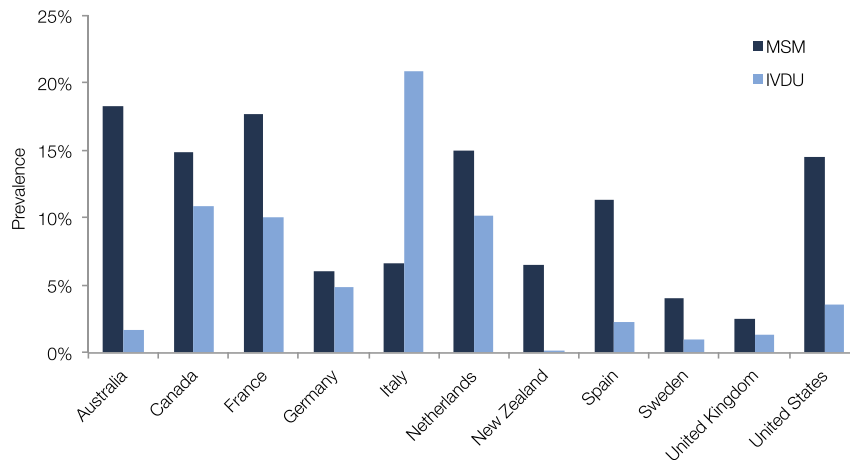
FIGURE 5. Estimated prevalence of human immunodeficiency virus (HIV) among increased-risk groups in selected high-income countries in 2016 (data source: www.aidsinfo.unaids.org, accessed February 2018). MSM, men who have sex with men; IVDU, intravenous drug users.

high-income countries for which estimates were available (estimates published by The Polaris Observatory HCV Collaborators).[65] Estimated HCV prevalence in Australia and New Zealand is relatively high compared to other high-income countries; the only high-income country with higher estimated viremic prevalence in 2015 was Italy (1.1%). Estimated HCV prevalence in the United States and the UK was 0.9% and 0.3% respectively. Globally, the countries with the highest estimated viremic prevalence of HCV in 2015 were Gabon (7%), Mongolia (6.4%), Egypt (6.3%), Uzbekistan (4.3%), Georgia (4.2%), Pakistan (3.8%), and Russia (3.3%).[65]

The estimated prevalence of HBV in Australia in 2016 was 0.9%.[37] Prevalence of HBV is much higher in New Zealand (~4%), related to immigration from highly endemic countries in the Pacific region.[66] Kiribati, Nauru, Niue, Papua New Guinea, Solomon Islands, Tonga and Vanuatu in particular have some of the highest rates of chronic HBV prevalence in the world, affecting between 12% and 23% of the total populations of these countries.[66]

The risk of BBV transmission from a solid organ donor to a recipient is dependent on the incidence, prevalence, and distribution of the virus in the donor population, the viral load in the donor, the specific organ transplanted, and the efficiency of virus transmission through contact with blood and tissues.

Historically, organ transplant systems in several countries have attempted to mitigate this risk by categorizing potential donors as either increased-risk or standard-risk with respect to their potential to transmit BBV, then screening increased-risk donors using NAT to minimize the possibility of a window period transmission. Stratification of potential donors according to their risk of BBV also has the advantage of simplifying the patient consent process. Risk of BBV is generally defined according to the presence of the following risk factors:

- MSM
- IVDU
- Incarceration in the previous 12 months
- Sexual partners of those in the categories above
- Unexplained fever/weight loss/cough etc.
- Partner with HIV/HBV/HCV
- Sex workers
- sexually transmitted infection (STI) in the past 12 months
- Cosmetic body piercing/tattooing
- Cocaine snorting
- Physician concern (based on medical history or physical examination).

The United States PHS published Guidelines for Preventing Transmission of Human Immunodeficiency Virus through
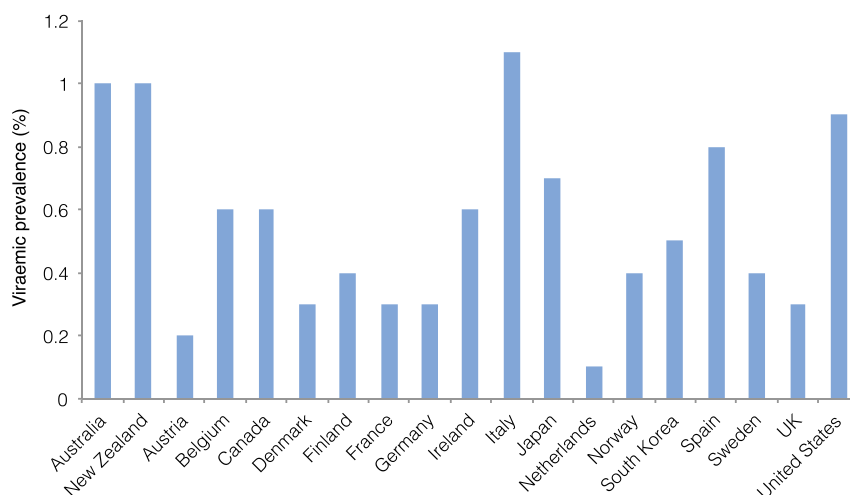
FIGURE 6. Viremic prevalence of hepatitis C virus (HCV) in selected high-income countries, estimated for the year 2015.[65]

Transplantation of Human Tissue and Organs in 1994, with an update subsequently published in 2013, and implemented in 2014.[45] These evidence-based guidelines outline behavioral and medical characteristics of the donor that put them at increased risk of transmitting a BBV, and have been widely cited as a basis for donor screening policies, including in Australia (see Table 12).

There are, however, problems with a binary risk-stratification approach. First, the extent to which next of kin are aware of illicit drug use and sexual history will often be limited, and misreported social histories are likely to translate into the systematic misclassification of many potential donors as standard-risk. Secondly, criteria defining "increased-risk" are broadly inclusive and define a large proportion of the potential donor population. For example the PHS criterion of "people who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, chlamydia or genital ulcers in the preceding 12 months" alone accounts for nearly 10% of the US adult population. Under the PHS Guidelines outlined in Table 12, 19.5% of potential donors were labeled as increased-risk in 2014.[13] Third, labeling organs as "increased-risk" has an impact on organ utilization as patients and physicians tend to be risk averse when it comes to acceptance decisions, despite the very low absolute risks of infectious disease transmission.[67] This risk aversion may be particularly pronounced when referring to stigmatized social behaviors (IVDU) and stigmatized diseases (HIV and HCV).[13] The criteria above, therefore, describe a large proportion of the population, yet the risk factors stipulated will be routinely underreported by next of kin; further,

despite systematic misclassification, patients and physicians will place undue emphasis on an "increased-risk" label when making acceptance decisions.

The challenge of mitigating the risk of BBV transmission is, therefore, a complex one, and one that is constantly evolving as social norms change and as the capacity to effectively treat disease in the event of disease transmission improves. For now, however, there remains a strong focus on population groups at increased risk of BBV, and therefore, it is important to have an accurate understanding of the current epidemiology of HIV, HCV and HBV in Australia and New Zealand.

BBV in Australia

After a spike in 2012, the number of newly diagnosed HIV infections in Australia has remained steady, with 1013 new cases diagnosed in 2016, 1027 in 2015, 1084 in 2014, and 1030 in 2013.[37] Of the estimated 26444 people estimated to be living with HIV in Australia in 2016, an estimated 75% of these infections are attributable to male-to-male sex exposure. Heterosexual sex accounts for approximately 22% of cases, IVDU for 2%, and other exposures (eg, sex work) for <1%.[37] Of all diagnoses of HIV notified since 1984, 91% were in males. Notification rates in 2016 were highest among males in the 20- to 29-year age group (17.1 per 100000), followed by the 30- to 39-year age group (16.1 per 100000). Of the total number of new HIV diagnoses in 2016, 5% were in Aboriginal and Torres Strait Islander (ATSI) people. HIV prevalence among ATSI people was estimated to be 0.11% in 2016.

It is estimated that nearly 90% of all HIV cases are diagnosed, and that of diagnosed cases 86% were receiving antiretroviral therapy as of 31 December 2016.[37] The proportion of HIV-infected persons taking effective treatments and achieving a suppressed viral load has increased significantly over the past 10 years. Of those on antiviral therapy, 93% had a suppressed viral load, corresponding to 72% of all people living with HIV in Australia having a suppressed viral load.[37] In addition, large, state-funded preexposure prophylaxis (PrEP) implementation programs were rolled out in 2016 in New South Wales, Victoria and Queensland. By the end of 2016, 23% of all estimated gay men at high risk of HIV according to PrEP eligibility criteria were taking PrEP.[37] It is likely that this will effect a reduction in HIV incidence in Australia in coming years. Already in NSW, an overall 11% decline in new HIV diagnoses was observed in 2017 compared to the previous 6-year average, whereas among Australian-born MSM, the number of new diagnoses was 19% less in 2017 compared with the previous 6-year average.[68] A decline in new HIV diagnoses was not observed in overseas-born MSM, however, nor among heterosexual people. The number of heterosexually acquired infections in NSW with an early diagnosis was has remained stable since 2011, but the number of new diagnoses with non–early-stage infection increased 31% in 2017 compared to the previous 6-year average.[68]

HCV infections in Australia are concentrated among IVDU, prisoners with a history of IVDU, people from high-prevalence countries, and HIV-positive MSM. In contrast to HIV trends, HCV notifications in Australia fell consistently between 2005 and 2012,[69] a trend which is thought to have been largely driven by a decrease in the number of people newly initiating injecting drug use. Some of this decrease may also be due to an increased use of needle and syringe

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TABLE 12.

Social risk factors for BBV identified by a systematic review of the literature regarding risks of HIV, HCV, and HBV transmission conducted by Seem et al[45]

Pathogens	Behavioral characteristics	Nonbehavioral characteristics
HIV	• MSM • IVDU • Noninjection illicit drug use • Multiple sex partners • Sex with partner known to be HIV-infected • Age ≤ 18 at first sexual intercourse	• STI • Marital status
HCV	• IVDU • Noninjection illicit drug use • Multiple sex partners • Sex worker • Inmates • Age ≤ 18 at first sexual intercourse • Sex with partner known to be HCV-infected • Sex with an injection drug user • Tattooing performed by a nonprofessional	• Hemodialysis • Receipt of blood transfusion • Signs and symptoms (eg, jaundice, elevated ALT) • STI • Marital status
HBV	• MSM • IVDU • Multiple sex partners	• Hemodialysis • STI • Marital status

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; MSM, men who have sex with men; IVDU, intravenous drug users; STI, sexually transmitted infection; ALT, alanine aminotransferase.

programs. Since 2012, the HCV notification rate had remained steady; however, a spike in notifications was observed in 2016 that is likely to be attributable to an increase in the number of people being newly tested for HCV in response to the availability of new DAA treatments. The majority (67%) of HCV notifications in 2016 occurred in males, with the highest notification rate in the 25- to 29-year age group (84.6 per 100000), followed by the 40+ years age group (56.4 per 100000).[37] Nine percent of HCV notifications occurred among ATSI people.

Interferon-free DAA regimens became available on the Pharmaceutical Benefits Scheme in Australia from March 2016. Of an estimated 227306 people living with HCV in Australia at the start of 2016, 32550 received treatment and 30434 (93%) were cured, reducing the number living with chronic HCV at the end of 2016 to 199412 (a decline in prevalence of 13%).[37] The uptake of HCV treatment in 2016 compared with previous years is illustrated in Figure 7. Importantly, according to the Australian Needle and Syringe Program Survey in 2016, there was an 11-fold increase in the rate of HCV-treatment among respondents with self-reported chronic HCV, from 2% in 2015 to 22% in 2016. The expanded availability of DAAs has an immediate impact on mortality associated with HCV: among people living with chronic HCV and those who have been cured of chronic HCV, the estimated number of HCV-related deaths approximately doubled between 2007 and 2015, but between 2015 and 2016 this number fell by 26%.

HBV notifications have been declining over the past decade in younger age groups due to the impact of vaccination programs. The greatest decline in newly acquired HBV cases has been in the 20- to 24-year age group (females in particular). Chronic HBV cases in Australia are concentrated among 4 key populations: migrants from high prevalence countries (especially Northeast and Southeast Asia), people who inject drugs, ATSI peoples, and MSM. Of the estimated 233034 people living in Australia with chronic HBV infection at the end of 2016, 38% were born in the Asia-Pacific, 9.3% were ATSI peoples, 6% were IVDUs and 4% were MSM.[37]

Australia-wide age- and sex-specific notification rates for HIV, HCV and HBV are shown in Figure 8. Age groups with the highest notification rates will have the highest residual risk of BBV transmission after donor screening. For example, the highest residual risk of HIV transmission would be among male donors aged 25 to 30 years. The highest residual risk of HCV transmission would be for male donors aged 35 to 40 years.

Rates of BBV Infection in Increased-risk Groups

MSM

Sexual contact between men is the main route of HIV transmission in Australia, accounting for 70% of all new cases in 2016.[37] Overall incidence of HIV among MSM in Australia was 0.85 per 100 person years in 2016, a rate which had not changed significantly for the prior 6 years.[69] The roll-out of expanded access to PrEP in 2016, however, has started to effect a decline in the number of new HIV diagnoses among Australian-born MSM—in NSW in 2017, the number of MSM newly diagnosed with HIV declined by 19% compared with the 2011 to 2016 average.[68] However, this decline did not extend to overseas-born MSM, among whom the number of new diagnoses increased 12% in 2017 compared to the 2011 to 2016 average.[68] In NSW in 2017, the number of newly diagnosed MSM who were born overseas exceeded the number of new diagnoses in Australian-born MSM (135 vs 97).[68] Regions of birth for MSM newly diagnosed with HIV in 2017 in NSW were Australia (41%), southeast Asia (17%), northeast Asia (14%), southern and central America (8%), southern and eastern Europe (6%), northern and western Europe (5%), and less than 5% from all other regions.[68]

Men who have sex with men are also significantly more likely to have HBV compared to the population overall, with an estimated chronic HBV prevalence of 3.0% versus 0.9% in the general population.[68] Based on a community-based cohort of MSM with serum samples stored between 2001 and 2007, the overall prevalence of HCV among MSM in Sydney was approximately 1% (or 2% when restricted to men 35 years and older); however, the rate among those who were HIV-positive was nearly 10 times that of those who are HIV-negative (HCV prevalence of 9.4% vs 1.1%).[70] In this study, IVDU was strongly associated with HCV seropositivity in MSM regardless of HIV-status.[70]

IVDU

Strategies to reduce HIV transmission among the IVDU population in Australia have been very successful. In 2016, IVDUs (without a history of male-to-male sex) accounted for only 14 new HIV diagnoses (1% of the total); IVDUs
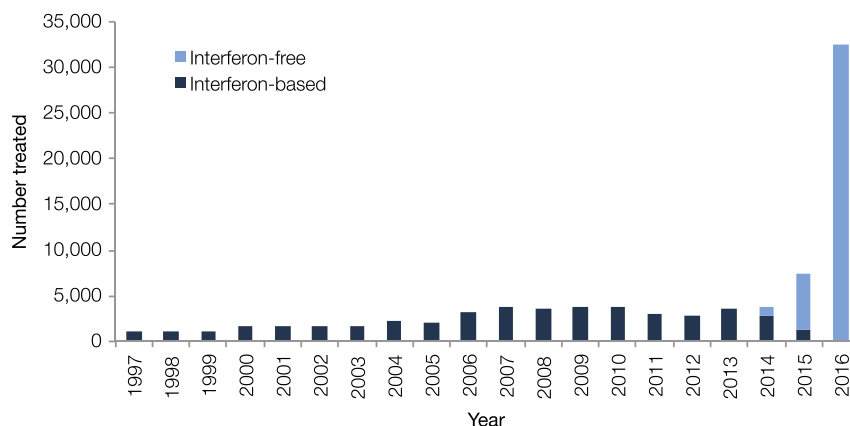
FIGURE 7. The estimated number of people living with hepatitis C who received treatment, 1997–2016.[37]
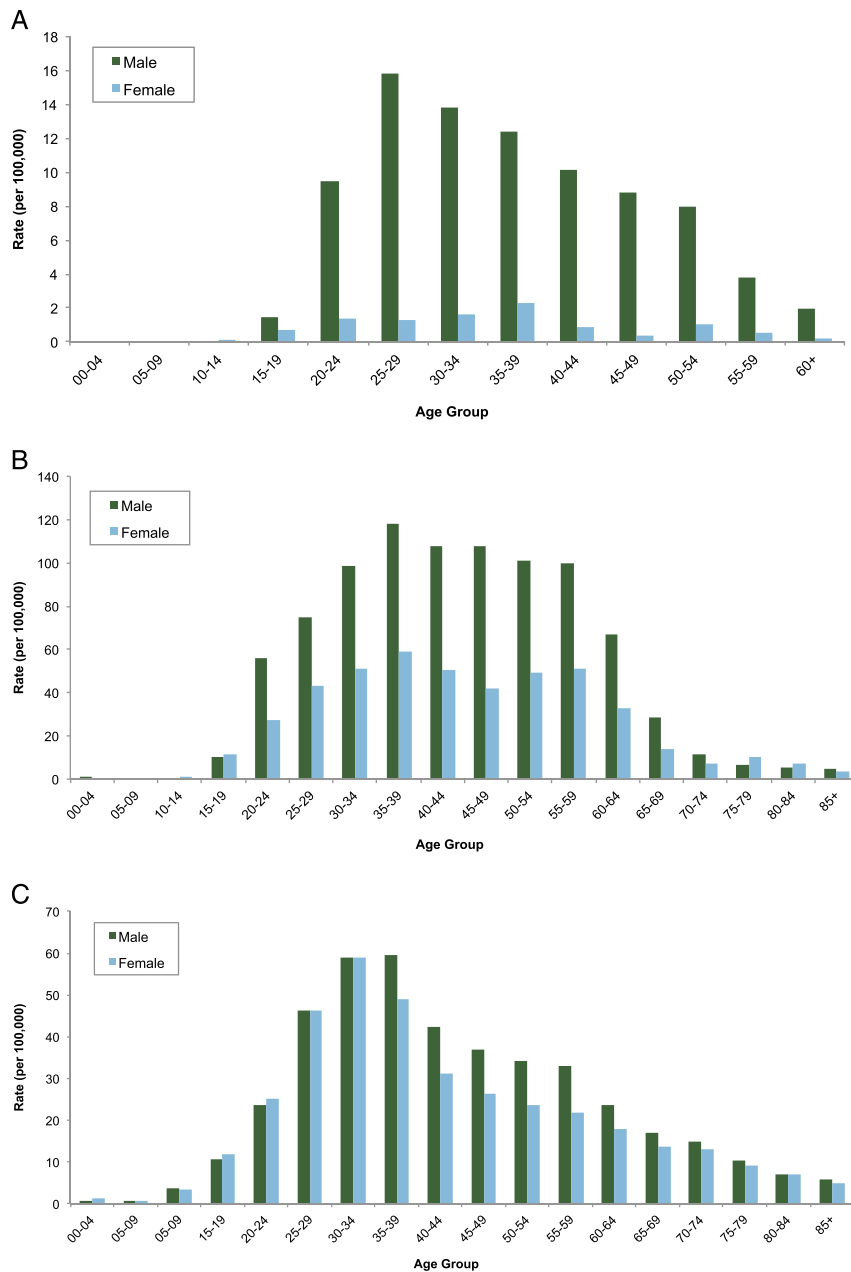
FIGURE 8. Graphs of (A) human immunodeficiency virus (HIV), (B) hepatitis C virus (HCV), and (C) hepatitis B virus (HBV) notification rates by age and sex (data sources: The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia—Annual Surveillance Report 2016, and The Kirby Institute, UNSW Australia, Sydney; 2015 Australian HIV Public Access Data set: http://kirby.unsw.edu.au/surveillance/Australian-HIV-Public-Access-Data Set—NB this data set excludes Queensland diagnoses).

who also reported male-to-male sex accounted for an additional 51 new diagnoses (5% of the total).[37] The prevalence of HIV in the IVDU population was 1.4% in 2016, or 0.7% if gay and bisexual men are excluded.[37] This is far lower than the HIV prevalence among IVDUs in the United States (9%), or Europe (11%).[22]

In contrast, the prevalence of HCV among IVDUs attending needle and syringe programs remained steady between 2009 and 2016 at 50% to 57%.[37,69] An overall decline in the absolute number of HCV notifications attributable to injecting drug users is thought to be due to a reduction in the number of people initiating injecting drug use and a simultaneous increase in the number of people receiving opioid substitution therapy, rather than an actual decline in the HCV infection rate in the IVDU population. Prevalence of HBV among IVDU in 2016 was 4.0%.[37]

Prison Population

There were no cases of HIV detected among 793 of 1235 prison entrants screened as part of the most recent Australian National Prison Entrants' Bloodborne Virus Survey.[71] The overall prevalence of HCV in the prison population was 31% in 2013, up from 22% in 2010, and was highest among those with a history of IVDU (58% in IVDUs vs 4% in non-IVDUs). HCV rates were also higher among female inmates

with a history of IVDU versus males with a history of IVDU (67% vs 56%). HBV prevalence is also relatively high among prisoners. Nationally, 18% of those tested under the National Prison Entrants' Bloodborne Virus Survey in 2013 were positive for HBV core antibody, and 3% (all male) were positive for HBV surface-antigen.[71]

Aboriginal and Torres Strait Islanders

The rate of HIV notifications was higher in the ATSI population in 2016 than in the Australian-born, non-Indigenous population (6.4 vs 2.9 per 100 000).[37] Whereas HIV notification rates in the Australian-born, non-Indigenous population have declined since 2014, in the ATSI population there has been a steady increase in the annual HIV notification rate over the past 5 years.[37] A higher proportion of HIV notifications in this population are attributable to heterosexual sex (20%) and IVDU (14%) than in the Australian-born non-Indigenous population (15% and 3% respectively). HIV prevalence, however, was the same in the ATSI population in 2016 as in the Australian-born, non-Indigenous population (0.11%).[37]

Whereas the HCV notification rate for the Australian population overall has been has been declining for the past 10 years, the rate of HCV notifications among ATSI people has been increasing, and in 2016 was nearly 4-times greater than for the non-Indigenous population (172.7 vs 45.2 notifications per 100 000).[37]

The estimated prevalence of HBV in ATSI people in 2016 was 3.7%, versus 0.2% in the Australian-born, non-Indigenous population.[37] Aboriginal and Torres Strait Islander people accounted for 10.6% of people living with chronic HBV infections in Australia in 2016.[37]

BBV in New Zealand

In 2016 there were 244 HIV notifications in New Zealand (217 men, 27 women; 30 previously diagnosed overseas).[62] Of new diagnoses, 159 (65%) were infected through male to male sex, 42 (17%) were infected through heterosexual contact, 1 person was infected through IVDU, and 5 men were infected either through sex with another man or IVDU.[62] The number of MSM newly infected with HIV each year in New Zealand has substantially increased since 2013, and in 2016 was the highest ever. Of all 159 MSM first diagnosed with HIV in 2016, 60% were European, 20% Asian,

9% Māori, 4% Pacific Islander, and 7% other ethnicities. The majority (59%) were living in Auckland; 13% were living in Wellington. A study of gay and bisexual men in Auckland found an HIV prevalence in this population of 6.5%, with 21% be unaware that they were infected.[72] The overall distribution of HIV notifications in New Zealand in 2016 by risk exposure type and ethnicity are shown in Figure 9.

There were 2278 adults (1898 men and 380 women) and 16 children receiving subsidized antiretroviral therapy at the end of June 2016. On the basis that ~80% of people with HIV in New Zealand have been diagnosed and are under specialist care, and ~85% of people with HIV who are under specialist care are receiving antiretroviral therapy, it is estimated that there were about 3500 people with HIV in New Zealand at the end of 2016, or a population prevalence of 0.077%.[62]

HCV prevalence in New Zealand is approximately 1.0%. After falling steeply from 1998 to 2004, HCV notification rates in New Zealand have remained steady at 0.4 to 0.8 cases per 100 000 population for the past decade (vs 2.4 cases per 100 000 in 1998).[38] HCV is highly prevalent among IVDUs in New Zealand. A 2015 study of HCV serology among IVDUs attending drug clinics in the lower north island found that, of 579 patients tested, 439 (76%) were positive for HCV antibody.[73] Of those with a PCR/viral load test on file, 50% had a positive result on their most recent test, and 32% had cleared their HCV infection without treatment. Of those who were referred and treated, 75% had achieved viral clearance.[73]

HBV notifications in New Zealand have gradually declined over the past 2 decades, from 2.3 per 100 000 population in 1998, to 0.7 per 100 000 population in 2015.[38] The relatively high prevalence of chronic HBV infection in New Zealand (~4%) is attributable to the high rates of HBV among immigrant populations from the highly endemic countries of the Pacific region, such as Kiribati, Nauru, Solomon Islands and Tonga, where up to a quarter of the population are chronically infected with HBV.[66]

BBV Prevalence and Risk Factors among Donor Referrals

A recent retrospective analysis of the NSW Organ and Tissue Donation Service logs found that 10% (309/2995) of all organ donor referrals from 2010 to 2015 had a reported history of BBV and/or social risk factors for BBV.[74] The proportion
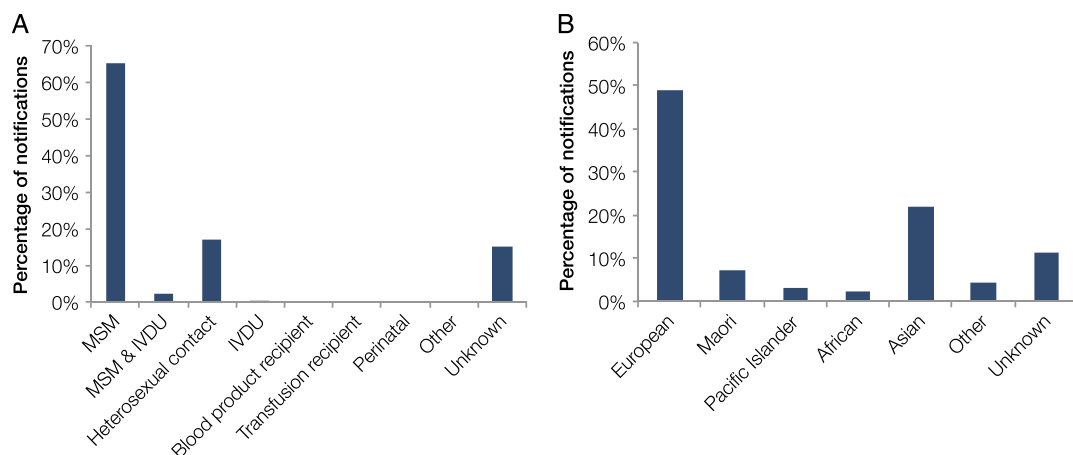
FIGURE 9. Distribution of human immunodeficiency virus (HIV) notifications in New Zealand in 2016 by (A) exposure category and (B) ethnicity.[62] MSM, men who have sex with men; IVDU, intravenous drug users.

of all donor referrals with a documented history of increased-risk behavior was 7.5% (224/2995), whereas the proportion with a known history of BBV was 6.4% (192/2995). The most common reported infection among referrals with a known history of BBV was HCV (84% of BBV diagnoses), with 19% of referrals having HBV and 3% having HIV. Of referrals with reported BBV, 10% reported more than 1 infection. The most commonly reported social risk factor for BBV was IVDU (84% of increased-risk donors, n = 191), followed by incarceration (11%), sexual partner in an at-risk category (6%), and MSM (3%).

Of the increased-risk referrals with a documented history of BBV and/or social risk factors for BBV, 16% (48/309) became actual donors. Of referrals with social risk factors but no history of BBV, 26% (n = 30) became actual donors. Overall, 3.3% (100/2995) of all referrals did not proceed primarily due to concern over BBV transmission risk. However, of the 100 increased-risk referrals that did not proceed primarily due to concerns about BBV transmission risk, only 15% had serology and/or NAT performed. Limiting the analysis to referrals with social risk factors only (no history of BBV), of the 33 referrals that did not proceed due to perceived BBV risk, 9% had serology and/or NAT performed. This means that from 2010 to 2015 in NSW there were 30 donor referrals where the donor had social risk factors for BBV but no documented history of BBV, who were ruled out from proceeding down the donation pathway on the basis of perceived BBV risk, but were not tested for presence of BBV.

By comparison, a similar study conducted in the United Kingdom found 3.8% of potential deceased donors had a documented history of increased-risk behavior, and 1.7% were seropositive for BBV markers.[75] The most common social risk factor was IVDU (47% of increased-risk potential donors), followed by incarceration (33%), and MSM (10%). Of potential donors who were seronegative for BBV, those with a history of IVDU were significantly less likely to become actual donors, after taking into account age and comorbidity.[75]

Table 13 shows the proportions of potential organ donors tested at South Eastern Area Laboratory Services (SEALS) that were positive for BBV in 2010. The finding of only 3.2% testing positive for HCV RNA suggests that increased-risk donors, especially those with a history of IVDU, form a small minority of those referred for NAT in NSW. This could either be the result of underreferral of potential donors at increased risk of BBV, or routine referral of potential donors at low risk of BBV for NAT, despite current guidelines.

Donor Screening and Utilization

Until recently, a key question for BBV screening in potential solid organ donors was whether NAT should be performed routinely for all potential donors, or whether it should be reserved for potential donors known to be at increased risk. Risk-benefit modeling by Humar et al published in 2010 predicted that NAT in average-risk donors would result in a net loss of quality-adjusted life years, as the number of false-positives would outweigh the number of transmission events averted.[44] By comparison, among increased-risk donors, higher incidence of BBV means a much higher chance of window period infection, thus NAT significantly reduces residual transmission risk and increases organ utilization by providing reassurance to physicians and patients who would otherwise be reluctant to accept these organs.

The recent introduction of newer-generation NAT systems —including the Cobas 6800 system from Roche Molecular Systems (currently used by SEALS) and the Panther system from Hologic—have reduced turnaround time to 3.5 hours, which is short enough to permit confirmatory testing within a timeframe suitable for organ donation.[76] Additional features of the Cobas 6800 system include a range of features that will reduce contamination risk and allow continuous sample loading (rather that batch runs). Using this new machine in conjunction with repeat/parallel testing protocols should effectively reduce the false-positive rate to negligible levels, and should permit prospective NAT for all organ donors.[77,78]

The Cobas 6800 system is now in use in NSW, Queensland and Western Australia, and NAT is already routinely ordered for all potential solid organ donors in Queensland. With the introduction of newer-generation NAT, the rationale for selective NAT testing is largely redundant, as donor losses due to false-positive tests are predicted to be rare using the new systems. Furthermore, most of the unexpected donor-derived BBV transmission events reported over the past 20 years (excluding those due to human error) occurred due to window period infections in donors with incomplete social histories or without known risk factors for BBV (see *Transmission Risk*). Selective NAT would not have averted such adverse events.

HIV

Serological screening for HIV should be performed using a fourth-generation antigen/antibody combination immunoassay which identifies antibodies against both HIV-1 and HIV-2,

TABLE 13.

Proportion of potential organ donors screened at the SEALS NAT laboratory between January 1 and December 3, 2016, testing positive for HIV, HCV and HBV using testing methods for current viremia (HIV-RNA, HCV-RNA, HBV-DNA) and evidence of infection (anti-HIV, anti-HCV, anti-HBc)

Virus	HIV		HCV			HBV	
BBV marker	Anti-HIV[a]	HIV RNA[b]	Anti-HCV[c]	HCV RNA[b]	HBsAg[d]	Anti-HBc[e]	HBV DNA[b]
% testing positive	0.00	0.00	6.95	3.20	0.64	2.67	1.06

[a] Architect HIV Ag/Ab combined assay.

[b] Cobas Amplicor and Cobas 6800-MPX assay.

[c] Architect Anti-HCV.

[d] Architect HBsAg Qualitative II.

[e] Architect Anti-HBc II.

S Ray and W Rawlinson, personal communication.

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; RNA, ribonucleic acid; BBV, bloodborne viruses.

TABLE 14.

Residual risk per 10000 of an HIV infection occurring during the window period, by ELISA and NAT, calculated for the Australian population (Karen Waller, personal communication; N.B. data are preliminary and may be subject to change pending formal publication)

Risk category	No. patients	No. HIV seroconverted	Person years	Pooled incidence per 100 PYS (95% CI)	Residual risk (95% CI), ELISA	Residual risk (95% CI), ELISA + NAT
MSM	10 414	175	15 280.5	1.05 (0.59–1.63)	6.3 (3.6–9.8)	2.0 (1.1–3.1)
IVDU	76 596	717	—	0.33 (0.30–0.35)	2.0 (1.8–2.1)	0.6 (0.6–0.7)
Incarcerated	196 784	348	—	0.04 (0.03–0.04)	0.2 (0.2–0.2)	0.1 (0.1–0.1)
Commercial sex worker	4555	12	—	0.07 (0.04–0.13)	0.4 (0.2–0.8)	0.1 (0.1–0.2)
High-risk partner	522	1	—	0.07 (0.00–0.40)	0.4 (0.0–2.4)	0.1 (0.0–0.8)

HIV, human immunodeficiency virus; MSM, men who have sex with men; IVDU, intravenous drug users; ELISA, enzyme-linked immunosorbent assay; NAT, nucleic acid testing.

as well as the presence of p24 antigen, which is detectable in the bloodstream shortly after infection. The serological window from HIV exposure to the development of HIV antibodies ranges from approximately 3 weeks to up to 6 months (average window period of 17–22 days); however, p24 antigen can be detected ~7 to 16 days after infection.[44] NAT permits detection of acute HIV infection within 5.6 to 10.2 days of exposure.[79] If an initial test is positive, this result should be confirmed with subsequent testing.

Neither negative serology nor negative NAT can entirely exclude the possibility of donor transmission of HIV, as there is always the risk that the donor recently acquired an infection that is still in the eclipse phase. This risk is a function of the underlying incidence of HIV in the population; that is, the lower the incidence of HIV, the lower the risk of window period infection. This risk has been estimated for the United States and Canadian populations[80,81] and more recently for the Australian population (personal communication Karen Waller). The estimates calculated by Waller et al are based on a systematic review and meta-analysis of HIV incidence and prevalence in Australia, which was used to estimate the pooled incidence of HIV among various increased risk groups in the population, and the estimate was then applied in the following formula:

Risk of window period infection

$$= 1 - e^{-(incidence\ rate\ x\ window\ duration)}$$

The risks of window period infection calculated by Waller et al are reported in Table 14. These estimates are provided in this report ahead of final publication, and therefore, are preliminary estimates that may be subject to minor revisions. It should also be noted that, given the rapid scale-up of PrEP in NSW and Victoria in recent years, HIV incidence is likely to decline and the residual risk of HIV transmission in Australia is expected to fall in the future and thus these figures may somewhat overestimate true contemporary residual risk.

HCV

The serological window for HCV antibody detection is long: at least 40 to 70 days. NAT reduces the HCV detection window to ~4 to 6 days and is highly sensitive, allowing for HCV RNA detection at levels as low as 2.0 to 9.4 IU/mL.[44,82,83] The ~10-fold reduction in the HCV detection window using NAT versus serological tests corresponds to a 10-fold reduction in the residual risk of HCV transmission.[82] Current TSANZ Guidelines recommend screening for anti-HCV in standard-risk donors, with HCV-NAT recommended for increased-risk donors. The highest-risk group for HCV transmission in Australia and New Zealand is IVDUs.

A positive HCV-NAT with or without a positive anti-HCV is an indication of active HCV infection. However, viral loads can fluctuate in HCV-infected people, sometimes falling below the NAT detection limit. Therefore, a negative HCV-NAT cannot alone be used to rule out HCV infection—anti-HCV results are also required. A positive anti-HCV with a negative HCV-NAT can indicate a resolved infection, a false-positive anti-HCV result, or an active infection with a viral load below the detection threshold for NAT (see Table 15). The false-positive rate for HCV-NAT in the Australian and New Zealand population is not known; in the United States it has been estimated at <0.2%.[46] An HCV infection is considered resolved when a person has been free of the virus for >12 weeks (demonstrated by 2 blood tests 12 weeks apart), with no new risk exposure over this interval.

Currently published international guidelines state that organs from HCV-positive donors may be used for HCV-positive recipients, given evidence of minimal impact on transplant outcomes in this context.[84-86] TSANZ guidelines also allow for transplantation of organs from HCV-NAT-negative, HCV antibody-positive donors to HCV-negative

TABLE 15.

Interpretation of results of HCV screening in organ donors and implications for utilization[5]

HCV test	Conclusion	Implications for liver utilization	Implication for utilization of nonliver organs
Anti-HCV + HCV-NAT not available	HCV viremia cannot be ruled out	HCV transmission may occur	
Anti HCV + HCV-NAT+	HCV viremia		
Anti HCV-HCV NAT+			
Anti HCV + HCV-NAT-	HCV viremia unlikely	HCV transmission is unlikely to occur but cannot be ruled out completely: transplantation may occur with the informed consent of the recipient	

HCV, hepatitis C virus; NAT, nucleic acid testing.

recipients in exceptional circumstances. Of actual organ donors in Australia and New Zealand in 2016, 3% (n = 18) were HCV-antibody–positive.[87] Currently, organs from HCV-NAT–positive donors are not formally acceptable for use in HCV-negative recipients except in exceptional circumstances, given the 100% infectivity rate and historical evidence of poor posttransplant outcomes.[88-90] However, the availability of DAAs able to successfully eradicate HCV infection in transplant recipients means that policies are rapidly changing, and the utilization of HCV-NAT-positive donors for both HCV-positive and HCV-negative recipients is likely to increase in future (see *Recipient Management*). Successful treatment of HCV in the community will also have the effect of diminishing the residual risk of donor-derived HCV infection over the next few years. Nonetheless, it will remain important to accurately identify active HCV infection in donors, ideally prospectively, to inform recipient management posttransplant.

HBV

HBV is an enveloped DNA virus consisting of surface and core. The surface incorporates the envelope protein, or hepatitis B surface antigen (HBsAg). The core contains a DNA polymerase, double-stranded DNA, a core antigen (HBcAg) and another antigen called "e" (HBeAg). When screening for HBV in potential organ donors, testing for HBsAg, HBsAb, and antibody to HBcAb (anti-HBc) are all required to identify and distinguish between current infection and prior cleared infection.[91] Serology that is positive for HBsAg indicates a current HBV infection, and in the absence of preventative measures, HBV may be transmitted by any organ or tissue in this scenario (see Table 16). Anti-HBc of IgM class indicates a current or recent infection with HBV, whereas anti-HBc of IgG class indicates a past infection. The presence of hepatitis B surface antibody (HBsAb) in the blood is indicative of an immunologic response to HBsAg, and the higher the HBsAb titer, the lower the infectious risk associated with anti–HBc-positive donors.

Individuals who have cleared a natural HBV infection typically become HBsAg-negative, anti–HBc-positive, and have an HBsAb titer greater than 10 IU/L. However, a donor serological profile with an isolated presence of anti-HBc may also indicate a current HBV infection at a point where HBsAg is no longer detectable in peripheral blood but HBsAb titers have not yet reached levels sufficient to clear the virus (or to be detected).[91] Presence of anti-HBc, therefore, carries the possibility of HBV transmission, although the extent of this risk depends on the organ being transplanted. The liver is a reservoir for HBV, with the HBV genome forming a stable microchromosome—the covalently closed circular DNA—in the hepatocyte nucleus, meaning that the immune system is unable to completely eradicate the infection. Thus in anti–HBc-positive donors the hepatocytes are latently infected with HBV, and reactivation may occur at any time in immunosuppressed patients.[92,93] Guidelines, therefore, recommend livers from anti–HBc-positive donors be used for recipients with previous HBV infection or for recipients who have been successfully vaccinated.[5]

Nonliver grafts from anti–HBc-positive donors with a cleared infection rarely transmit HBV; however, current international guidelines recommend that organs from such donors preferentially be used in recipients with current or previous HBV infection or successful vaccination (see Table 11). Nonliver organs may be used for HBV-naïve recipients after informed consent and with special monitoring of the recipient for the appearance of HBV, with or without hepatitis B hyper Immune-immunoglobulin (HBIG) and antiviral prophylaxis. Current TSANZ policy is that anti–HBc-positive donors may be accepted with caution after specialist advice, taking into account the recipient HBsAb titer.[52] HBsAg-positive donors can be considered for HBsAg-positive recipients, or for HBsAg-negative recipients in exceptional circumstances after specialist advice. This position is similar to that of the UK and Europe.[5,29]

As a first-line screening tool, HBV-NAT has a relatively minor benefit in countries with low endemic rates of HBV. HBsAg assays have a detection window of 35 to 44 days; NAT reduces this window to 20 to 22 days.[44] Nucleic acid testing is still useful, however, because it will detect viral replication in potential donors who are anti–HBc-positive but HBsAg-negative, that is, where the immune response has not entirely cleared the infection.[94] Occult HBV infection occurs where there is persistence of HBV DNA in the liver, and is characterized by undetectable HBsAg and low-level plasma HBV DNA.[95] Approximately 50% of occult HBV infections are positive for anti-HBc, but about 20% are negative for all serological markers of HBV except for HBV DNA.[96] If HBV-NAT is positive, donors should be treated as if they were HBsAg-positive. If HBV-NAT is negative, transplantation can proceed with considered given to antiviral therapy and/or HBIG treatment for the recipient, unless the recipient is already immune.[5]

What constitutes a protective HBsAb level for preventing HBV transmission has not been precisely determined: a threshold of greater than 10 IU/L has been demonstrated to be

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TABLE 16.

Interpretation of results of HBV screening in organ donors and implications for utilization[5]

HBV test	Conclusion	Implications for liver utilization	Implication for utilization of nonliver organs
HBsAg+Anti-HBc–	HBV infection	HBV transmission occurs. Transplantation of organs to HBV-infected recipients, or in exceptional circumstances after specialist advice.	
HBsAg+Anti-HBc+	HBV infection		
HBsAg-Anti-HBc+	Hepatocyte infected, usually no viremia but low-level viremia should be considered	HBV transmission occurs with liver transplantation: allow transplantation of organs in HBV-infected recipients or recipients with an immune response to vaccination and HBV prophylaxis[a]	Transmission is unlikely: allow transplantation of organs in vaccinated or infected recipients. Organs may also be used in other recipients with/without prophylaxis[a] and with monitoring for at least 12 months.

[a] HBV prophylaxis, antiviral treatment (and HBIG) as well as lifelong monitoring (serology and NAT) required In recipients with appropriate own immunological protection against HBV after vaccination, discontinuation of antiviral treatment can be considered on a case-by-case basis.

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

TABLE 17.

Reports of unexpected donor to recipient transmission of HIV and clinical outcomes (deceased donors only)

Organ	Ref	Year of transplant	Donor risk factors	Time from transplantation to diagnosis, months	Follow-up interval, months	Recipient died at end of follow-up	Graft failure during follow-up period
Kidney	Poli, 1989[99]	1984	Presumed illicit drug use	27	27	No	No
	Poli, 1989[99]	1984	Presumed illicit drug use	40	40	No	No
	Poli, 1989[99]	1984	Illicit drug use	13	19	No	No
	Poli, 1989[99]	1983	Illicit drug use	11	21	No	No
	Poli, 1989[99]	1983	Illicit drug use	16	33	Yes	No
	Poli, 1989[99]	1982	Illicit drug use	2	59	Yes	No
	Briner, 1989[100]	1984	IVDU	<1	59	Yes	No
	Erice, 1990[101]	1984	Transfusion[a]	33	67	No	No
	Simonds, 1992[102]	1985	None known	17	32	Yes	No
	Simonds, 1992[102]	1985	None known	7	14	Yes	Yes
	Schwarz, 1987[103]	1986	IVDU, alcoholism	2	15	No	Yes
	Schwarz, 1987[103]	1986	Homelessness, alcoholism	1.5	33	No	No
	CDC, 1987[104]	1986	None known	2	7	No	No
	Bowen, 1988[105]	1988	MSM	<1[b]	15	No	No
	Borchi, 2010[106]	2007	None known	<1	35	No	No
	Bellandi, 2010[58]	2007	None known	<1	35	No	Not reported
	Ison et al, 2011[54]	2007	MSM	10[c]	14	No	Yes
	Ison et al, 2011[54]	2007	MSM	10[c]	24	No	Yes
	Mukhopadhya, 2012[107]	.	.	9	9	No	Not reported
Liver	CDC, 1987[104]	1986	None known	3	7	No	No
	Samuel, 1988[108]	1986	Not reported	<1	1.5	Yes	No
	Simonds, 1992[102]	1985	None known	<1[d]	<1	Yes	No
	Bellandi, 2010[58]	2007	None known	<1	35	No	Not reported
	Ison et al, 2011[54]	2007	MSM	11[c]	12	Yes	No
Heart	Erice, 1990[101]	1984	Transfusion[a]	25	72	No	No
	Simonds, 1992[102]	1985	None known	8	9	Yes	No
	Ison et al, 2011[54]	2007	MSM	11[c]	35	Yes[e]	No
Pancreas	Erice, 1990[101]	1984	Transfusion[a]	1	6	Yes	No
Lung				No reports			

[a] The donor received a transfusion shortly before death with blood from a seropositive donor.
[b] HIV detected on donor serology performed at the time of organ retrieval.
[c] Both HIV and HCV were simultaneously transmitted from the donor.
[d] HIV detected post mortem.
[e] Recipient died due to withdrawal from care.
Excludes reports with no evidence of donor origin of infection.
IVDU, intravenous drug users; MSM, men who have sex with men; CDC, Centers for Disease Control.

protective for recipients of anti–HBc-positive kidneys; however, in liver recipients, a threshold of HBsAb greater than 100 IU/L is often applied.[97] In 1 study, the risk of anti-HBc seroconversion postliver transplant was 4% when pretransplant HBsAb titers in the recipient were >100 IU/L, and 10% when pretransplant titers were less than 100 IU/L.[98]

Transmission Risk

HIV

Table 17 summarizes published reports of unexpected HIV transmission from deceased donors to recipients. Reports were identified as per the search strategy described in **Materials and Methods 1, SDC** (http://links.lww.com/TXD/A152). Given that transmission events are not systematically reported in peer-reviewed journals, it is unlikely that Table 17 captures all cases of unexpected HIV transmission. Furthermore, given the limited number of case reports it is also difficult to draw conclusions about rates of mortality and graft failure resulting from donor-derived HIV transmission. For this reason, as descriptive summary of these case reports is provided only.

The relatively large number of reports of donor-derived HIV transmission around the mid-1980s coincides with the introduction of serological tests for HIV. Routine donor screening was introduced in 1985, and recipient screening also conducted around this time retrospectively identified several cases of donor-derived transmission. There was then gap of approximately 20 years before the next cases of donor-derived HIV transmission were reported. The absence of reported cases over this interval probably reflects a cautious approach to donor selection during this era. With the growing demand for organs of the past decade and the corresponding expanded utilization of increased-risk donors, cases of donor-derived HIV transmission have reappeared. However, the implications for donor-derived HIV transmission have altered profoundly since the introduction of effective antiretroviral therapy in 1996. Reviews of HIV infection in solid organ transplantation from the early 1990s reported 5-year mortality rates among recipients who seroconverted posttransplantation of 30% to 50%.[101,109] From 3 cases of HIV transmission reported in the past decade affecting 8 recipients,

there was only 1 death (a liver transplant recipient who was co-infected with HCV) over a median follow-up interval of 29.5 months.

In the case reported jointly by Borchi et al and Bellandi et al, HIV transmission from an Italian donor to 3 recipients (2 kidney recipients and 1 liver recipient) occurred due to a "chain of errors during the donation process".[58,106] The donor in this case was a woman in her forties who died of a brain hemorrhage at home, but had no clinical history of any diseases. Her family consented to her donating her organs with no idea that she was HIV-positive.[110] Routine blood tests showed that the donor was infected with HIV; however, the laboratory report of the anti-HIV test was mistakenly hand-transcribed from HIV-positive to -negative. The protocols of the donor hospital at the time were to manually transcribe results from the laboratory machine into the laboratory information system, because this was not automated. The incorrect result was sent to the Regional Transplant Centre without the supporting machine report and included in the donor record. On this basis, the Regional Transplant Centre authorized the donation. Tissues were also procured from the donor and tested again in a second laboratory in a different city, where HIV was detected again but, instead of communicating this information by phone, the laboratory operators sent the results by fax to the laboratory of the hospital where the donor organs had been taken for transplantation. The results were sent on a Saturday, and were not seen by the laboratory direction until Monday, 5 days after the transplants had taken place. Only then was the Regional Transplant Center alerted and the patients contacted.[58]

This case demonstrates, first, that biovigilance systems with clear lines of communication are essential for rapid notification of recipients potentially affected. Second, there is always the potential for human error, and systems, therefore, need to be computerized as far as possible, and designed with the potential of human error in mind. A similar case was also reported in Taiwan in 2011, where the transplant team did not check the donor's HIV status in their computer record but instead the laboratory technician read the HIV result over the phone, and the result of "reactive" was misheard as "nonreactive" by the transplant coordinator.[111] Precautionary measures proposed by the regional health authorities subsequent to the Italian HIV transmission event were included[110]:

- cross-checking of laboratory reports and transcription of test results confirmed by double signature,
- computerized delivery of test results,
- introduction of clearly visible graphic symbols to indicate donor suitability,
- Including the number of antibodies and positivity threshold next to the positive/negative test result,
- Introduction of specific accreditation pathways for laboratory personnel.

In the case reported by Ison et al,[54] a 39-year-old male donor transmitted HIV and HCV to 4 recipients (2 kidney recipients, 1 heart recipient, and 1 liver recipient). The donor tested negative on serological screening for HIV (HIV-1/HIV-2 recombinant DNA enzyme assay) and HCV (Ortho HCV version 3.0 enzyme-linked immunoassay); his family members were unable to provide a social history, but a social contact subsequently disclosed a history of sex with another man. NAT was not performed before donation, which was consistent with the screening guidelines of the time. Three months after transplantation, investigation of elevated liver enzymes in the recipient of the left kidney resulted in HCV being detected; 10 months after transplant the onset of acute rejection and proliferative glomerulonephritis in the same recipient lead to a concurrent diagnosis of HIV. The OPO notified the other recipients at this time. Kidney function in the recipient of the left kidney deteriorated steadily, resulting in nephrectomy 14 months posttransplant. The recipient of the right kidney experienced graft rejection that resulted in transplant nephrectomy 19 months posttransplant. The recipient of the liver, despite aggressive treatment, died 12 months after transplantation (less than 2 months after the detection of HIV and HCV). The recipient of the heart stopped adhering to treatment 9 months after being diagnosed with HIV and HCV, and died 3 months later.

This case highlights a number of important points for donor screening and recipient management. First, obtaining an accurate social history is a difficult undertaking, and next of kin may be the least likely to be aware of high-risk behaviors. Where there is doubt (which there arguably is in most cases), potential donors might be prudently regarded as increased risk. Second, mechanisms need to be in place to detect an unexpected transmission event as early as possible posttransplant so that prophylactic treatment can be commenced. The long interval between transplantation and detection of HIV and HCV in the recipients in this case is likely to have contributed to the poor outcomes (compared with the cases reported by Borchi et al and Bellandi et al). Data from DTAC clearly demonstrate improved outcomes with early recognition and expedited communication.[112] If NAT is not performed before donation, it should be performed retrospectively for increased-risk donors, and recipients should be routinely screened with HIV-NAT 7 days after transplantation. More importantly, there were key flags that should have led to recognition and reporting by the teams but were missed opportunities for detection. Third, the outcome of the heart recipient in this case is a reminder of the potential psychological impact of the transmission of BBV.

It is also worth noting the impact of this transmission event on physician practice in the United States. A survey of attitudes and practices of transplant surgeons with respect to increased-risk donors in the 12 months after this event occurred found that 42% of surgeons had decreased their use of increased-risk donors, 35% had increased their emphasis on informed consent, 17% had increased their used of NAT, and 6% had implemented a formal policy at their transplant center.[113]

Notably, there have been no reported cases of unexpected HIV transmission where NAT was performed and returned a negative result. Where HIV transmission from donor to recipient(s) has occurred, either NAT was not performed or a positive result was misread or miscommunicated.

HCV

Before HCV screening became available in the early 1990s, HCV transmission during organ transplantation—either from the donor organ or blood transfusion—was not uncommon, resulting in chronic hepatitis, cirrhosis, and hepatocellular carcinoma in approximately 80% of those recipients who were infected.[114,115] When an organ from

an HCV-positive donor is transplanted, whether HCV transmission occurs depends on whether there was active viral replication at the time of transplantation, the specific organ that was transplanted, and the HCV status of the recipient.[114] A positive HCV-NAT indicates current active infection, whereas a positive test for HCV antibodies in the absence of a positive NAT result likely indicates a cleared infection or false-positive serologic test. HCV-NAT–positive donors will transmit infection in virtually all cases.[116] Currently, HCV-NAT–positive allografts are used for HCV-negative recipients in lifesaving circumstances. The risk of transmission from NAT-negative HCV antibody-positive donors to HCV-negative recipients, however, has not been quantified.[49]

A review of outcomes of anti–HCV-positive heart donor transplants in the United States between July 1994 and December 1999 reported a 3-year actual survival rate of 40% for recipients who were at risk of imminent death before transplantation, and 70% for recipients who would not have otherwise been offered heart transplantation due to age or other medical risk factors.[117] Of this cohort, 4 of 17 recipients who survived more than 60 days posttransplant seroconverted to HCV-positive; of these 4, only 1 began to show elevated liver function tests at 1 year posttransplant. The donors in the analysis were restricted to those testing positive for HCV on enzyme-linked immunosorbent assay (ELISA) but without recent or ongoing clinical history of liver dysfunction and markers of liver function within normal limits. By contrast, an analysis of the outcomes of heart transplants involving anti–HCV/HCV-RNA-positive donors and anti–HCV-negative recipients found 100% of recipients became HCV RNA–positive posttransplant and 6 of 9 patients surviving beyond 3 months posttransplant developed evidence of hepatitis, including severe liver injury in 2 patients.[118]

Table 18 summarizes case reports of unexpected HCV transmission events and their clinical outcomes, going back as far as it was possible to screen for HCV and theoretically avoid transmission. The cases reported by Krajden et al[119] and Nampoory et al[120] both involve infection occurring during the serological window for HCV detection. The donors in each case would not be considered at increased risk of HCV based on usual criteria: the donors were a 25-year-old woman with no known risk factors and an 11-year-old boy; both were seronegative for HCV. In the case reported by Nampoory et al, HCV was detected in both kidney recipients 4 and 8 months after transplantation when their liver function began to deteriorate. One of the recipients experienced progressive deterioration of liver function and died while awaiting liver transplantation abroad.[120] In the case reported by Krajden et al,[119] none of the recipients had died or lost their graft within the 14-month follow-up time frame.

The 2011 case reported by the CDC was primarily a case of human error. The donor (a middle-aged man who died of traumatic head injury) was known to have a history of schizophrenia, substance abuse and incarceration, and was, therefore, at increased risk of BBV infection. Serological tests were negative but NAT was positive for HCV; however, the reaction wells were misread and misreported as negative.[121] Recipients of the 2 kidneys both had positive results on HCV-NAT when tested 6 months after transplantation; the liver recipient was HCV-positive before transplantation.

In most cases of unexpected HCV transmission, only serological test results were available at the time of transplantation, thus the residual risk of a window-period infection was higher than if NAT had been performed. However, HCV transmission during the eclipse window is still a possibility. Suryaprasad et al[122] reported 3 clusters of solid organ-transmitted HCV occurring in the United States despite NAT screening.[122] Each of the donors in these clusters had a known history of IVDU preceding death and, therefore, underwent NAT in accordance with guidelines. In the first of these cases, the donor was a 25-year-old woman found unresponsive with a hypodermic needle in her arm. Four days before donation, NAT for HCV, HBV, and HIV were all negative, and the heart, liver, and both kidneys transplanted into 4 recipients after consent was obtained to receive organs from an increased-risk donor. The liver and right kidney recipients had known HCV infection before transplantation: 9 days posttransplant, the left kidney recipient was found to be newly HCV NAT-positive on routine screening. The heart transplant recipient had detectable HCV RNA 31 days posttransplant, and treatment with pegylated interferon (27 weeks postdiagnosis) and ribavirin (16.5 weeks postdiagnosis) was commenced. The heart recipient had a sustained virological response and remained free of clinical liver disease and without graft rejection. The left kidney recipient was unable to receive interferon therapy due to comorbidities and had a peak HCV RNA level greater than 69 million IU/mL approximately 8 months posttransplant. After the patient developed cirrhosis due to nonalcoholic steatohepatitis approximately 2 years posttransplant, sofosbuvir and ribavirin were commenced, and at the time of last follow-up, HCV RNA was undetectable in the patient.

The donor in the second case reported by Suryaprasad et al had a history of incarceration and evidence of recent IVDU, however, NAT screening was negative for BBV. The 2 kidneys were transplanted into 2 HCV-negative recipients after providing informed consent. Hepatitis C virus RNA was detected in the recipient of the right kidney 1 month posttransplant; however, the left kidney recipient had undetectable HCV RNA at 1, 2, and 3 months posttransplant. The right kidney recipient developed a low level of elevated liver enzymes at 4 months posttransplant and died 19 months posttransplant due to transplant pyelonephritis, sepsis, and refusal of dialysis. In the third case, the donor also had a history of IVDU but negative NAT results for HCV, HBV, and HIV. The lungs, left kidney/pancreas, right kidney, liver, and heart were transplanted into 6 recipients. HCV RNA was detected in the recipient of the left lung on routine screening 66 days posttransplant, and in the kidney/pancreas recipient 73 days posttransplant. The right lung recipient developed primary graft dysfunction and died shortly after transplantation: retrospective testing detected HCV RNA in a sample taken 20 days posttransplant. HCV RNA was not detected in the right kidney and heart recipients at 7 and 6 months posttransplant, respectively.

These cases highlight the importance of routine posttransplant screening for BBV for the early detection and treatment of BBV transmission and the need for a high degree of clinical suspicion in the case of donors with clear evidence of active IVDU. What is also noteworthy about these cases is that they coincide with the introduction of DAAs for HCV, which have transformed the ability to

TABLE 18.

Reports of unexpected donor-derived transmission of HCV and clinical outcomes. Restricted to reports proving information on clinical outcomes; deceased donor transplants only

Transplanted organ	Reference	Year of transplant	Donor risk factors	Screening test(s) performed	Time from transplantation to diagnosis, months	Follow-up interval, months	Recipient died at end of follow-up	Graft failure during follow-up period
Kidney	Krajden et al, 1995[119]	1995	None known	Serology	<1	10	No	No
	Krajden et al, 1995[119]	1995	None known	Serology	8	12	No	No
	Nampoory et al, 1999[120]	1996	None known	Serology	8	36	No	No
	Nampoory et al, 1999[120]	1996	None known	Serology	4	Not reported	Yes	No
	Ison et al, 2011[54]	2007	MSM	Serology	10[a]	14	No	Yes
	Ison et al, 2011[54]	2007	MSM	Serology	10[a]	24	No	Yes
	CDC, 2011[121]	2011	Substance use, incarceration	Serology, NAT	6	6	No	Not reported
	CDC, 2011[121]	2011	Substance use, incarceration	Serology, NAT	6	6	No	Not reported
	Suryaprassad et al, 2015[122]	2011	IVDU (COD drug overdose)	Serology, NAT	<1	24	No[b]	No
	Suryaprassad et al, 2015[122]	2012	IVDU	Serology, NAT	1	19	Yes[c]	No
	Choe, 2017[123]	2016 (?)	Opiate overdose	Serology	1.5	Not reported	No[d]	No
	Choe, 2017[123]	2016 (?)	Polysubstance abuse	Serology	1	Not reported	No[d]	No
Liver	Krajden, 1995[119]	1995	None known	Serology	<1	18	No	Not reported
	Ison et al, 2011[54]	2007	MSM	Serology	11[a]	12	Yes	No
Heart	Krajden, 1995[119]	1995	None known	Serology	<1	18	No	Not reported
	Ison et al, 2011[54]	2007	MSM	Serology	11[a]	35	Yes	No
Lung	Suryaprassad et al, 2015[122]	2011	IVDU (COD drug overdose)	Serology, NAT	1	Not reported	No	No
	Krajden, 1995[119]	1995	None known	Serology	3	14	No	Not reported
	Tugwell, 2005[124]	2000	Alcoholism	Serology	Not reported	14	Yes	Not reported
	Tugwell, 2005[124]	2000	Alcoholism	Serology	Not reported	Not reported[e]	Yes	Not reported
	Suryaprassad et al, 2015[122]	2013	IVDU	Serology, NAT	2	7	No	No
	Suryaprassad et al, 2015[122]	2013	IVDU	Serology, NAT	2	3	Yes[f]	Yes
Pancreas	Suryaprassad et al, 2015[122]	2013	IVDU	Serology, NAT	73	Not reported	No	No

[a] Both HIV and HCV were simultaneously transmitted from the donor.

[b] Recipient developed cirrhosis due to nonalcoholic steatohepatitis 2 years posttransplant at which point he was initiated on sofosbuvir and ribavirin; HCV RNA was undetectable in the patient at the end of follow-up.

[c] Recipient developed low level liver enzymes 4 months posttransplant and died at posttransplant 19 months due to transplant pyelonephritis, sepsis and refusal of dialysis. Autopsy revealed chronic cirrhosis presumed to be due to steatohepatitis without findings suggestive of HCV-related disease.

[d] Following HCV detection, recipients were treated with a 12-week course of DAAs; viral load has been undetectable since completion of treatment.

[e] Recipient died of causes unrelated to HCV infection (date of death/length of follow-up not reported); a third organ recipient in this case series was also infected and died; however, no details were provided.

[f] Recipient of right lung died shortly after transplantation after developing primary graft dysfunction, however, after HCV detection in the left lung recipient, stored serum samples obtained pretransplantation and posttransplantation were tested and showed HCV RNA was undetectable on pretransplant samples but weakly detectable in a sample taken on day 20 posttransplant.

MSM, men who have sex with men; IVDU, intravenous drug users; COD, cause of death; NAT, nucleic acid testing.

successfully treat donor-derived HCV transmission.[114] In particular, the recipient of the left kidney in the first cluster reported by Suryaprasad et al[122] was unable to receive interferon therapy at the time of HCV diagnosis in 2011, but 2 years later was treated with sofosbuvir and ribavirin and achieved a sustained virologic response.

Two recent cases of unexpected donor-derived HCV transmission in the United States highlight the profound shift in the clinical implications of HCV transmission in the current era.[123] In the first case, the donor suffered a cardiac arrest after an opiate overdose. Hepatitis C virus serology was negative; however, routine recipient follow-up at day 40 posttransplant identified proteinuria and recurrent focal segmental glomerulosclerosis. Evaluation for apheresis detected HCV RNA, at which point, a 16-week course of sofosbuvir/declatavir was initiated. HCV viral load was undetectable within 2 weeks of treatment and remained undetectable. In the second case, the donor was a 36-year-old with a history or polysubstance abuse and negative HCV serology. One month posttransplant, HCV seroconversion was reported in the liver recipient, and testing of the kidney recipient was positive for HCV RNA. The recipient completed 12 weeks of elbasvir/grazoprevir and HCV viral load remained undetectable upon completion of treatment.[123]

In addition to the cases above, 2 additional cases of unexpected HCV transmission in organ transplantation are worth mentioning. The first is a case of HCV transmission through the use of stored blood vessels used as conduits in organ transplantation.[125] Second is a case of an unexpected severe HCV infection in a recipient of a deceased donor kidney due to a genotype mismatch between the HCV-positive recipient (genotype 2) and the HCV-positive donor (genotype 1) combined with a change to tacrolimus-based immunosuppression.[126]

HBV

Donors testing positive for HBsAg have a very high risk of transmitting HBV to an HBV-negative recipient, although this risk is attenuated for vaccinated recipients and with the use of antiviral prophylaxis. Donors who are anti–HBc-positive, but HBsAg-negative, have a lower risk of disease transmission, although transmission is still possible, especially in the context of liver transplantation.[127-130] Retrospective analysis of liver transplant outcomes in Spain from 1995 to 1998 found that, in the absence of prophylaxis, HBsAg-/anti–HBc-negative recipients of livers from anti–HBc-positive donors developed de novo HBV (defined as detection of HBsAg in serum on 2 consecutive samples posttransplantation) in 50% of cases.[131] Similar rates of transmission from anti–HBc-positive donors to HBV-negative liver recipients have been reported from Italy (43%) and the United States (50%-78%).[92,93,130]

By contrast, reported rates of de novo HBV in recipients of kidneys from anti–HBc-positive donors range from 0% to 2.4%.[93,130] In a retrospective study of 45 kidney recipients with a history of prior HBV infection or reported vaccination who received organs from HBcAb-positive donors, none became HBsAg-positive within 12 months of transplantation, although 18% acquired HBsAb and 13% acquired HBcAb.[132] None of the recipients developed signs of clinical HBV infection. A large retrospective analysis of the US United Network for Organ Sharing database found that—after taking into account donor and recipient characteristics—although anti–HBc-positive donor kidneys resulted in a higher incidence of anti-HBc seroconversion in HBV-negative recipients, this was not associated with a higher incidence of HBsAg detection posttransplant, nor with worse graft or patient survival compared to D–/R– pairs.[133]

From 122 heart/heart-lung transplants reported in the published literature involving anti–HBc-positive donors, there has been a single report of HBV transmission to an HBsAg-negative heart recipient who did not receive prophylaxis posttransplant.[93,130,134-136] There have been at least 2 reports of heart transplantation involving HBsAg-positive donors that did not result in HBV infection in HBV-negative, vaccinated donors receiving HBV prophylaxis.[137,138] Similarly, in the context of lung transplantation, the risk of HBV transmission from anti–HBV-positive donors appears to be extremely low.[139-141] A large retrospective registry study of lung and heart-lung transplants found no significant difference in 5-year survival based on donor anti-HBc status and concluded anti–HBc-positive donors may be safely used in lung/heart-lung transplantation.[139]

The risk of HBV transmission from anti–HBc-positive donors to organ recipient is determined by 3 factors[142]:

1. The size of the inoculum: the risk of HBV transmission is greater for liver transplantation than for other organs because of the large viral DNA load within the liver graft.
2. Recipient pretransplant HBV status: HBsAb levels in the recipient greater than 10 IU/L confer protection against de novo HBV infection, irrespective of whether anti-HBs was produced by previous HBV infection or by vaccination.
3. Use of antiviral prophylaxis: treatment with HBV immune globulin and/or entecavir or tenofovir is highly effective in preventing de novo HBV infection posttransplantation.

Table 19 summarizes reports of donor-derived HBV transmission according to donor serological status. Only 3 reports of HBV transmission by kidney transplantation were identified that also provided information on patient outcomes. Wolf et al[143] reported 3 cases of HBV transmission from HBsAg-positive kidney donors to recipients occurring at the University of California San Francisco between 1975 and 1977. Although none of the recipients developed abnormal liver function over the relatively short follow-up period (range, 6–23 months), one of the recipients died 23 months posttransplant.[143] In the case reported from Iowa in 1980, the donor's HBV serostatus was unknown at the time of transplantation, but there was no evidence in the medical or social history of increased risk. The recipient experienced early severe rejection, and the kidney was removed on day 12 posttransplant; however, complications continued to develop over the following weeks, including wound infection with dehiscence, rupture of the right external iliac artery and massive recurrent lower gastrointestinal hemorrhage. The patient was found to be HBsAg-positive 10 weeks posttransplant, and retrospective testing of posttransplant blood samples showed serum was first HBsAg-positive on day 6 posttransplant.[144] In the case reported by Magiorkinis et al,[55] a kidney from an HBsAg-positive donor was transplanted into a vaccinated recipient under the cover of prophylaxis (IV hyperimmune gammaglobulin). The recipient developed acute HBV hepatitis 4 months posttransplant and died 1 month later from encephalopathy, Child-Pugh class C, and renal hepatic syndrome type 1 despite treatment with entecavir. Genotype

TABLE 19.

Reports of donor-derived transmission of HBV in recipients seronegative for HBV before transplantation

Transplanted organ	Reference	Year of transplant	Results of donor serological testing available before donation				Donor HBV-NAT (serum)	Recipient serological status (pretransplant)			Time from transplantation to diagnosis, months	Follow-up interval, months	Recipient died at end of follow-up	Graft failure during follow-up period
			HBsAg	anti-HBc	HBsAb	HBeAg		HBsAg	anti-HBc	HBsAb				
Kidney	Wolf et al, 1979[143]	.	Positive	.	.	Positive	.	Negative	.	.	.	21	No	Yes
	Wolf et al, 1979[143]	.	Positive	.	.	Positive	.	Negative	.	.	.	23	Yes	No
	Wolf et al, 1979[143]	.	Positive	.	.	Negative	.	Negative	.	Negative	.	6	No	No
	Lutwick et al, 1983[144]	1980	.	.	.	.	.	Negative	.	Negative	2	18	No	Yes
	Magiorkinis et al, 2012[55]	2007	Positive	.	.	Negative	.	Negative	Negative	11.6 IU/L	2	17	Yes	No
Liver	Douglas et al, 1997[145]	.	Negative	Positive	Positive	.	Positive (serum)	Negative	Negative	Negative	<6	124	No	No
	Douglas et al, 1997[145]	.	Negative	Positive	Positive	.	Negative	Negative	Negative	Negative	<6	116	No	No
	Douglas et al, 1997[145]	.	Negative	Positive	Positive	.	Positive (liver)	Negative	Negative	Negative	>24	63	No	No
	Gow and Mutimer, 2001[146]	1990	Negative	.	.[b]	.	.	Negative	Negative	Negative	36	96	Yes[a]	No
	Gow and Mutimer, 2001[146]	1993	Negative	b	.	.	.	Negative	Negative	.	9	24	Yes[c]	Yes
	Gow and Mutimer, 2001[146]	1994	Negative	Positive	.	.	.	Negative	Negative	.	48	72	No	No
	Gow and Mutimer, 2001[146]	1999	Negative	b	.	.	.	Negative	Negative	.	14	14	No	No
	Castells et al, 1999[147]	.	Negative	Positive	13 IU/L	.	Negative	.	Negative	181 IU/L	24	36	No	No
	Castells et al, 1999[147]	.	Negative	Positive	88 IU/L	.	Positive	.	Negative	5 IU/L	48	48	No	No
	Cahlin et al, 2001[148]	.	Negative	b	.	.	.	Negative	Negative	Negative	2	19	Yes	Yes
	Cahlin et al, 2001[148]	.	Negative	b	.	.	.	Negative	Negative	Negative	10	19	No	No
	Moraleda et al, 2006[149]	2006	Negative	Positive	Positive	.	.	Negative	Negative	Negative	7[d]	40	No	No
	Molina Rueda et al, 2013[56]	2007	Negative	Negative	.	.	.	Negative	Negative	Negative	60[d]	60	No	No
Heart	No reports													
Lung	No reports													
Pancreas	No reports													

[a] Recipient died from metastatic colonic carcinoma.

[b] Donor was negative for HBsAg at the time of donation, but was not screened for HBcAb. Subsequent testing of stored serum revealed the donor to be HBcAb positive.

[c] Recipient was infected with HBV on receipt of their first transplant, which failed due to refractory acute cellular rejection 3 weeks after transplantation. They were transplanted 2 more times, and died due to primary nonfunction of the third transplant.

[d] Mutation(s) in the HBV S gene resulted in a loss of immunoreactivity in an infectious donor.

Restricted to reports proving information on clinical outcomes; deceased donor transplants only.

HBsAg, hepatitis B surface antigen.

analysis of the transmitted HBV strain found multiple mutations in the S, pre-S, core, and X regions, and in particular a G145R escape mutation.

The majority of case reports of donor-derived HBV transmission occurred via liver transplantation. Several of the cases summarized in Table 19 involve HBsAg-negative donors who were found to be anti–HBc-positive on retrospective testing posttransplantation. Gow and Mutimer[146] retrospectively searched the database of the liver transplant unit at the Queen Elizabeth Hospital, Birmingham, for cases of de novo HBV posttransplantation from 1982 to 2000, when screening for HbsAg was standard but routine screening for anti-HBc had not yet been implemented in the United Kingdom. They found 4 cases of transmission from HBsAg-negative donors from a total of 1354 adult liver transplants—an infection rate of 0.3% in the absence of routine anti-HBc screening. In one of the reported cases, the donor was known to be anti–HBc-positive but the liver was transplanted into the recipient without prophylaxis regardless, because at that time the infectious risk was not appreciated (see Table 19).

Although the risk of infection derived from organs from HBV-positive donors to unvaccinated liver recipients is now appreciated and vaccination and prophylaxis are now standard, a number of cases of transmission have been reported in vaccinated recipients as a result of mutations in the HBV genome—in particular, mutations resulting in structural variations in the surface antigen recognized by anti-HBV, resulting in a loss of immunoreactivity.[150] "Vaccine escape mutants" may evade detection via standard serological testing, and cause infection in immunized recipients and recipients receiving immunoprophylaxis with polyclonal anti-HBs (HBIG).[150] Moraleda et al[149] report a case of a female recipient of a liver transplant from a HBcAb- and HBsAb-positive donor, who despite responding to recombinant HBV vaccine in the preliver transplant period (anti-HBs titer, >10 IU), was found to have active HBV infection 7 months posttransplant. Retrospective analysis of the stored donor serum showed mutations in the "a" determinant of the HBV S gene at positions 127 and 145. Similarly, Molina Rueda et al[56] reported a case of HBV transmission in the recipient of a liver from a HBsAg-negative, HBcAb-negative, HBsAb-negative donor.[56] HBV NAT was performed on stored donor serum and found mutations at 118V + 128V + 142T.

No detailed case reports of donor-derived HBV transmission in heart, lung, or pancreas transplantation were identified.

In none of the cases of HBV transmission described above were the results of HBV-NAT available at the time of transplantation. With the introduction of routine HBV-NAT, it will be easier to distinguish which potential donors with positive serological test results do in fact pose a threat of infection. HBV-NAT would also detect vaccine escape mutants that are able to evade detection by standard serology.

Recipient Management

The case reports described in *Transmission Risk* highlight the importance of close monitoring of recipients for de novo infection with BBV in the weeks and months after transplantation. Recipients who are on immunosuppression may not seroconvert despite being viremic, and therefore, screening recipients for viral infection requires both serology and NAT testing to be performed.[1,119] For recipients of an organ from an increased-risk donor in particular, posttransplant monitoring

for donor-derived BBV infection should ideally include NAT screening for HIV, HBV, HCV at 2 and 4 weeks, and screening by both NAT and serology at 12 and 48 weeks.[1,7,44,45]

Unlike HCV and HBV, HIV infection in the potential donor currently remains an absolute contraindication to donation. Donation would only be considered in the circumstances that a suitable HIV-positive recipient exists, in which case donation may be considered after specialist advice. Transplantation of organs from HIV-positive donors to HIV-positive patients receiving highly active antiretroviral therapy before and after transplantation has shown excellent results in the context of careful selection and monitoring by experts.[151-153] For HIV-negative patients receiving organs from increased-risk donors who test negative for HIV on serology and NAT, prophylaxis with antiretroviral therapy to prevent HIV transmission is not deemed necessary in the Australian context due to the very low estimated residual risk of disease transmission and uncertainties about efficacy (personal communication, P Boan).

The proportion of actual donors in Australia and New Zealand in 2016 who were anti–HBc-positive was 4.6% (n = 26), and a total of 3 HBsAg-positive donors were used.[87] Current TSANZ guidelines do not recommend use of donors who are HBsAg-positive except in exceptional circumstances and/or where the recipient is also HBsAg-positive, given the high likelihood of transmission even in vaccinated patients and regardless of which organ is transplanted.[52,127] Exceptional circumstances typically indicate a patient who is highly likely to die on the transplant waiting list before further organ offers. If, after appropriate expert consultation and patient consent is obtained, organ transplantation from an HBsAg-positive donor does go ahead, an example of appropriate prophylaxis and recipient management posttransplant in this case would involve (P Boan, personal communication):

a) HBIG if recipient HBsAb less than 100 IU/L or unknown. One regimen described is 800 IU/L intramuscularly daily for 7 days, then monthly for 12 months[154];
b) potent antiviral therapy (eg, entecavir and/or tenofovir) for 12 months for recipients of nonliver transplants and indefinite antiviral therapy for recipients of liver transplants.

Donors who are HBcAb-positive but HBsAg-negative should be tested for plasma HBV DNA. If HBV DNA is positive, the donor should be treated as if they were HBsAg-positive. If HBV DNA is negative and the decision is made to proceed with transplantation, the after prophylaxis might be observed (P Boan, personal communication):

a) If recipient has HBsAb greater than 100 IU/L recorded in the last 3 months, no prophylaxis is required. If recipient has HBsAb less than 100 IU/L or if HBsAb titer is unknown, intramuscular HBIG 800 IU should be administered daily for 1 week for nonliver transplant recipients. For recipients of liver transplants, treatment should extend to 12 months of HBIG 800 IU monthly.
b) Nonliver transplant recipients should receive entecavir 0.5 mg daily (adjusted if creatinine clearance <50 mL/min) for 1 month. For liver recipients, entecavir therapy should be extended for 12 months.

Prophylaxis strategies according to donor/recipient HBV serology profiles, as proposed by the American Society of Transplantation Infectious Diseases Community of Practice, are summarized in Table 20.

For all recipients of organs from donors testing positive for HBsAg and/or HBsAb, ongoing posttransplant surveillance for the appearance of HBV infection is essential. Patients receiving prophylaxis should be screened for HBV DNA at least every 3 months posttransplant to 12 months postantiviral cessation. Patients not receiving prophylaxis should be tested monthly for 12 months posttransplantation. European guidelines recommend lifelong monitoring for any recipients of HBsAg-positive donor organs, and for recipients of livers from anti–HBc-positive donors, due to the possibility of HBV reactivation or breakthrough mutation of the virus.[5]

Before transplantation, all potential recipients who are not infected with HBV and do not have current immunity should be vaccinated. Unfortunately, the proportion of who seroconverts is only in the range of 16% to 62%, and up to 73% of liver transplant recipients lose HBsAb within 12 months of transplantation as HBsAb titers tend to wane in immunocompromised individuals.[127] For this reason, the higher-dose (40 μg antigen) vaccine is recommended in the pretransplant setting, with repeat or booster HBV vaccination recommended at approximately 12 months posttransplant.[97,127] Vaccination before transplantation is more successful than vaccination posttransplant, when achieving seroconversion is even more problematic.

The introduction of DAAs for HCV has entirely changed the landscape of recipient management in relation to the risk of HCV infection. Before 2011, the standard of care in the treatment of HCV in transplant recipients was 48 weeks of peginterferon with ribavirin, achieving a relatively poor response rate of between 13% and 43%, in part due to treatment-limiting side effects leading to discontinuation and serious adverse events, including graft loss and death.[155-161] The first DAAs for HCV, boceprevir and telaprevir, were approved for use by the US Food and Drug Administration (FDA) in 2011. These first-generation protease inhibitors, also administered in combination with peginterferon and ribavirin, improved the patient response rate to 60% to 75% but were still associated with a high rate of adverse events, including skin rashes, cytopenias, allograft rejection, decreased kidney function, and death.[162,163] In late 2013, second-generation NS3/4 protease inhibitor simeprevir and nucleotide analog NS5B polymerase inhibitor sofosbuvir were approved to be used alongside peginterferon and ribavirin for the treatment of HCV. Based on the results of the COSMOS study showing a sustained virological response rate greater than 90% using simeprevir and sofosbuvir with or without peginterferon and ribavirin, this interferon-free DAA regimen was approved by the FDA in 2014.[164]

Additional DAAs have subsequently been approved since 2014, and numerous studies have demonstrated interferon-free DAA regimens to be safe and highly effective in patients with advanced liver disease and liver transplant recipients.[162] Clinical trials of interferon-free DAA regimens in liver transplant recipients with HCV genotype 1 recurrence have achieved sustained virological response rates at week 12 of 90% to 98%, based on patients without severe hepatic impairment/advanced fibrosis at baseline.[163,165,166] Response rates of between 96% and 100% have been demonstrated in liver transplant recipients with fibrosing cholestatic hepatitis, and between 60% and 75% in recipients with severe hepatic impairment.[166,167] Only minor side effects—for example, fatigue, headache and cough—were reported, and any required adjustments to immunosuppression dosage were minimal.[163] There have also been a number of case reports of successful treatment of HCV infection with interferon-free DAA regimens in kidney transplant recipients.[168] As a consequence, HCV-NAT–positive donors are now being used with greater frequency for HCV-positive recipients and a reduction in HCV-positive organ discard has been reported in the United States.[162]

Given the high HCV cure rate for DAAs and their manageable side-effect profile, organs from HCV-infected donors might now be made available to all potential recipients, not only those who are already HCV-positive/in extremis. The results of the first pilot trial of transplantation of HCV-NAT–positive kidneys into HCV-negative recipients—transplanting hepatitis C kidneys into negative kidney recipients—conducted at the University of Pennsylvania, were reported in June 2017.[47] This trial included adults on dialysis who were expecting long transplant waiting times (and did not have elevated risks of liver disease, allograft failure, or all-cause mortality). Donors were restricted to those with an HCV genotype-1 infection.

TABLE 20.

Suggested HBV prophylaxis for liver and nonliver transplantation[127]

Donor		Recipient			HBIG	Prophylaxis	Vaccination
HBcAb	HBsAg	HBcAb	HBsAg	HBsAb			
Liver transplantation							
−	−	+	−	−/+	No	No	Consider if HBsAb-ve or lost
−/+	−/+	+	+	−	Yes[a]	Yes	No
+	−	−/+	−	+	No	Yes, unless HBsAb persists	Consider if HBsAb lost
+	−	−/+	−	−	No	Yes, unless HBsAb persists after vaccination[b]	Yes
+	+	−/+	−	−/+	c	c	Consider if HBsAb-ve or lost
Nonliver transplantation							
−	−	+	−	−/+	No	No	Consider if HBsAb-ve or lost
−/+	−/+	+	+	−	No	Yes	No
+	−	−/+	−	+	No	Yes, unless HBsAb persists	Consider if HBsAb-ve or lost
+	−	−/+	−	−	No	Yes, unless HBsAb persists after vaccination[b]	Yes
+	+	−/+	−	−/+	c	c	Consider if HBsAb-ve or lost

[a] If HBV DNA-negative at transplant, consider short-term HBIG therapy; if HBV DNA positive at transplant, consider long-term or indefinite HBIG.

[b] If donor HBV DNA is performed and negative, no prophylaxis is required, although close monitoring for HBV recurrence is recommended.

[c] Transplant typically contraindicated but may consider in select exceptional cases, in the setting of indefinite antiviral prophylaxis and close monitoring.

HBIG, hyper Immune-immunoglobulin; HBsAg, hepatitis B surface antigen.

Recipients were given IV glucocorticoids and rabbit antithymocyte globulin, followed by oral tacrolimus, mycophenolate mofetil, and prednisone. HCV viral load was measured 3 days posttransplant, and elbasvir-grazoprevir was to be initiated as soon as recipients had detectable HCV RNA. Ten recipients were transplanted with HCV-infected kidneys as per protocol. All were HCV-RNA–positive by day 3 posttransplant, and elbasvir-grazoprevir was initiated, with a total treatment course of 12 weeks. All 10 recipients were cured of HCV (defined as a sustained virologic response 12 weeks after the end of DAA treatment). At 6 months, none of the recipients had died or experienced graft failure, acute rejection, or other major morbidity.

A second trial of transplantation of HCV-NAT–positive kidneys into HCV-negative recipients—EXPANDER-1—is currently underway. In this trial, recipients are preemptively treated with elbasvir-grazoprevir, with a single dose given pretransplant, and then daily doses for 12 weeks posttransplant.[169] If HCV genotype 2 or 3 was detected, then sofosbuvir was added to the treatment regimen. HCV RNA was quantified on postoperative day 1 and then weekly for the first month, then every 4 weeks until 12 weeks posttransplantation. Preliminary results for 8 HCV-negative recipient/HCV-positive donor pairs were presented at the 2017 American Society of Transplantation meeting: HCV RNA was detected in 4 recipients on posttransplant day 1 but no later timepoints, no graft failure was observed, and no adverse events related to elbasvir-grazoprevir were observed. Three recipients had delayed graft function.[169]

The first report of the deliberate transplantation of a liver from an HCV-viremic donor to a nonviremic recipient was published in August 2017.[170] The recipient was a 57-year old woman with a history of Child-Turcotte-Pugh class A HCV cirrhosis, who had been on the liver transplant waiting list for 3 years. She had HCV genotype 1A, which had previously been treated with 12 weeks of sofosbuvir/simeprevir combination therapy as part of an industry-sponsored clinical trial, and a sustained virological response had been achieved. However, 6 months later the patient developed hepatopulmonary syndrome and was granted 22 MELD exception points. The patient agreed to accept an HCV-positive liver, understanding that she would have to be retreated with DAAs. The donor was an 18-year-old man who had died from an IV heroin overdose: the donors' HCV genotype was not known at the time of transplantation, but 3 days after transplantation, the recipient's HCV genotype was reported as 1A. Treatment with ledipasvir/sofosbuvir was commenced on posttransplant day 25, and HCV RNA was undetectable by week 8 posttransplant. Two years postliver transplant, the patient remained HCV-RNA–negative, with excellent graft function.[170]

One of the areas, where more evidence is currently required, is with regard to the safe use of DAAs for HCV in patients with impaired kidney function. In most of the trials of DAA-based therapies, patients with severe renal impairment were excluded; in addition, the nucleotide polymerase inhibitor sofosbuvir is eliminated through the kidney and is, therefore, not appropriate for patients with estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2.[171] The HCV protease inhibitor asunaprevir and the Ns5A inhibitor daclatasvir are mainly eliminated through the liver, and combination therapy with daclatasvir and asunaprevir has been demonstrated

to be highly effective and safe in genotype 1 HCV-infected patients with estimated glomerular filtration rate less than 45 mL/min per 1.73 m^2.[172] Other drug protocols, including ombitasvir/paritaprevir/ritonavir without ribavirin, or elbasvir and grazoprevir combination therapy, have also been shown to be safe and effective in genotype 1 HCV-infected patients with chronic kidney disease stages 4 and 5, including hemodialysis patients.[173-175] Effective DAA therapies for genotype 2 HCV-infected patients with impaired kidney function are lacking, however. A Japanese study of the outcomes of sofosbuvir and ribavirin combination therapy in genotype 2 HCV-infected patients with chronic kidney disease stages 1 to 3 found that patients with stage 3 chronic kidney disease were significantly more likely to not experience a sustained virological response, but that otherwise the regimen was safe for patients with kidney impairment.[171] Other studies have reported serious adverse events of sofosbuvir therapy in patients with kidney impairment.[176]

Current TSANZ guidelines allow for transplantation of organs from HCV-positive donors to HCV-negative recipients in exceptional circumstances only; however, this is likely to evolve in the light of successful trials of DAAs in D+/R− pairs. At the present time, if there is a patient who is highly likely to die on the transplant waiting list before receiving another organ offer, transplantation with an HCV-NAT-positive organ may go ahead after discussion with an infectious disease or hepatology specialist. The recipient would be then monitored frequently (eg, twice weekly) by plasma HCV RNA, with initiation of DAA therapy as soon as RNA became positive (personal communication P Boan). Factors affecting the choice of DAA regimen would include HCV genotype, renal function, interaction with immunosuppressant medications (eg, protease inhibitors with calcineurin inhibitors), and any organ-specific protocols.[46] HCV infection itself affects dosing requirements of calcineurin inhibitors, and thus the eradication of HCV requires a corresponding close monitoring of immunosuppression trough levels.[166] Treatment protocols are still being refined at the time of writing—when to introduce DAAs, the optimal duration of treatment, and the full extent of drug interactions are questions that are rapidly being addressed.[163,165-167,177,178]

More data and longer term follow up of clinical trial participants are now required to establish whether HCV-negative recipients transplanted with organs from HCV-positive donors experience any survival detriment. In the case of liver transplantation, chronic HCV infection in the donor may have caused fibrosis of the donated liver, which could still affect graft and patient survival even if HCV is successfully cleared in the recipient posttransplant. Also, little is currently known about the risk of treatment failure, which has implications for the informed consent of D+/R− transplants.[179] In addition, there is a need for data on the cost effectiveness of HCV-positive transplantation that inform the appropriate usage of DAAs in organ transplantation—from expanding the donor pool, to reducing the liver transplant waiting list, to preventing and treating donor-derived HCV transmission.

HTLV-1

Epidemiology

The Human T-cell lymphocytic virus-1 (HTLV-1) is an oncogenic retrovirus that preferentially infects CD4+ T-cells.

Transmission may occur as a result of breast feeding, IV drug use, sexual intercourse or blood transfusion. Although infection is usually asymptomatic in most individuals, approximately 2% to 5% of infected individuals will subsequently develop acute T-cell leukemia/lymphoma (ATL) around 20 to 30 years after infection.[5] A smaller proportion (0.25–4%) will develop HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) soon after the initial infection.[180] The majority of HTLV-1–infected individuals will not develop clinical manifestations of ATL or HAM/TSP in their lifetime. However, infection with HTLV-1 suppresses immune surveillance and increases susceptibility to other infections including parasitic infection with *Strongyloides stercoralis* and scabies, bacterial infections including *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and infectious dermatitis, and viral infections including HIV, HCV, and HBV.[181] Breaches in the skin or intestinal mucosa as a consequence of HTLV-1–associated infections (especially scabies and *S. stercoralis*) may lead to bloodstream infections with *S. aureus*, *Escherichia coli*, *Streptococcus pyogenes*, or other organisms.[181] In addition, HTLV-1 infection is associated with pulmonary disease, including bronchiectasis.[181] Therefore, in affected individuals, HTLV-1 infection is likely to be associated with an increased risk of morbidity and indirectly with increased mortality risk.

HTLV-1 is not a ubiquitous virus, rather, it is present throughout the world in clusters of high endemicity.[182] The main foci of HTLV-1 are southwestern Japan (Kyushu Island and the Okinawa archipelago), sub-Saharan Africa (Guinea-Bissau, Ghana, Nigeria, Zaire), the Caribbean (Martinique, Jamaica, Haiti), parts of South America (French Guyana, Peru), and parts of the Middle East and Australo-Melanesia.[182] It is hypothesized that this highly specific geographical distribution originates from a founder effect in certain population groups with the persistence of a high viral transmission rate.[182] On the other hand, large global regions have not been investigated for HTLV-1 infection and population-based studies to estimate HTLV-1 prevalence at the country level are rare, thus the prevalence remains unknown in many areas of the world. What is clear from the areas that have been studied is that HTLV-1 distribution is not homogenous. In Australia, HTLV-1 is endemic among ATSI populations in Central Australia, where infection with the Australo-Melanesian HTLV-1 subtype C predominates[183]; by contrast, studies conducted among mostly non-Indigenous blood donors living in Australian cities found a very low prevalence of HTLV-1, ranging from 0.001% to 0.032%.[182] A retrospective assessment of serology requests made to the Northern Territory Government Pathology Service between 2008 and 2011 found a gradient of HTLV-1 prevalence from Central Australia (highest) to Northern Australia (lowest), ranging from a regional high of 51.7% in the Anangu Pitjantjatjara Lands in northern South Australia, 50% in Ngaanyatjarraku Shire in Western Australia, and 25.3% in the MacDonnell Shire of the Northern Territory, to less than 1% in the greater Darwin region, East and West Arnhem Shire, Roper Gulf Shire, and Tiwi Islands.[184] In terms of the wider Australo-Melanesian region, estimates of the population prevalence of HTLV-1 in the Solomon Islands range from 1.2% to 3%, and a population-based study in the Vanuatu archipelago reported HTLV-1 prevalence of 0.62%.[182] Studies in Fiji and New Caledonia did not detect HTLV-1 in these populations.[182]

Risk factors for HTLV-1 among Indigenous Australians living in Central Australia include older age, male sex, previous STI, and residence in the south or west of Central Australia.[183] Each of the major recognized complications of HTLV-1—ATL, HAM/TSP, infective dermatitis, strongyloidiasis, HTLV-1–associated pulmonary disease, crusted scabies—has been described in the Indigenous residents of this region.[183,185]

Although immunosuppression might theoretically affect the rate of onset of HTLV-1–associated disease, reports regarding outcomes among HTLV-1–infected solid organ recipients have been mixed. Retrospective studies of HTLV-1–infected kidney transplant recipients in Japan found no HTLV-1–associated disease in 2 case series of 10 and 16 recipients followed up for an average of 13 and 8 years, respectively.[186,187] In contrast, a third case series Japan observed 3 cases of ATL at 6, 9, and 25 months after living donor liver transplantation from 8 HTLV-1–infected recipients.[188] There has also been 1 report of an HTLV-positive recipient developing HAM/TSP after a living donor kidney transplant, and 1 report in which 3 recipients from a single deceased donor rapidly developed HAM/TSP posttransplant.[189,190]

Donor Screening and Risk Minimization

Standard testing for HTLV-1 is performed using a combined serological test for HTLV-1 and HTLV-2. An important issue with serological tests for HTLV-1/2 is the extremely high rate of false-positive results in low HTLV prevalence settings.[191,192] False-positive rates of up to 100% have been reported for potential organ donors in nonendemic settings.[193] A second issue with serological tests is that, at the current time, available assays are unable to distinguish between HTLV-1 and HTLV-2, which is a relevant limitation as HTLV-2 has not been found to be associated with any human disease and should not preclude transplantation.[191] HTLV-1 and HTLV-2 can be distinguished by confirmatory NAT testing, or by virus-specific Western blot or line immunoassay.[194]

Given the high false-positive rate, testing is generally not performed in countries where seroprevalence of HTLV-1 is low, or alternatively it is restricted to donors coming from high-risk subpopulations or endemic areas.[191,195] OPTN has removed the requirement for pretransplant screening for HLTV-1, and it is left to individual organ procurement agencies to decide whether to perform targeted screening on donors thought to be at increased risk of HTLV-1 infection.[194] OPTN recommends that positive HTLV-1/2 screening test results be confirmed using Genelabs HTLV 2.4 (Western blot) or inn genetics HTLV-1/2 Line Immunoassay.[194]

European guidelines recommend screening in endemic areas and for donors coming from endemic populations only, and also stipulate that any initial reactive test must be confirmed as a true-positive for HTLV-1 before decisions are made about organ utilization.[5] France and Portugal currently screen for HTLV-1/2, and Spain recommends HTLV-1/2 screening for donors at higher risk of HTLV-1 including immigrants or sexual partners of immigrants from endemic areas and children at risk of vertical transmission.[5,195]

In the Australian context, HTLV serology should be considered for donors from endemic regions (the Caribbean, South America, Africa, Asia, Iran, Romania) and for ATSI people living in the Northern Territory, Queensland, Kimberley, and northern South Australia.

Transmission

Between 1994 and 2001, the UNOS reported 12 HTLV-positive deceased donors, from whom 5 organs were transplanted. As of 2003, 4 of 5 recipients were alive and without malignancy, and a heart transplant recipient of an HTLV-positive organ had died 1 month posttransplant from multiorgan failure although there was no indication that this was related to HTLV-1 infection.[192] A retrospective analysis of outcomes among liver transplant recipients in the United States who received their transplants before August 2007 found no statistically significant difference in graft or patient survival according to the HTLV status of the donor.[196] However, the authors note that their analysis was limited by the short recipient follow-up period (mean, 1.2 years) and the high false-positive rate for HTLV testing.

The first European cases of donor-derived HTLV-1 transmission were reported in Spain in 2001.[190] Three recipients of organs from the same donor (a liver and 2 kidney recipients) presented 2 years posttransplant with clinical manifestations of subacute myelopathy. The donor was retrospectively found to be seropositive for HTLV-1 and, despite having no apparent risk factors for HTLV-1, it was found on further investigation that his mother was originally from Venezuela, where HTLV-1 is endemic. Genetic analysis of the transmitted strain of HTLV-1 in this case showed multiple substitutions in the tax gene characteristic of the taxA subgroup, which is associated with greater risk of HAM/TSP development. The investigators hypothesize that the presence of taxA may at least in part account for the rapid onset of neurological disease in these organ recipients.

This cluster of HTLV-1 cases in Spain prompted a survey of HTLV-1 seroprevalence among potential organ donors to inform an appropriate national approach to donor screening. This survey, conducted from January 2002 to December 2003 screened for HTLV-1 antibodies in 1298 organ donors. Not a single seropositive donor was identified. Simultaneously, HTLV screening was conducted in a sample of 1079 immigrants, finding a prevalence of asymptomatic carriers of 0.5% (with carriers predominantly originating from South America or Africa).[195] These findings supported the existing policy in Spain of testing for anti-HTLV antibodies only among organ donors from HTLV-1 endemic areas or among native Spaniards with a high suspicion of HTLV-1 infection.[195]

Recipient Management and Outcomes

There are currently no treatments for HTLV-1 infection. OPTN guidelines state that if the donor is confirmed to be HTLV-1–positive, the recipient(s) should be screened by HTLV-1–specific NAT and serology at 1, 3, and 12 months posttransplant, and should receive ongoing clinical monitoring for the appearance of unexplained neurological disease and/or T-cell leukemia/lymphoma.[194] Counseling to avoid secondary transmission to sexual partners or breast-fed infants of recipients may also be required.

The effect of immunosuppression on the outcomes of HTLV-1 infection is not well characterized. Immunosuppression may promote a rapid increased in HTLV-1 proviral load due to a lack of cytotoxic T lymphocyte response to infection, thus leading to a more rapid onset of neurological disease.[190] However, the immunosuppressed status of the organ recipient is only one of several factors that will potentially affect the outcomes of HLTV-1 infection. Certain HTLV-1 subtypes

are more likely to result in HTLV-1–related disease than others (eg, Cosmopolitan A viruses carrying the taxA gene are linked to greater risk of TSP/HAM development), and the proviral load is typically higher in patients with TSP/HAM versus asymptomatic carriers.[197,198] Host factors, including HLA haplotype, may influence the outcome of infection, with the class I allele HLA-A*02 appearing to confer protection against TSP/HAM.[199] Lastly, the route of transmission is also likely to have a role in patient outcomes: HTLV-1 transmission by organ transplantation or blood transfusion exposes the patient to a much larger viral inoculum than by other transmission routes, and it is hypothesized that this results in a shorter latency period and greater risk of TSP/HAM.[200] These factors are likely to account for the variation in outcomes of HTLV-1 infection in solid organ transplant recipients reported in the published literature: although there have been several cases of ATL and TSP/HAM in HTLV-1–positive organ recipients after transplantation,[190,201,202] there have also been multiple studies demonstrating an absence of HTLV-1–related diseases in HTLV-1–infected recipients and recipients of HTLV-positive donor organs over long-term follow-up.[186,191,203]

HERPES VIRUSES (EXCLUDING EBV AND CMV)

Epidemiology

Herpes Simplex Virus

Data on the epidemiology of HSV types 1 and 2 (HSV-1 and HSV-2) in Australia come from the baseline AusDiab survey, a population-representative survey of adults 25 years and older conducted between 1999 and 2000.[204] Serum analysis of a stratified random sample of 4000 individuals from the original cohort of 11 000 found a seroprevalence of HSV-1 in the Australian population of 76% and a seroprevalence of HSV-2 of 12%. Seroprevalence of HSV-1 peaked in the 65- to 74-year age groups at 85% compared with a seroprevalence of 67% in the 25- to 34-year age groups. Seroprevalence of HSV-2 peaked in the 35- to 44-year age groups at 16% compared with the lowest seroprevalence of 8% in the 65- to 74-year age groups. Seroprevalence of both HSV-1 and HSV-2 were higher in women than in men (80% vs 71% and 16% vs 8%, respectively). Seroprevalence of HSV-2 was higher in capital cities (14%) and metropolitan areas (13%) compared with rural and remote areas (9%). Estimated seroprevalence of both HSV-1 and HSV-2 was higher in Aboriginal and Torres Straight Islander people than non-Indigenous Australians (100% vs 75% and 18% vs 12%, respectively). Although not analyzed as part of the AusDiab survey, international studies have reported HSV-2 seroprevalence among MSM of 24% to 87%.[205,206]

Kaposi Sarcoma Herpes Virus or Human Herpes Virus-8

Since its identification in 1994, Kaposi sarcoma herpes virus (KSHV) has been demonstrated to be associated with all forms of Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman's disease, and is the most common malignancy of HIV-1–infected persons.[207] KSHV is homologous with, but distinct from, the gamma herpes viridae, EBV, and herpes virus saimiri, and—unlike most herpes viruses—human infection with KSHV is not ubiquitous but has a wide geographic variation. Seroprevalence is estimated to be less

than 10% in North America and northern Europe, and between 20% and 80% in the Mediterranean and parts of Africa.[207] Modes of KSHV transmission vary in different parts of the world: in nonendemic regions, sexual transmission is likely the main route of transmission; in endemic regions, primary KSHV infection also commonly occurs in childhood (probably via salivary transmission), and cases of vertical transmission have also been reported.[208]

Multiple cases of KSHV transmission from organ donors to recipients have been reported in the literature.[209-214] Primary infection with KSHV in immunocompromised persons is characterized by fever, splenomegaly, lymphoid hyperplasia, pancytopenia, and in some cases, rapid onset Kaposi sarcoma. In immunosuppressed transplant recipients, KSHV is more commonly associated with neoplastic disease.[5]

Donor Screening and Risk Minimization

Herpes Simplex Virus

International guidelines do not require any specific donor screening for HSV-1 or HSV-2, and no contraindication exists to organ donation from donors with latent herpes family viral infections due to high rates of donor and recipient exposure and routine effective antiviral prophylaxis (acyclovir, valaciclovir, ganciclovir, valganciclovir.[5] Nonetheless, it is important to note the potential for fatal de novo infections in naïve recipients from organs recovered from latently infected donors (see *Transmission*), as well as the potential for reactivation in latently infected recipients. Active infection in the potential donor should also not be disregarded. Some transplant centers perform retrospective additional donor tests for latent HSV in cases of seronegative recipients (usually in the case of pediatric recipients) to decide on specific antiviral prophylaxis or treatments and follow-up, although there is minimal evidence to support this approach. European guidelines state that organs can be accepted from donors with latent herpes family viral infections, except in the case of acute herpes viremia in the donor without effective antiviral treatment.[5]

KSHV or Human Herpes Virus-8

Kaposi sarcoma herpes virus DNA is not detectable in all infected individuals; therefore, KSHV must be detected by serological assay. Given that donor-derived primary KSHV infection can be associated with severe disease, European guidelines recommend screening donors for KSHV antilytic antilatent antibodies in areas of high KSHV prevalence (eg, Mediterranean region).[5] As KSHV serology is generally unavailable before deceased donor organ transplantation, screening for KSHV antibodies may be performed retrospectively in the days immediately after transplantation. In the case of a transplant from a positive donor to negative recipient, European guidelines recommend close monitoring of KSHV DNA in the blood to detect infection early.[5]

Transmission

Herpes Simplex Virus

A case of donor-derived HSV-2 infection affecting 6 solid organ recipients occurred in Victoria in 2014.[18,215] Lungs, kidneys, pancreas, and liver were retrieved from the original donor and transplanted into 4 recipients. The recipient of the kidney-pancreas had an acute myocardial infarction and cardiac arrest 2 days posttransplant and subsequently deteriorated, with brain death declared on day 9. Serological testing on day 9 was negative for HSV-2 IgG, but subsequent HSV-2 NAT later performed on stored samples was positive. This recipient then became a donor, with his lungs and the recently transplanted kidney from the original donor going to new recipients. The original donor had died of hypoxic brain injury; no clinical evidence of HSV-2 infection was seen and no history of recurrent HSV-2 infection was reported. On retrospective laboratory testing, HSV DNA was not detected; however, the donor's serology was positive for HSV-2 IgG (but not for HSV IgM). Biopsy of the kidney originally transplanted into the kidney-pancreas recipient (biopsy performed before retransplantation) showed histiocytes with enlarged nuclei containing possible viral inclusions, and HSV-2–specific staining confirmed the diagnosis of disseminated HSV-2 infection.

Of the other recipients of organs from the original donor, only the recipient of the liver developed HSV viremia and clinical symptoms. Evidence of hepatitis was observed on day 13 posttransplant, and HSV-2 viremia was detected. Valaciclovir treatment was increased to 1 g 8 hourly, but on day 19 a disseminated rash developed suspected to be cutaneous HSV. The patient was admitted and IV acyclovir 600 mg was administered 8 hourly, and eventually, the hepatitis and rash resolved and the patient remained symptom free at 12 months posttransplant.

None of the other recipients in this case became symptomatic. The recipient of the lungs from the original donor had received CMV prophylaxis with IV ganciclovir and CMV hyperimmune globulin due to CMV-status mismatch, and there was no evidence of viremia or HSV disease up to 12 months posttransplant. The recipient of the second kidney from the original donor also received anti-CMV prophylaxis (valganciclovir 450 mg 12 hourly) and did not develop viremia or any symptoms of HSV disease.

The recipient of the retransplanted kidney was seropositive for HSV-1 IgG and HSV-2 IgG at the time of transplantation but negative for HSV IgM and was commenced on valaciclovir 1 g daily on day 1 posttransplant. HSV-2 viremia was noted on day 5 and treatment switched to IV acyclovir 400 mg; viremia resolved and the patient was asymptomatic at 12 months posttransplant.

Finally, the recipient of the bilateral lung transplant from the kidney-pancreas recipient was similarly HSV-1 IgG and HSV-2 IgG-positive at the time of transplantation but negative for HSV IgM and was treated with IV ganciclovir 5 mg/kg on day 1 posttransplant. HSV-2 viremia was detected on day 2 posttransplant, and the patient switched to valaciclovir 1 g every 8 hours. Viremia resolved, and the patient was asymptomatic at 12 months posttransplant.

These 2 clusters of cases demonstrate that HSV-2 may be transmitted by HSV DNA-negative donors; however, the impact on the recipient depends on whether they have preexisting immunity and on the prophylaxis regimen used. Symptomatic HSV disease only occurred in the recipients who were serologically negative and did not receive prophylactic antiviral therapy.

KSHV or Human Herpes Virus-8

Studies of the seroprevalence of human herpes virus-8 (HHV-8) in organ donors and recipients pretransplantation

and posttransplantation have reported rates of seroconversion in D+/R− pairs of between 12 and 29%.[211,212,216] The risk of KSHV seroconversion appears to be higher for liver transplant recipients than for kidney transplant recipients.[217] Although relatively rare, the development of KS or other lethal nonmalignant illnesses after donor-derived transmission of HHV-8 has been reported on multiple occasions.[212,214,216,218] It has also been demonstrated that Kaposi sarcoma progenitor cells may be transmitted through solid organ transplantation, with individual HHV-8–infected neoplastic cells able to seed tumors in the recipient.[210] Table 21 summarizes published cases of donor-derived KSHV transmission and their outcomes.

CMV and EBV

The majority of adult populations worldwide are latently infected with CMV and/or EBV, which affect somewhere between 20% to 100% and 50% to 90% of populations older than 18 years, respectively.[5,222-224] The most recent available data on EBV prevalence in the Australian population come from a 1975 study of a Caucasian population in Western Australia, which found antibodies to EBV in 41% of 9- to 10-year-olds, 80% of 16- to 19-year-olds, and in 92% of young adults.[223] More recent data are available on CMV prevalence: in 2002, 3593 nationally representative serum samples were tested for CMV under the National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases (NCIRS) serosurveillance program. This survey found CMV seroprevalence of 38% in the 1- to 2-year age group, increasing to 50% in the 15- to 19-year age group, and reaching 79% in the 55- to 59-year age group, with little difference in seroprevalence between males and females.[225]

CMV and EBV cause lifelong infection, and organs from seropositive donors may transmit infection, potentially causing severe disease in a seronegative recipient. Latent CMV and EBV may also reactivate in immunosuppressed seropositive patients posttransplantation. No contraindications exist for organ donation in the case of donors with latent CMV infection, although recipient morbidity increases in the case of D+/R− combinations. De novo infection in the recipient can be avoided by matching the donor and recipient for CMV serological status, and/or by prophylaxis or virological monitoring with preemptive treatment.

EBV transmission to naïve recipients increases the risk of posttransplant lymphoproliferative disorders. In immunocompetent individuals, EBV is latent in the cells of the reticuloendothelial system. However, in immunosuppressed transplant recipients, EBV may activate, proliferate, and induce the malignant transformation of B lymphocytes, increasing the risk of PLTD. In the case of donor-derived primary EBV infection posttransplantation, viral loads are higher and the risk of PLTD greater than in the case of EBV reactivation. In a large, retrospective study of the incidence of PLTD in kidney transplant recipients in the United States, the risk of PLTD was more than 6 times higher for D+/R− deceased-donor transplants compared with R+ transplants.[226] For chemoprophylactic protocols it should be considered that there is no prophylactic treatment that can prevent primary EBV infection; therefore, EBV-DNA monitoring and early treatment should be considered for all D+/R− recipients.

UK guidelines recommend that patients who are seronegative for CMV should receive a donation from a CMV seronegative donor if possible. If the donor and/or recipient is seropositive, routine CMV prophylaxis should be administered posttransplant and/or routine CMV viral load surveillance instituted. In the case of EBV, ideally, the donor and recipient should be matched for EBV serostatus if possible—especially children. Given the risks of PLTD in an immunocompromised, naive recipient, UK guidelines advise close monitoring of EBV DNA levels posttransplantation in patients at risk.[29]

European guidelines recommend specific antiviral prophylaxis for CMV-naïve recipients and virological monitoring and preemptive therapy where there is a risk of de novo infection or reactivation of a latent infection in the recipient. Organs can be accepted independently of the anti-EBV IgG status of the donor. However, given the risk of PLTD and potential for fatal complications associated with de novo EBV infection, regular follow-up/surveillance regarding posttransplant lymphoproliferative disorder is essential, particularly in children and D+/R− cases.[5]

The risks of D+ R− CMV and EBV transplants are well reported and ideally would be avoided, but in many circumstances this relative risk is accepted and managed to use a life-sustaining organ. For D+ R− CMV transplants, antiviral prophylaxis according to international guidelines will be used, with CMV hyperimmune globulin also considered in some thoracic transplant units. For EBV D+ R− transplants, EBV viral load in blood is recommended (eg, monthly for 6 months then 3 monthly to 12 months posttransplant; most EBV-related PTL presents within 1 year posttransplantation) with investigation (eg, PET scan) and consideration of intervention (eg, reduction in immunosuppression, rituximab) with a significant rise in viral load (eg, $>10^3$ IU/mL).

Yearly Epidemic Influenza

Epidemiology

Influenza affects 5% to 10% of the Australian population each year and is estimated to cause over 3000 deaths, and more than 13 500 hospitalizations among Australians older than 50 years alone.[227,228] The National Influenza Surveillance Scheme, guided by the CDNA's Enhanced Influenza Surveillance Framework for Australia, exists to monitor the onset and severity of annual epidemics and to trigger an appropriate public health response. This Scheme encompasses a range of influenza surveillance systems coordinated by the Australian Government Department of Health that capture information about influenza activity in the community, general practice, emergency departments and hospitals. Community information relies on self-report systems: Flutracking and the National Health Call Centre Network. Surveillance in general practices and hospitals operates by a national network of sentinel practices and hospitals (the Australian Sentinel Practices Research Network [ASPREN] and the Influenza Complications Alert Network [FluCAN]).

The highest months for reporting influenza-like symptoms are June, July and August, with the peak influenza-like illness week usually falling in August.[229] During the influenza season, a potential lung donor has about a 1% to 2% chance of excreting and potentially transmitting influenza, based on up to 10% of the population being infected over a season lasting ~8 weeks, given that influenza virus can be recovered from respiratory secretions of infected persons for approximately 1 week.[230]

TABLE 21.

Case reports of donor-derived KSHV in solid organ transplant recipients (deceased donors)

Transplanted organ	Reference	Year of transplant	Time from transplantation to diagnosis, months	Total follow-up time, months	Clinical course	HHV-8 associated diseases	Treatment	Recipient died at end of follow-up
Kidney	Luppi et al, 2000[218]	1998	5	12	Fever, enlarged spleen, anemia, thrombocytopenia, acute kidney failure	No	Acyclovir, ganciclovir	Yes
	Luppi et al, 2002[219]	1998	4	24	.	KS, hemophagocytosis	Reduction of immunosuppression, foscarnet, microsomal daunorubicin	No
	Chiereghin et al, 2017[216]	.	1.5	2	Severe lung infection	No	.	Yes
	Chiereghin et al, 2017[216]	.	6	.	None (HHV –8 detected on routine screening)	No	.	No
	Park et al, 2017[220]	.	5	6	maculopapular skin rash, fever, pancytopenia	KS	Change in immunosuppression then reduction immunosuppression, then discontinuation, acyclovir, foscarnet, cytotoxic therapy (etoposide and dexamethasone)	Yes[a]
Liver	Marcelin et al, 2004[221]	2000	5	5	Rash, polyadenopathy, fever, anemia, thrombopenia	KS, solid form of primary effusion lymphoma (lung, spleen, stomach)	.	Yes
	Pietrosi et al, 2011[214]	2007	2	3	Fever, cough, bilateral pleural effusion, multiorgan failure	No	Cidofovir, probenecid	Yes
	Pietrosi et al, 2011[214]	2007	6	2	Ascites, increase in liver function tests, kidney failure, liver failure	No	Cidofovir	Yes
	Pietrosi et al, 2011[214]	2008	6	15	Fever, weakness, severe sinus tachycardia and maculopapular skin rash	KS	Cidofovir, liposomal-doxorubicin	No
	Pietrosi et al, 2011[214]	2010	<1	4	None (HHV-8 detected on routine screening)	No	Cidofovir	No
	Chiereghin et al, 2017[216]	.	1.5	10	Dyspnea, malaise, pancytopenia, pleural effusion, kidney failure, liver failure, multiorgan failure.	No	Reduction of immunosuppression, cidofovir	Yes

[a] Death was due to septic shock due to a multidrug-resistant bacterial infection with lobar pneumonia.

In general, nonlung organs from donors with influenza infection can be safely used. As patients infected with influenza viruses (other than H1N1 virus) generally do not have virus in nonlung tissues, the risk of transmitting infection to recipients of solid organs other than lungs is low.[231] Evaluation of potential lung donors for influenza-like symptoms or respiratory tract infection is essential to avoid life-threatening infection in the recipient in the early posttransplant period.[232] In the event of donor-derived influenza transmission, however, successful antiviral treatment is possible: in a case of influenza transmission through bilateral lung transplantation, the presence of influenza A in the recipient was confirmed on day 6 posttransplant and after a 5-day course of oral oseltamivir 2 × 75 mg daily, the patient was cleared from the virus and was doing well 3 years later with no criteria for bronchiolitis obliterans.[230]

The Australian Organ & Tissue Authority issued a Guideline for Assessing and Managing the Possible Risk of Transmission of Influenza in 2009.[231] This guideline states that the donor coordinator must establish whether the potential donor has a fever, flu-like symptoms, or respiratory tract infection. The following diagnostic tests are recommended, in order of utility:

1. Influenza-specific NAT,
2. Influenza A subtyping (for example to identify A/H1N1 09, A/H3N2, A/H1N1) performed on any patient with confirmed influenza A (generally using NAT),
3. Influenza virus culture (turnaround time 3–5 days),
4. Influenza rapid antigen detection (point of care test or immunofluorescence),
5. Serology.

If influenza-like illness is suspected, the donor coordinator should inform the medical consultant on call, who may consult an infectious disease specialist. If indicated, an influenza-specific NAT to determine the influenza A subtype may be ordered, although it is not essential to wait for the result before proceeding with organ donation. All nonlung solid organs are considered suitable for transplantation; the purpose of confirming or excluding influenza is to determine (a) whether the lungs are acceptable for retrieval and transplantation and (b) whether the recipient units should consider prescribing an antiviral agent to the recipient as secondary prophylaxis. The utilization of lungs should be considered on a case-by-case basis, taking into account the following factors:

• the potential infection risk of the donor respiratory tract,
• at what stage in the potential donor's influenza-like-illness has the patient become a potential donor,
• if the potential donor is considered to still be infective,
• if the potential donor received an antiviral agent and, if yes, if the duration has been greater or less than 48 hours.

By comparison, UK guidelines state that lungs and bowel should not be used from donors with confirmed influenza infection. Other organs may be offered, and the final decision lies with the transplanting surgeon, weighing the balance of risks for the recipient and noting that pathogenicity of some strains of virus may be enhanced by immunosuppression.[29]

The American Society of Transplantation recommends that potential organ donors who have been diagnosed as recently having influenza (eg, within the previous 2 weeks) should likely be deferred for lung and small-bowel transplantation; however, this may be considered if the donor has received appropriate antiviral therapy with input from the OPO's medical director and an infectious diseases expert. They state there is currently no data on the duration of influenza therapy before donor organs can be safely used, and recommend a 5- to 10-day course of influenza therapy for the recipient if the donor did not complete a course of treatment.[233]

In line with these international recommendations, donors with suspected influenza should be tested rapidly by NAT, being the most sensitive test. Organs apart from lung and small bowel from donors with confirmed influenza may be used with 10 days influenza treatment to the recipient. Lung and small bowel transplantation from donors with confirmed influenza may be considered on a case-by-case basis taking into account the donor response to influenza treatment and likelihood of another donor for the recipient.

Other Viral Pathogens

Other Viral Hepatitis

Hepatitis A virus infection in the donor does not pose a risk to the recipient except in cases of acute infection. Reactivity to antihepatitis A IgG indicates a cleared infection or immunity acquired through vaccination.

Hepatitis D virus (HDV) is a satellite virus/virusoid of HBV that requires the HBV envelope proteins (HBsAg) for replication. Hepatitis D virus can, therefore, only be transmitted where there is concomitant HBV infection—either as a simultaneous HBV/HDV coinfection or as an HDV infection in someone with an existing HBV infection (superinfection). Hepatitis D virus coinfection/superinfection complicates the management of HBV and results in a poorer prognosis—compared with monoinfection with HBV, persons with HDV are 3 times more likely to develop cirrhosis, typically at a younger age, and a high proportion will subsequently require liver transplantation.[234] Coinfection may result in more severe hepatitis compared with superinfection; of those with superinfection, approximately 90% will develop chronic HDV, which will then lead to cirrhosis within 5 to 10 years in 70% of patients.[235] Coinfection usually appears first as IgM anti-HDV and then converts to IgG anti-HDV while HDV RNA levels remain low.[234] Markers of acute HBV infection such as HBV IgM and anti-HBc are a feature of coinfection. In the case of superinfection, HDV IgM antibodies appear first, followed by HDV IgG, whereas anti-HBc IgG only would be observed.[234]

Internationally, the burden of HDV is highly variable and does not follow patterns of HBV prevalence.[236] In the high prevalence countries of the Mediterranean, parts of eastern Europe, the Middle East, Pakistan, central and northern Asia, Japan, Taiwan, Greenland, western and central Africa, the Amazonian basin, the Pacific Islands, and Vietnam, HDV affects between 15% and 40% of chronic HBV patients.[234,237] Elsewhere, the average proportion of chronic HBV patients who are also infected with HDV is 5%, although wide local/regional variation exists.[234] For a detailed map of global HDV prevalence among HBV carriers, see reference.[238] Transmission can be bloodborne, sexual, percutaneous, permucosal, or perinatal. Prevalence of HDV is generally highest in the 20- to 40-year age group, and the majority of transmission is thought to be sexual or related to IVDU.[234]

In the 2 decades since its discovery in 1977, HDV prevalence declined in most high-income countries as a result of HBV vaccination programs and the introduction of public health policies to reduce the spread of BBV (such as needle exchange programs and safe sex campaigns).[239] As a result, awareness of HDV and rates of testing fell, contributing to the perception that HDV was being eradicated.[239] However, more recent epidemiological data show HDV prevalence remains high in many countries, and prevalence is in fact increasing among chronic HBV patients in Europe—a finding which is largely attributable to increased immigration from high-prevalence countries.[234] A German study, for example, showed that 75% of HDV-positive patients were originally from Turkey or Eastern Europe.[240]

A study of HDV diagnoses in Victoria, based on data from the Victorian Department of Health surveillance notifications and Victorian Infectious Diseases Reference Laboratory, reported 87 HDV notifications from 2000 to 2009.[241] The median age at diagnosis was 34 years, and the majority of cases were male (77%) and/or born overseas (71.4%). The predominant countries of birth of HDV cases were Vietnam, Sudan, Liberia, and Romania (see Table 22). There was 1 notification of an ATSI individual; however, Indigenous status was not reported for one third of the cohort so it is not possible to comment on HDV prevalence in Indigenous Australians. Of the total number of people tested for HDV over the study period (n = 2314), 4.75% returned a positive result. The annual number of notifications remained steady at between 14 and 16 notifications per year. Forty-one percent of HDV notifications occurred within 1 year of HBV notification (median lag time between HBV and HDV notification of 2 years).

In the context of organ donation and transplantation, organs donors who are HBsAg-positive and come from countries with a high prevalence of HDV pose a high risk to the recipient, regardless of recipient HBsAg status. Serological tests for HDV-Ab have low sensitivity, whereas HDV-Ag is only briefly detectable in serum. In the Victorian study, for example, only 6 people tested positive for HDV-Ag. NAT is, therefore, the most reliable method for detection of HDV.[234] Nevertheless, measures to prevent transmission of HBV to the recipient will also prevent HDV.

Oral antivirals are largely ineffective against HDV, and current treatment options are limited to interferon-alpha (IFNα) and its derivative pegylated IFNα. Treatment may be combined with nucleoside analogs (eg, tenofovir or entecavir) to control HBV replication. Nucleoside analogs, however, target HBV reverse transcriptase but do not directly affect envelope protein expression of HBV, and therefore, do not suppress HDV replication or assembly in HBV-infected cells.[242] IFNα works by directly suppressing HDV replication to some extent (mechanism unknown) and, in rare cases, by inducing negativation of HBsAg, possibly by eliminating HBsAg producing hepatocytes. Trials of peg IFNα alone or in combination with nucleoside analogs showed generally low response rates after for 48 to 96 weeks of treatment, and relapse was common even in patients who experienced RNA negativation.[242,243] Three novel drugs are currently in phase 2 trials in HDV-infected patients: (1) lonafarnib, an oral prenylation inhibitor preventing enveloped HDV particles leaving the hepatocyte; (2) nucleic acid polymers, such as REP2139-Ca that interfere with the molecules involved in cell entry; and (3) myrcludex B, a myristoylated L-HBsAg-derived 47-mer lipopetide, which blocks the formation of new HDV RNA.[242] Given the urgent need for effective treatment for HDV, lonafarnib and myrcludex B have received orphan drug status by the European Medicines Agency and Fast-Track status from the US FDA. For a thorough review of these new therapeutic agents, see Lempp and Urban.[242]

Hepatitis E virus (HEV) is overall the world's most common cause of acute viral hepatitis. First identified in Kashmir in 1978, HEV has 2 distinct epidemiological patterns: in low- and middle-income countries, HEV presents as endemic and epidemic disease, with an annual estimated burden of 3.4 million cases and 7000 deaths.[244] Modes of transmission in low- and middle-income countries are primarily waterborne, person-to-person contact, or vertical (mother to fetus/infant). Risk factors include cirrhosis and being pregnant, and the majority of those affected are aged 15 to 40 years. Hyperendemic countries (where disease incidence and prevalence are consistently high) and endemic countries are shown in Table 23. In high-income countries, HEV occurs as autochthonous or sporadic cases, or as case clusters, with transmission most commonly attributable to contaminated food (pork, game meats and shellfish). Avian HEV has also been isolated in Australia, the United States and Europe.[244] Those affected in high-income countries are generally older (>50 years), with risk factors including cirrhosis, liver transplantation, and HIV.[244] Although in the viremic phase, HEV can also

TABLE 22.

Notifications for HDV in Victoria 2000–2009[241]

Country of birth	No. notifications	Proportion of total	Proportion with injecting drug use as a risk factor	Median time lag (IQR), years
Australia	16	18.4%	68.8%	3.58 (0.07–7.54)
Vietnam	9	10.3%	77.8%	6.35 (1.94–8.52)
Sudan	9	10.3%	0%	0.32 (0.22–1.61)
Liberia	4	4.60%	0%	1.59 (0.08–3.29)
Romania	3	3.45%	0%	1.51 (0.02–8.84)
Lebanon	2	2.30%	50%	10.5 (8.99–12.0)
Other (overseas)[a]	13	—	—	—
Not stated	31	35.6%	29.0%	1.69 (0.27–3.43)
Total	87	—	34.5%	2.02 (0.21–4.83)

[a] Countries of birth with 1 notification each: Afghanistan, Croatia, Kenya, Kiribati, Laos, Nauru, New Zealand, Sierra Leone, Uganda, Ukraine, "Sub-Saharan Africa," "South East Asia," and "Overseas not further defined."

TABLE 23.

Global distribution of HEV[244]

Hyperendemic zone[a]		Endemic zone	Distinctive pattern[b]	Sporadic zone
Southern Asia	North Africa	Middle East	Egypt	High-income countries including Australia and New Zealand.
India	Algeria	Turkey		
Bangladesh	Morocco	Saudi Arabia		
Bhutan	Sudan	Yemen		
Nepal	Tunisia	Libya		
Pakistan	East Africa	Oman		
Sri Lanka	Kenya	Bahrain		
Southeast Asia	Uganda	Iran		
Burma	Burundi	Kuwait		
Cambodia	West Africa	United Arab Emirates		
Indonesia	Ivory Coast	Southeast Asia		
Thailand	Liberia	Singapore		
Vietnam	Nigeria	South America		
Laos	Mali	Brazil		
Central Asia	North America	Argentina		
Kazakhstan	Mexico	Ecuador		
Tajikistan		Uruguay		
Uzbekistan				

[a] In hyperendemic countries, HEV infections present as epidemic and endemic disease, with HEV-1 being the most common genotype (with the exception of Mexico and west Africa, where HEV-2 is more prevalent).

[b] HEV infection in Egypt usually occurs at a young age and is caused by subtypes of genotype HEV-1 that are not seen in the Asian population.

be transmitted by blood transfusion, and several cases of transfusion-transmitted HEV have been reported.[245-247]

There are 4 major HEV genotypes that infect humans (G1 to G4). G1 and G2, which infect human hosts only, occur primarily in Asia and Africa, where they are responsible for waterborne, horizontal and vertical transmission of HEV.[248] G3 is found worldwide and infects humans, pigs and other mammalian species, and is responsible for transmission via contaminated meat products. G4 infects humans and pigs only, and is found primarily in Southeast Asia.[248]

The clinical presentation of HEV is similar to HAV, although asymptomatic cases are not uncommon, especially in children. HEV infects the intestinal tract first, then the blood and the liver. HEV RNA can be detected in serum within days of infection, but may be difficult to detect by the time the person experiences symptoms.[249] Anti-HEV IgM titers peak at 6 to 8 weeks postinfection but then rapidly wane; anti-HEV IgG antibody titers rise slowly and persist for months to years. Challenges for serological testing for HEV infection include issues related to genotype applicability, poor test performance in immunocompromised persons, cross-reactivity with other viral infections, and variable sensitivity and specificity by test type. Acute HEV infection will be detected in approximately

90% of immunocompetent persons at 2 weeks postinfection, but HEV RNA testing is recommended for persons who are immunosuppressed.[244]

Infection is usually cleared from the body within 120 days, though chronic HEV infection may occur in profoundly immunosuppressed patients, and HEV infections have been observed in liver, lung, kidney, hematopoietic stem cell, heart, and kidney-pancreas recipients.[5] Those with existing liver damage are more likely to experience serious morbidity, including acute liver failure, after HEV infection. HEV is amenable to treatment with ribavirin monotherapy—for a summary of the effect of different antivirals and immunosuppressant's on HEV-3 replication, see Table 24.

Two cases of suspected donor-derived HEV transmission have been reported in the literature: the first occurred in Germany in 2008, and the second involved a Singaporean recipient of an organ from a commercial deceased donor in 2009.[250,251] In the German case, the donor, who had died from a myocardial infarction, was negative for HBV and HCV but had alanine aminotransferase (ALT) values 4 times the upper limit of normal. Although histological assessment of the donor liver showed mild fatty liver changes, there were no signs of chronic hepatitis or fibrotic alterations. No

TABLE 24.

Effects of antiviral and immunosuppressant therapy on HEV replication in the context of chronic HEV infection in solid organ transplant patients[244]

Class	Drug	Effect on HEV replication	Clinical use
Calcineurin inhibitors	Cyclosporine, tacrolimus	Stimulates HEV replication with increase in HEV load and promotes HEV persistence	Reduce dose
mTOR inhibitors	Rapamycin, everolimus	Stimulates HEV replication with increase in HEV load	Reduce dose
Antimetabolite immunosuppressant	Mycophenolate mofetil	Inhibits HEV replication and helps HEV clearance	Continue the drug
Guanosine analog	Ribavirin	Inhibits HEV replication and causes HEV clearance	Primary drug for therapy
Cytokines	Pegylated interferon α	Inhibits HEV replication and causes HEV clearance	Indicated if Ribavirin therapy fails
Nucleotide analog	Sofosbuvir	Inhibits HEV replication in vitro	Unclear, clinical trials indicated

HEV, hepatitis E virus.

further information was provided about the donors (travel history was not given). At 37 days posttransplant, the liver recipient experienced elevations in ALT, aspartate aminotransferase (AST) and alkaline phosphatase. Liver biopsy showed fatty liver degeneration but no evidence of acute or chronic hepatitis. Another biopsy was performed at 150 posttransplant due to increasing ALT levels, and at this stage chronic inflammation with portal and interface hepatitis was observed, possibly indicative of acute rejection, and the patient was treated with steroid therapy. At day 333 posttransplant, the patient presented with edema of the lower limb, and liver cirrhosis with advanced fibrosis was diagnosed. Three months later, the recipient died from septic shock. Retrospective analysis of blood samples taken before death detected anti-HEV IgM and IgG antibodies. Stored donor samples were then screened and, although antibody screening and RT-PCR of donor serum were negative for HEV, HEV RNA was detected in high concentrations in the liver tissue of the donor. Phylogenetic analysis showed the donor and recipient were infected with the same strain of HEV-3. This case demonstrates that HEV can persist in liver tissue without serological evidence of HEV infection.[250]

In the case from Singapore, the recipient was a 48-year-old man with chronic HBV and multifocal hepatocellular carcinoma that was outside of the eligibility criteria for liver transplantation in Singapore.[251] The donor procured a commercial deceased donor liver graft in 2009 (country not reported), and was deeply jaundiced on returning to Singapore 3 weeks later for follow-up. Serology and NAT were positive for EBV and HEV-3, and acyclovir was commenced. Magnetic resonance imaging suggested an anastomotic biliary stricture and a biliary stent were successfully inserted; however, despite regular stent changes and good bile outflow, the patient's liver tests did not improve and he remained jaundiced. A liver biopsy 1 month after transplantation showed moderate acute cellular rejection, which responded well to pulse methylprednisolone, yet his liver function continued to deteriorate and 6 months posttransplant he was admitted to hospital with jaundice, ascites, peripheral edema, and constitutional symptoms, and he died shortly after from graft failure with disseminated bacterial and fungal infection. HEV RNA was still detectable at the time of death.[251] In this case, it is not certain whether HEV was donor-derived, or whether the patient acquired it from eating contaminated meat shortly after transplantation.

In June 2017, the British Transplantation Society published guidelines for HEV detection and management in transplantation recipients, prompted by surveillance data from England indicating a recent rise in indigenous G3 HEV infection.[252] Seroprevalence of HEV in the general English population is estimated to be as high as 13%, and data from the NHS Blood and Transplant selective screening program indicated that 1 in 2500 blood donations were HEV RNA-positive as of February 2017.[253] A study of recipients of HEV-containing blood products found that 42% developed HEV infection, thus the approximate risk of transfusion-related HEV infection in England is 1 in 5000.[254] On this basis, universal screening of blood components for HEV is now recommended by the UK Advisory Committee for the Safety of Blood, Tissues and Organs.[255] The recommendations of the British Transplantation Society with regard to donor screening and management of HEV in solid organ transplant recipients are summarized in Table 25.

In summary, HAV and HEV pose a threat to transplantation in their acute phase, although outbreaks occur rarely in

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TABLE 25.

Statements of recommendations regarding HEV and solid organ transplantation, British Transplantation Society. Adapted from[255]

Testing of solid organ donors for HEV
- All solid organ donors are screened for HEV in line with the SaBTO recommendations.
- The detection of HEV viremia in a donor is not an absolute contraindication to the use of an organ from that donor, but will inform clinical management decisions posttransplant.

Management of HEV infection in solid organ transplant recipients
- The initial management of newly diagnosed or acute HEV infection in solid organ transplant recipients includes observation and monitoring of HEV RNA levels and liver enzymes for spontaneous clearance of infection.
- A strategic reduction in immunosuppression is considered in patients with acute or persistent HEV.
- Early treatment with ribavirin may be considered in specific cases, such as patients who develop severe liver dysfunction.
- Persistent HEV infection is diagnosed when HEV RNA is detectable in blood or stool for more than 3 months after disease onset, raised liver enzymes or first positive HEV RNA test.
- Individuals with persistent HEV infection should receive treatment with ribavirin, with the aim of achieving a sustained virological response.
- A baseline quantitative HEV RNA assessment should be undertaken on both plasma and stool at the start of treatment.
- Treatment with ribavirin should continue for at least 3 months for transplant recipients with persistent infection.
- Monthly HEV RNA testing in plasma and stool should be undertaken until a decision is made to stop treatment.
- Ribavirin should be continued until stool tests are negative for HEV RNA on 2 occasions 1 month apart.
- A test of sustained virological response should be conducted by testing plasma and stool samples for HEV RNA at 3 and 6 months after stopping antiviral treatment.
- Regular hemoglobin monitoring should be conducted during ribavirin treatment, as anemia is a common side effect.
- Assessment of the change in plasma HEV RNA after 7 days of ribavirin treatment is suggested to assess the likelihood of sustained virological response after 3 months of treatment, and to predict the likely length of ribavirin treatment required.
- The dosage of ribavirin is suggested to be adapted according to kidney function, to minimize side effects.
- Patients with persistent HEV who relapse after a first course of ribavirin are suggested to be retreated for at least 6 months with ribavirin at dosages toward the higher dose range, where tolerated.
- Routine baseline sequencing of HEV for mutations is not indicated.
- PEG-interferon treatment may be considered in cases of ribavirin-refractory persistent HEV infection, although patients will require very close monitoring for rejection. PEG-interferon is not recommended as a first line treatment in transplant recipients.

HEV, hepatitis E virus; SaBTO, Advisory Committee on the Safety of Blood, Tissues & Organs; RNA, ribonucleic acid.

Australia. HDV is of greater concern, as coinfection/ superinfection with HBV may seriously affect the outcome of transplantation and effective treatment is currently unavailable; however, measures to prevent HBV transmission to the recipient will prevent HDV transmission. Accordingly, the European Guide to the Quality and Safety of Organs for Transplantation states that organs from donors with HDV are usually not accepted, whereas organs are accepted regardless of the anti-HAV IgG/anti-HEV IgG status of the donor, except in cases of acute HAV/HEV infection.[5] Other international guidelines do not include specific recommendations with respect to HAV, HDV, or HEV. An algorithm for the treatment of HEV-3 infection in transplant recipients has been developed in the event of donor-derived disease transmission or infection posttransplant (see Table 26). Australia and New Zealand are not endemic areas for HEV; therefore, there is no requirement for routine donor screening. HEV transmission is a risk only in the acute phase, so testing for this virus using NAT needs to occur only in donors with clinical suspicion (eg, acute hepatitis) and epidemiological risk for HEV infection.

Arboviruses

Arboviruses refer to any viruses transmitted by arthropod vectors (eg, mosquitoes, ticks, sandflies). Arboviruses endemic to Australia include the flaviviruses Murray Valley encephalitis virus, the Kunjin lineage of WNV, and Japanese encephalitis virus, and the alphaviruses Ross River virus and Barmah Forest virus. Rates of infection are seasonal, peaking between approximately January and May when mosquitoes are most active, although seasonal trends vary between and within States and Territories according to differences in local mosquito vectors, hosts and climate.[257] Ross River fever is the most common mosquito-borne disease of humans in Australia (6920 notifications in 2017), followed by Barmah Forest virus (449 notifications in 2017). Symptoms of Ross River virus most commonly include arthralgia, and less commonly rash and fever; however, up to 75% of Ross River virus infections are asymptomatic.[258] Symptoms of Barmah Forest virus similarly include arthralgia, rash, fatigue, and flu-like symptoms, although again many people infected will be asymptomatic.[257] Ross River virus and Barmah Forest virus infections have been reported in all Australian states (including Tasmania), with the highest notification rates occurring in Queensland, tropical Western Australia and the Northern Territory. The number of Ross River virus notifications in each State and Territory from 2007 to 2017 is shown in Figure 10. It should be noted, however, that there are known issues with unreliability of serological tests for Ross River virus and Barmah Forest virus, leading to overdiagnosis particularly in the off-season.[257]

There have been no cases of transmission of Ross River virus or Barmah Forest virus infection by organ transplantation reported to date, although the potential for donor-derived transmission presumably exists given the ubiquity of these alphaviruses in Australia and 1 report in the literature of a case of Ross River virus transmission via blood transfusion occurring in Western Australia in 2014.[259] The blood donor developed fatigue and arthralgia 2 days after giving blood and was subsequently diagnosed with Ross River virus infection; however, some of the components had already been transferred to a patient before the recall of the affected donation. The recipient was receiving regular blood transfusions due to myelodysplastic syndrome associated with chronic fatigue and joint pains, and had reported a worsening of symptoms in the months after the transfusion of the infected blood.[259] Serological tests were positive for Ross River virus; however, the recipient experienced no further symptoms or sequelae. The potential outcomes in the event of transmission to an immunosuppressed organ transplant recipient are unknown.

In contrast to endemic alphaviruses, notifications of the Kunjin lineage of WNV and Murray Valley encephalitis virus are infrequent and mostly sporadic, with approximately 10 cases in recognized outbreak years, generally affecting residents of and visitors to the Kimberley region of Western

TABLE 26.

Notifications of nonendemic arboviral diseases in Australia in 2017, by country of acquisition[256]

Country	Chikungunya	Dengue	Zika
Bangladesh	35	10	—
Cambodia	1	7	—
China	—	1	—
Colombia	2	2	—
Congo, Republic of	—	1	—
Cuba	—	—	2
Ethiopia	—	1	—
Fiji	—	42	—
India	26	129	1
Indonesia	8	195	—
Italy	—	1	—
Malaysia	—	35	—
Maldives	—	3	—
Mexico	—	2	1
Myanmar	—	8	—
Nauru	—	10	—
Nepal	—	2	—
New Caledonia	1	9	—
Nigeria	—	2	—
Niue	—	1	—
Pakistan	2	—	—
Papua New Guinea	2	24	—
Peru	1	—	—
Philippines	5	33	1
Samoa	—	40	—
Sierra Leone	—	1	—
Singapore	—	5	—
Solomon Islands	—	31	—
Somalia	4	2	—
South Africa	1	—	—
Sri Lanka	—	85	—
Thailand	4	119	2
Timor-Leste	—	25	—
Uganda	—	1	—
Vanuatu	—	89	—
Vietnam	4	39	—
South-East Asia, NFD	1	8	—
Southern and East Africa, NFD	1	—	—
Americas, NFD	—	—	1
Other/unknown	—	106	1

NFD, not further defined.
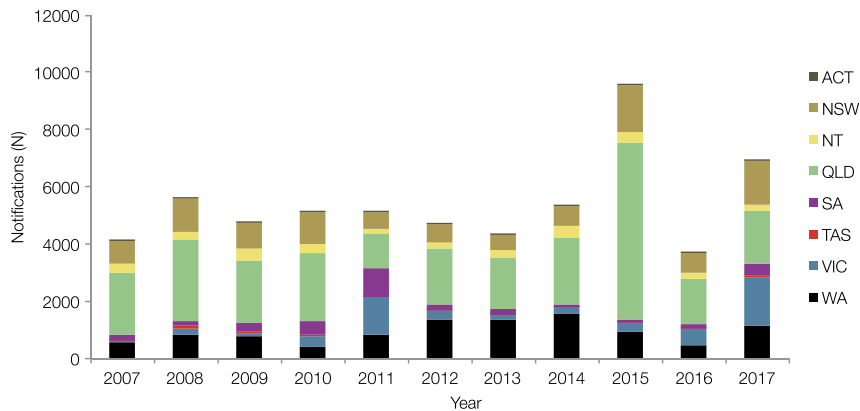
FIGURE 10. Ross River virus notifications (number) received from State and Territory health authorities, 2007 to 2017.[36] NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, Southern Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia.

Australia or the Northern Territory.[36,260] However, despite the low notification rate, it is recognized that for every clinical case of there may be hundreds of asymptomatic infections, because the vast majority of Kunjin virus and Murray Valley encephalitis virus infections are asymptomatic.[259] Anecdotal evidence suggests Kunjin virus causes symptomatic disease more often than Murray Valley encephalitis virus, with symptoms of Kunjin including arthralgia, myalgia, fever, headache, and occasionally, a rash.[260] When Murray Valley encephalitis virus does cause clinical disease, symptoms are generally more than severe than for Kunjin virus: an estimated 1 in 1000 infections with Murray Valley encephalitis virus results in clinical encephalitis.[261] Encephalitis is less common in cases of Kunjin virus infection.[260] To date, there have been no cases of Kunjin virus or Murray Valley encephalitis virus transmission via blood transfusion or organ donation; however, precautions may be warranted particularly in regions where there are active outbreaks of disease.

Other nonendemic arboviruses of public health importance to Australia include dengue virus, chikungunya virus, and Zika virus. Nonendemic arboviruses are of concern primarily in the case of donors whose recent travel history includes south and southeast Asia, tropical Africa, or the Pacific Islands. Imported cases of dengue fever are relatively common among travellers returning from endemic areas, in particular India, Sri Lanka, southeast Asia, and the Pacific Islands (see Table 26).

In New Zealand, virtually all notified cases of arboviral infections to date have occurred in overseas travellers, although a local case of sexual transmission of Zika virus was reported in 2016.[39] Only 1 arbovirus is endemic to New Zealand–the Sindbis-like alphavirus Whataroa virus which is established in bird populations on the West Coast of the South Island; however, human infection has only ever been documented serologically (absent of disease).[40] There are 3 mosquito species established in New Zealand that have the potential to be vectors for human diseases: *Culex quinquefasciatus* (a potential vector for encephalitis viruses), *Aedes notoscriptus* (a vector for dengue virus), and *Aedes australis* (a vector for dengue and Whataroa viruses). All 3 are potential vectors for Ross River virus, by none are particularly effective arboviral vectors are would be unlikely to support endemic transmission of arboviruses in New Zealand.

In 2016, there were 191 cases of dengue virus infection (4.1 per 100 000) in New Zealand, 28 cases of chikungunya virus infection (0.6 per 100 000 population), 100 cases of

Zika virus infection (2.1 per 100 000 population), and 4 cases of Ross River virus infection.[39] Countries of acquisition included Indonesia (dengue), Fiji (dengue, chikungunya, Ross River, Zika), Tonga (Zika virus), Samoa (dengue, Zika), Thailand (dengue), India (chikungunya), Brazil (chikungunya), and Australia (Ross River virus).[39]

The flaviviruses Zika virus and WNV are discussed separately as pathogens of special interest in sections *Zika Virus* and *West Nile Virus*, respectively. The WHO declaration of global public health emergency in relation to the 2015/2016 Zika outbreak in Brazil and Central America prompted international authorities to develop targeted recommendations for the prevention of Zika transmission via organ and tissue transplantation, and these are discussed in detail in section *Zika Virus*. West Nile virus is also of special interest given its widespread global distribution and the relatively large number of reported cases of transmission via solid organ transplantation, with frequently fatal outcomes. The risks of donor-derived transmission of other arboviruses appear to be relatively low, and there are limited case reports of transmission events in the published literature. One case of possible donor-derived dengue transmission was reported from Singapore in 2005. The recipient was a 23-year-old male with end-stage kidney disease due to lupus nephritis, who received a living donor kidney transplant from his mother, who was known to have had a history of dengue fever 6 months before donation.[262] Five days posttransplant, the recipient developed a high fever and, given the donor history, NAT was performed and returned a positive result for dengue virus serotype 1. Twelve days posttransplant, the recipient developed upper gastrointestinal bleeding, gross hematuria and tachycardia. Three days later, he complained of left flank pain and abdominal distension, and a large retroperitoneal hematoma at the bed of the transplanted kidney was revealed on computed tomography (CT). Emergency surgery to evacuate the hematoma was successful, and repeat NAT was negative for dengue. The recipient then went on to have an uneventful recovery, with resolution of hematemesis and hematuria and excellent graft function. In this case, the clinical presentation of dengue in the transplant recipient was similar to that in immunocompetent persons but with longer duration—19 days versus mean duration of 2 to 7 days.[262]

European guidelines recommend ruling out acute infection with arboviral diseases including dengue, chikungunya and WNV for donors living in or coming from endemic regions

or areas with ongoing outbreaks.[5] In Australia and New Zealand, a similar approach would be warranted: where the donor is a resident of or has a history of travel to an endemic region or area with an ongoing outbreak of arboviral disease, acute infection should ideally be ruled out before proceeding with transplantation.

Pulmonary Viral Infections

The lung virome consists of transient infections (influenza, human respiratory virus, etc.) as well as resident viruses that are present in both healthy and disease states.[263] Next-generation sequencing techniques have permitted a new appreciation of the diversity of resident viral species within individuals, a large proportion of which remain uncharacterized.[263] Metagenomic studies of samples from cystic fibrosis patients and lung transplant recipients have found that up to 88% of lung virome sequences were unknown.[264,265] These studies identified a wide range of bacteriophages, as well as herpes virus, adenovirus, human papillomavirus, and torque teno virus. The complexity of the respiratory virome complicates the diagnosis of the causative agent of disease, because pathogenic viruses may be present among the resident viruses of healthy individuals. In an example of this, a metagenomic study of nasopharyngeal aspirates from febrile versus afebrile children detected rhinovirus in both groups.[266]

To date, there has been a single study characterizing the lung virome of lung transplant recipients.[265] Young et al found that the majority (>68%) of reads that could be mapped to reference viruses mapped to various anelloviruses, including torque teno viruses, torque teno midi viruses, torque teno mini viruses and small anelloviruses (each with multiple subtypes). These anellovirus sequences were 56-fold more abundant in bronchoalveolar lavage (BAL) from transplant recipients compared to healthy controls. Anelloviruses are ubiquitous in humans and have not yet been causally linked to human diseases[267]; however, Young et al[265] also observed that high anellovirus loads correlated with dysbiotic bacterial communities in the allograft, that is, the higher the anellovirus titer, the greater the divergence between the corresponding bacterial community and healthy controls. The cause and clinical implications of this observation are not yet clear. Other viruses detected within the lung virome by this study included EBV, human herpesvirus, human papillomavirus, and various bacteriophage genomes (eg, phages of *Enterobacteria*, *Salmonella*, *Pseudomonas*, *Streptococcus*, and *Yersinia*). Notably, an average of 81% of reads could not be mapped to reference viruses in the NCBI viral database. The authors speculate that many of these correspond to DNA phage sequences.

Currently, there are minimal data available on the impact of transplanting the lung virome; however, longitudinal studies are underway and the potential importance of the respiratory virome to outcomes of lung transplantation should be noted. Although next-generation sequencing may be of use for lung donor screening in the future, currently, for practical purposes, viral testing of the donor before implantation and BAL postimplantation will capture most viruses provided that samples are properly handled (personal communication A Glanville).

Meningoencephalitis of Viral Origin

Donors with undiagnosed meningoencephalitis are an uncommon but potentially lethal source of donor-derived infection.[268] Transmission of rabies, LCMV, WNV, *Mycobacterium tuberculosis*, *Cryptococcus*, *Coccidiodes immitis*, *Aspergillums*, and *Balamuthia* have occurred when donors with meningitis or encephalitis of unknown cause have been used as organ donors.[269] For this reason, any meningitis or encephalitis without a proven cause should be an absolute contraindication to transplantation, according to the international guidelines.[5,7,29,269]

Recognition of transmissible infections in potential deceased donors with meningoencephalitis is often complicated by the circumstances of brain death, which might not raise the suspicion of the presence of a central nervous system infection, for example, stroke in the case of a patient with amoebic encephalitis, or cocaine use in a patient with intracerebral hemorrhage who had rabies.[268,270] Distinguishing between such ubiquitous causes of death in potential donors as anoxia, head trauma, or cerebrovascular accident and a potentially transmissible central nervous system infection is extremely difficult. In addition, many of these pathogens are not part of routine donor screening in Australia and New Zealand (or elsewhere) and, therefore, would not be detected as part of a standard donor evaluation. Based on reporting to the United States OPTN Ad Hoc Disease Transmission Advisory Committee, the most common diagnoses for central nervous system infections in deceased donors were tuberculosis, endemic fungi, cryptococcosis, coccidiomycosis, and WNV, followed by syphilis, histoplasmosis, toxoplasmosis, and Chagas disease.[268]

In some cases, donors diagnosed with treatable forms of meningoencephalitis might be safely used for organ transplantation after a suitable period of antimicrobial treatment for the donor and the recipient.[5,269] Donors with meningoencephalitis of viral origin other than HSV or VZV, however, present an extremely high risk for disease transmission. If the pathogen in unknown or if the suspected pathogen is one for which no treatment options are available, transplantation should be avoided or pursued with extreme caution only after weighing the risks of adverse recipient outcomes with the risks of waiting for another organ.[269] Where the cause of the meningoencephalitis is confirmed as a virus that is amenable to treatment, for example, HSV encephalitis, the organs might be used if the donor is not viremic and provided that the recipient is seropositive pretransplant and/or is given appropriate prophylaxis.[5,29] Meningitis of bacterial origin is discussed in the *Bacteremia and Meningitis* section, and WNV is discussed as a special case in the *West Nile Virus* section.

Published reports of transmission events from donors with unrecognized central nervous system infections highlight the extreme risks associated with such donors, as well as the challenges of recognizing central nervous system infection. In 2004, 4 recipients of organs from a single donor died of encephalitis of unknown cause shortly after transplantation. The donor in this case had presented to the emergency department with nausea, vomiting and difficulty swallowing. He was subsequently admitted to a second hospital with altered mental status requiring intubation, with a fever and fluctuating blood pressures. His toxicology screen was positive for cocaine and marijuana, and a CT of the brain revealed a subarachnoid hemorrhage, which progressed to brain death 4 days after admission. Standard donor screening did not reveal any infection precluding organ donation, and the donor's kidneys, liver and lungs were retrieved for transplantation. Encephalitis developed in all 4 patients within 30 days of transplantation and was accompanied by rapid

neurologic deterioration and death an average of 13 days after the onset of symptoms—rabies was subsequently confirmed in all of the organ recipients. Contact investigations revealed that the donor had been bitten by a bat shortly before becoming ill.[270]

A second report of unrecognized central nervous system infection involved 2 clusters of LCMV, in which 7 of 8 recipients died.[271] Lymphocytic choriomeningitis virus is a rodent-borne, Old World arenavirus that normally causes only mild, self-limited disease in humans, though, in very rare cases, can cause fatal meningitis.[272] Transmission can occur vertically from mother to fetus, but other forms of human-to-human transmission do not normally occur. The 2 transplant-related clusters of LCMV occurred in the United States in 2003 and 2005, respectively. The donor in the 2003 cluster was a 51-year-old man found unresponsive with subdural hematoma, but without fever or other specific signs of infection. The donor in the 2005 cluster was a 45-year-old woman with a history of hypertension presenting with headache and left-sided weakness, and diagnosed with cerebral infarction. After LCMV was determined to be the etiological agent causing the deaths of the recipients, LCMV could not be detected in either of the 2 organ donors, even after testing multiple donor tissues by immunohistochemical analysis, cell culture, and PCR. Subsequent contact tracing interviews with the donors' families revealed that the female donor had contact at home with a pet hamster that was tested and found to be infected with an LCMV strain identical to that detected in the organ recipients; the male donor, however, had no known rodent exposure. Symptoms in the transplant recipients included abdominal pain, altered mental status, thrombocytopenia, elevated aminotransferase levels, coagulopathy, graft dysfunction, and either fever or leukocytosis, with onset within 3 weeks of transplantation. The 1 patient who survived was a recipient of a kidney from the female donor. LCMV was identified as the etiological agent on day 25 posttransplant, and IV ribavirin was initiated for the kidney recipient on day 26 (loading dose of 30 mg/kg every 6 hours for 4 days then 8 mg/kg every 8 hours); unfortunately, by this time, all of the other recipients of organs from the female donor had already died without confirmation of the etiological agent and without receiving targeted treatment. After the patient's clinical condition had stabilized, they were switched to oral ribavirin (400 mg each morning and 600 mg each evening), and by day 63, a renal biopsy specimen was negative for LCMV DNA and serum IgM was detectable. By day 311 posttransplant, the patient had stable graft function and was able to resume full immunosuppressive therapy.[271]

A cluster of fatal donor-derived arenavirus cases was reported in Australia in 2008, in which the infectious agent was a previously unidentified LCMV-related arenavirus.[17] The donor in this cluster was a 57-year-old man who died of cerebral hemorrhage 10 days after returning to Australia from a 3-month visit to the former Yugoslavia, where he had travelled in rural areas. No viral nucleic acids were detected in the donor, and no history of acute infectious disease was reported; however, IgG and IgM antibodies were present. He donated his liver and both kidneys to 3 recipients, all of whom developed febrile illness with varying degrees of encephalopathy and proceeding to death within 4 to 6 weeks of transplantation. Bacterial and viral cultures, NAT, and viral and panmicrobial oligonucleotide microarray assays revealed no candidate pathogens, and therefore, RNA was extracted from the brain, cerebrospinal fluid (CSF), serum, liver, and kidney of one of the kidney recipients, and from the CSF and serum of the liver recipient. High-throughput sequencing of amplified RNA samples and examination of Vero E6 cells inoculated with homogenized fresh-frozen kidney tissue revealed the presence of an arenavirus with an identical but previously uncharacterized genetic sequence in the recipients.

TABLE 27.

Questions for consideration when completing screening procedures for potential organ donors[269]

Question
What is the potential donor's age and cause of brain death? Were there any comorbidities that may support stroke/CVA diagnosis (ie, diabetes, hypertension, prior CVA) vs possible meningoencephalitis noted? Pediatric and young adult donors are less likely to have a stroke or CVA compared to older adults. Accordingly, caution should be used in evaluating younger potential donors given this diagnosis. Although older adults being evaluated are more likely to have stroke/CVA diagnosis, atypical presentations and/or the absence of comorbidities should prompt consideration for meningoencephalitis.
Did the potential donor have a fever at presentation of illness/admission (eg, fever defined as >37.5–38.3°C)? If yes, was there a clear explanation for this fever? If not, meningoencephalitis should be considered.
Were altered metal status and/or seizures part of the presentation that led to the donor's hospitalization? If these were new and/or unexplained events, meningoencephalitis may be considered.
Was a CT of the head, or MRI of the head or lumbar puncture consistent with an infectious process? For example, was there an unexplained CSF pleocytosis, low CSF glucose, or elevated CSF protein without a clearly defined bacterial pathogen? Is there unexplained hydrocephalus—another potential indicator of CNS infection? Abnormal CSF due to clearly defined case of bacterial meningitis currently under treatment would be an exception. MRI may show a focal finding like infarct or hemorrhage; however, this may not necessarily exclude a diagnosis of meningoencephalitis.
Was the donor an immunosuppressed host? This includes donors with a prior history of transplant on immunosuppressive medication (including steroids), a donor on immunosuppressive medications for other reasons, or with a history of an underlying condition associated with immunosuppression (ie, cirrhosis, end-stage renal disease, and other immune disorders).
Did the donor have any potential environmental exposures associated with organisms causing meningoencephalitis? These exposures will vary depending on the region of the country and the time of year. For example, a donor with a recent bat exposure and mental status changes could have rabies. A donor who spent a lot of time outdoors in an area with heavy WNV activity would be at greater risk for WNV meningoencephalitis.
It should be noted that homeless donors or any donors in whom obtaining an adequate medical social history is problematic may pose a unique risk due to difficulty in collecting medical-social history and living conditions that may put them at increased risk for transmitting infection (eg, tuberculosis or extended outdoor exposure that may increase risk for vector borne illness—like WNV, Lyme Disease, rabies, etc).

CSF, cerebrospinal fluid; WNV, West Nile virus.

The case above highlights the challenges of identifying central nervous system infections particularly in donors dying from CVA and the potential for rare and uncharacterized infectious agents to be transmitted by organ transplantation. To aid decision making in this context, the United States OPTN has formulated a guidance document for recognizing central nervous system infections in potential deceased organ donors. Issues for consideration highlighted by this document are listed in Table 27.
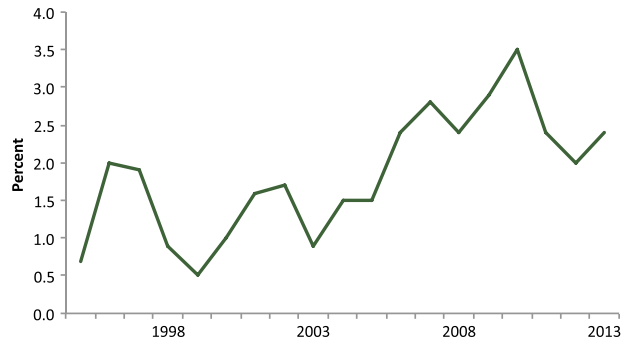
BACTERIAL INFECTIONS IN THE DECEASED DONOR

Mycobacterium tuberculosis

Epidemiology

The number of tuberculosis notifications in Australia in 2016 was 1217 (5.1 per 100000 population, National Notifiable Disease Surveillance System 2016 data set). The vast majority (approximately 90%) of these cases occurred in Australia's overseas-born population, among which the incidence of tuberculosis is approximately 20 times that of the Australian-born, non-Indigenous population (18.4 vs 0.7 notifications per 100000 in 2013 respectively).[273] NSW and Victoria account for more than 50% of all tuberculosis cases in Australia, whereas the Northern Territory has the highest jurisdiction-specific notification rate (17.1 per 100000 in 2013). Tuberculosis incidence in ATSI peoples was 4.6 cases per 100000 in 2013.[273]

The most frequently reported countries of birth for tuberculosis cases in Australia in 2013 were India, Vietnam, the Philippines, and China. Relative to population size, the highest rates of tuberculosis in 2013 were reported for Australian residents born in Somalia, Nepal, Myanmar, Afghanistan, Papua New Guinea, and Sudan.[273] Of those diagnosed within 4 years of arrival in Australia, international students accounted for 21% of tuberculosis cases in 2013. The contribution of international students and the demographics of the Australian resident migrant population (median age, 37 years; ABS 34120DO001_201415) would account for the bimodal distribution of tuberculosis notifications seen in Figure 11.

Major risk factors contributing to notified cases of tuberculosis in Australia in 2013 were past travel or residency in a high-risk country (81% of cases), household, or other close contact with tuberculosis (11% cases), or current or previous employment in the health industry (7%). Other risk factors that were present in a small proportion of cases (5%) included current or prior incarceration, current or prior residence in an aged care facility, current or prior employment at a correctional facility, aged care facility or homeless shelter, current or prior homelessness, parent born in a high-risk country, or being treated with immunosuppression.[273]

Australia has had very few cases of multidrug-resistant tuberculosis, and these have occurred almost exclusively in the overseas-born population. Of cases where drug sensitivity testing was performed in 2013, 0.3% had resistance to rifampicin alone, 5.2% to isoniazid alone, and 2.4% to both rifampicin and isoniazid (MDR-TB).[273] Zero cases of extensively drug-resistant tuberculosis were reported in 2013—only 2 cases of XDR-TB have been reported since 1995.[273,274] Figure 12 shows trends in the proportion of tuberculosis cases that were multidrug-resistant since 1995. The spike in 2010 is accounted for by 10 patients with MDR-TB from Papua New Guinea accessing healthcare services in the outer Torres Strait Protected Zone.[274]

Tuberculosis in Organ Donors and Recipients

Incidence of tuberculosis among solid-organ transplant recipients is much higher than the general population, especially among lung transplant recipients.[275] Tuberculosis
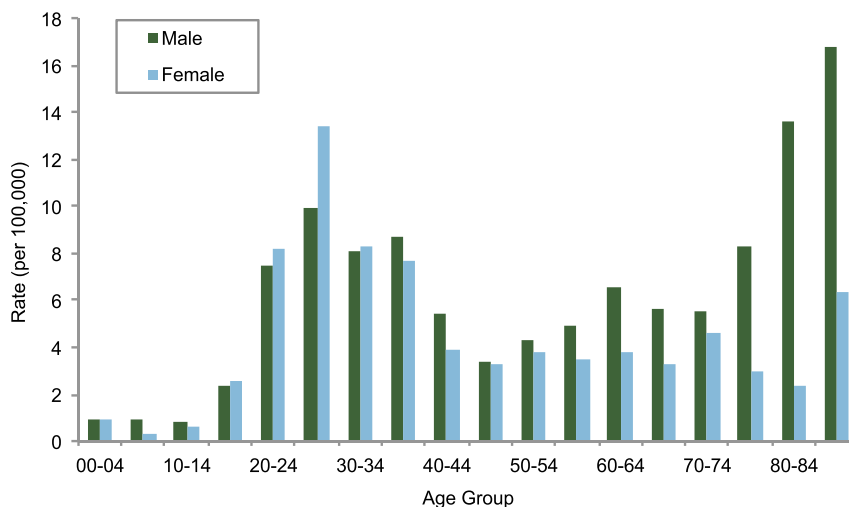

FIGURE 12. Percentage of tuberculosis cases with drug resistance testing indicating multidrug resistance.[273,274]

FIGURE 11. Notification rate of tuberculosis in Australia in 2016, by age group and sex (data: http://www9.health.gov.au/cda/source/cda-index.cfm).

most commonly appears in the transplanted population due to reactivation of latent infection—an audit at Westmead Hospital Sydney estimated that 30% of waitlisted patients had latent tuberculosis (personal communication: A Webster)—but it may also be acquired as a de novo infection posttransplant, or be transmitted via the donor organ. In the United States, tuberculosis is one of the most common donor-derived bacterial infections.[1] Data from Europe and the United States indicate that 0.4% to 7% of solid-organ recipients develop tuberculosis, and donor-derived transmission accounts for less than 5% of these cases.[276] Risk factors for tuberculosis among potential donors include (1) social factors—country of origin or prior residence in an endemic country, history of homelessness, incarceration or alcoholism, and/or contact with persons infected with tuberculosis; and (2) medical risk factors—history of untreated tuberculosis, radiographic evidence of prior tuberculosis, body mass index less than 18.5, diabetes mellitus, and/or cigarette smoking.[277]

A recent matched cohort study comparing the clinical features and outcomes of tuberculosis in transplant recipients versus the Spanish general population found that time from clinical suspicion of tuberculosis to diagnosis (positive acid-fast bacilli smear, histopathological pattern of tuberculosis, positive NAT or *M. tuberculosis* culture) was longer in transplant recipients than in the general population (median, 14 days vs 0 days) and more often required invasive procedures.[278] This study also found that rates of tuberculosis-related mortality were higher among transplant recipients than the general population (18% vs 6%), as were rates of toxicity associated with antituberculosis treatment (38% vs 10%).[278] Tuberculosis in transplant recipients often resists timely diagnosis and is associated with worse outcomes than observed in the general population.

One of the challenges for the detection of donor-derived tuberculosis is that disease in donors and recipients may not present as a primary respiratory infection and, therefore, may not be recognized straight away, contributing to delays in diagnosis and reporting.[277] Pulmonary disease accounts for approximately 60% of cases in the Australian general population, with 40% being extrapulmonary.[273] By comparison, extrapulmonary disease accounts for closer to half of tuberculosis cases in the transplant population, and disseminated tuberculosis is substantially more common.[278,279] Where the donor was born in, or recently travelled to, an endemic country, or where other tuberculosis risk factors are present, the possibility of extrapulmonary tuberculosis should be considered in recipients presenting with an infection of unknown origin. This is of course dependent on the availability of a detailed, accurate donor history, which will not exist in all circumstances.

Donor Screening and Risk Minimization

In living donors, it is possible to perform tuberculosis screening in accordance with recommended guidelines; however, in potential deceased donors, this is problematic because there are no proven methods for screening deceased donors for tuberculosis. Chest X-ray and direct microscopy of BAL for acid-fast bacilli have a low sensitivity, and cultures may take up to 8 weeks to turn positive.[277] Tuberculin skin testing is also impractical in the context of deceased donation given a turnaround time of at least 48 hours. NAT can identify *M. tuberculosis* in clinical specimens from donors with active infection only. Therefore, when these tests are performed, a negative/normal result does not definitively rule out infection with *M. tuberculosis*, due to the high rate of false negatives and because organisms can remain dormant in the host without causing disease for decades, without any detectable radiographic abnormality. Conversely, abnormal pulmonary findings from a range of causes are common in deceased donors and may confound donor evaluation.[277]

Interferon-gamma release assays (IGRAs) might theoretically be useful given their shorter turnaround time (~24 hours). These assays work by stimulating peripheral blood cells with specific antigens; in response, T cells recognizing these antigens are rapidly activated and secrete a variety of cytokines, of which interferon gamma is measured to indicate the pathogen-specific activation of T cells.[277] Interferon gamma release assays are available commercially as T-SPOT.TB (Oxford Immunotec, UK) and QuantiFERON-TB Gold in-Tube (Cellestis, Australia). Drawbacks of these tests include high cost and indeterminate results in immunosuppressed persons; moreover, IGRAs have not yet been validated for use in deceased donors, and it is not known whether brain death impacts the performance of this assay.[5,277] Further, false-positive results will be common in low-risk populations, whereas false-negative may occur in cases of miliary or disseminated tuberculosis. Therefore, the results of IGRAs cannot be relied upon to either definitively exclude active disease nor as grounds for rejecting a given donor.[277]

Given the limitations of tuberculosis screening tools in deceased donors, it is important to evaluate social and medical risk factors in the potential deceased donor. Country of origin and/or prior residence in a highly endemic country is a key risk factor. Tuberculosis country profiles can be reviewed at www.who.int/tb/data., Although difficult to obtain, patient histories for possible contacts with persons infected with *M. tuberculosis* are important.

Given the global challenges of tuberculosis screening in potential organ donors, an international consensus group was formed to provide expert recommendations on this subject.[277] A summary of the recommendations of this group is provided in Table 28.

Current UK and European donor screening guidelines make the following recommendations with respect to tuberculosis and organ donation:

SaBTO: Donation of organs, tissues and cells is contraindicated from donors with active disease or within the first 6 months of antituberculosis treatment. However, organs can be considered for transplant if a recipient has received a 6-month course of chemotherapy, unless the isolate is found to be resistant to appropriate antituberculosis drugs. If there is a history of tuberculosis at the site of the organ to be used for donation, use of that organ is contraindicated by the donation of other organs is acceptable.[29]

EDQM: Organs from donors with disseminated tuberculosis should not be used. Organs from donors with a history of TB and with successful treatment for at least 6 months may be considered, with prophylaxis and/or empiric treatment considered for the recipient in accordance with international guidelines.[5]

Transmission

Numerous cases of unexpected tuberculosis transmission from donors to recipients have been reported in the literature

TABLE 28.

Summary consensus recommendations of the Donor-Derived Infections Consensus Conference on *Mycobacterium tuberculosis*—recommendations relating to deceased donors[277]

Tuberculosis epidemiology recommendations:

(1) Organ donors can be divided into low, moderate and high-risk categories for risk of tuberculosis infection or latent tuberculosis infection based on detailed history and prior countries of residence/exposure. It should be noted that some donors thought to have latent tuberculosis infection might actually have undiagnosed active tuberculosis at the time they became an organ donor. Individuals with active tuberculosis will likely pose a greater risk for transmission; therefore, it is especially critical to identify these patients before donation.

(2) Risk stratification based on donor social and medical history may be predictive of tuberculosis infection (either latent or unrecognized active tuberculosis) in donors and hence possible risk of tuberculosis transmission to organ recipients.

(3) Diagnosis of latent tuberculosis infection and assessment of risk for transmission in organ donors optimally should be based on objective medical data such as prior historical results of tuberculin skin testing, interferon-gamma release assays, or chest x-rays.

(4) The presence of tuberculosis 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 tuberculosis through transplantation. Factors such as recipient immunogenetics may confound donor risk stratification when evaluating transplant outcomes.

Tuberculosis screening recommendations—all donors

(1) Reasonable efforts must be made to rule out active tuberculosis in the donor with any identified historical or epidemiologic risk factors. For suspected or confirmed cases of active tuberculosis, donation should be deferred except in dire circumstances.

(2) All solid-organ donors should have a careful epidemiologic and personal medical history, physical and chest radiograph. During the organ retrieval surgery the lungs must be visually inspected and palpated for all donors where there is a concern. Abnormal lesions need to be biopsied and tissue sent for testing.

(3) Tuberculin skin test and interferon-gamma release assay 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 tuberculin skin test and interferon-gamma release assay does not rule out active tuberculosis.

(4) For lung donors, bronchoscopy specimens should be obtained for mycobacterial testing for tuberculosis and atypical mycobacteria (acid-fast bacilli smear and culture at a minimum) before donation.

(5) Molecular methods from mycobacterial culture and species identification are preferred to standard culture if available, due to the shorter turnaround time.

(6) There is insufficient evidence to recommend interferon-gamma release assay testing of all solid-organ donors at this time. Further research into the utility of interferon-gamma release assays in donors is needed. Interferon-gamma release assays have potential utility for identification of increased tuberculosis risk in deceased donors at moderate or high risk.

(7) Donation need not be deferred for the diagnosis of latent tuberculosis in any solid-organ donor including lung donors.

(8) Urinalysis with microscopy, genitourinary imaging and urine acid-fast bacilli smear and culture should be considered for all organ donors in intermediate- and high-risk countries. This is particularly important for kidney donors.

Tuberculosis screening recommendations—deceased donors

(1) In deceased donors of solid organs other than lungs, who have an abnormal chest radiograph suspicious for active tuberculosis, specimens should be collected for acid-fast bacilli smear and culture, and specimens should be sent for nucleic acid amplification testing. 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 interferon-gamma release assay testing of deceased donors. However, if interferon-gamma release assay is performed, the following considerations should be taken into account:

(a) Results are generally not available for 24 hours; therefore, the decision to use the organs must be a clinical decision;

(b) Interferon-gamma release assays have relatively high rates of indeterminate results in different subpopulations; however, 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 interferon-gamma release assay is positive or indeterminate and the deceased donor of any organ except lung is from an area of low incidence for tuberculosis but otherwise in a high-risk group for tuberculosis, clinical history and chest imaging should be carefully reviewed for correlation. This should precede donation if the positive result is known before procurement. Regardless, the interferon-gamma release assay result alone should not influence suitability for donation, but may be used to guide follow-up

assessments or tuberculosis 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 interferon-gamma release assays;

(e) There is minimal published information regarding the performance characteristics of interferon-gamma release assays in infants and young children.

(see Table 29). Given the difficulties of detecting tuberculosis in deceased donors, many of these cases involved donors with normal chest x-rays, no microscopic evidence of acid-fast bacilli, and/or negative cultures for *M. tuberculosis*.[288,290,294] For example, in a case of multidrug-resistant tuberculosis in a lung transplant recipient in Hong Kong, the donor—a 51-year-old recent immigrant from China—had no history of tuberculosis, and chest x-ray, microscopy of tracheal aspirate, and cultures showed no evidence of *M. tuberculosis* infection.[290] Other similar cases of donor-derived tuberculosis in solid organ recipients, in which the donor was negative

for tuberculosis based on acid-fast bacilli stain, culture, and chest x-ray, demonstrate the importance of donor history in the assessment of potential tuberculosis risk.[281,282,294]

Table 29 summarizes the tuberculosis risk factors present in donors who subsequently transmitted *M. tuberculosis* to 1 or more organ recipients. The most common risk factors among reported cases were recent arrival from or previous residence in an endemic country, followed by donor characteristics such as homelessness, alcoholism, incarceration, and health and hygiene status. Cases of drug-resistant tuberculosis transmission further emphasize the importance of donor

TABLE 29.
Case reports of unexpected donor-derived tuberculosis transmission in solid organ transplantation (deceased donors)

Transplanted organ	Reference	Year of transplant	Donor risk factors	Time from transplantation to diagnosis, mo	Presenting symptoms	Follow-up interval, mo	Drug resistant	Recipient died at end of follow-up	Treated for rejection during follow-up
Kidney	Weile 2013[280]	2011	Severely reduced health and hygiene status, alcoholism, pneumonia	<1 month	None	5	No	Yes[a]	Not reported
	Weile 2013[280]	2011	As above	<1 month	None	17	No	No	No
	Edathodu 2010[281]	2009	Immigrant from Indonesia with CNS infection of unknown cause	2	Fever	12	No	No	Not reported
	Edathodu 2010[281]	2009	As above	<1	Fever	1	No	Yes (week 3)	Yes
	CDC 2008[279]	2007	Alcoholism, homelessness, incarceration, pneumonia	1.5		2	No	Yes (week 9)	No
	CDC 2008[279]	2007	As above	1.5		12	No	No	No
	Malone 2007[282]	2003	Immigrant from the Philippines	29	Nausea, deteriorating renal function	48	No	No	No
	Mourad 1985[283]	1982	None	4	Fever, asthenia, disorientation	26 (?)	No	No	No
	Mourad 1985[283]	1982	As above	7	Fever, cough, headache	26 (?)	No	No	No
	Peters 1984[284]	1981	Active disseminated TB that was confirmed 3 weeks after transplantation	1	Deteriorating renal function	5	No	Yes (week 22)	Yes
Liver	Peters 1984[284]	1981	As above	1	Not reported	12 (?)	No	No	Yes
	Edathodu 2010[281]	2009	Immigrant from Indonesia with CNS infection of unknown cause	3	Fever	9	No	No	Not reported
Heart	Coll 2013[275]	Between 1998–2011	Parents from a highly endemic country	2	Not reported	17	No	No	Not reported
	Weile 2013[280]	2011	Severely reduced health and hygiene status, alcoholism, pneumonia	<1 month	None (detected after notification of donor culture turning positive for *M. tuberculosis*)	3	No	Yes[a]	No

Transplanted organ	Ref	Year of transplant	Donor risk factors	Time from transplantation to diagnosis, months	Presenting symptoms	Follow-up interval, months	Drug resistant	Recipient died at end of follow-up	Treated for rejection during follow-up
Lung	Jensen 2016[16]	2015	History of latent TB treated with isoniazid	3[b]	Cough	9	Yes	No	No
	Kumar 2013[285]	2012	Immigrant from Vietnam	3	Cough	Not reported	No	No	Not reported
	Coll 2013[275]	Between 1998 and 2011	Immigrant from a highly endemic country	<1	Not reported	14	No	No	Not reported
	Mortensen 2014[286]	2008	Recent immigrant from Mexico, incarceration	6	Fever, dyspnea	10	No	Yes[a]	Yes
	Mortensen 2014[286]	2008	Proximity to TB outbreak, incarceration	2	None (detected during scheduled BAL specimen collection)	3	No	No	No
	Mortensen 2014[286]	2009	Recent prior residence in the Philippines	4	None (detected during scheduled BAL specimen collection)	7	No	No	Yes
	Boedefeld 2008[287]	2008	Immigrant from Peru	3	Sepsis	3	No	Yes	Yes
	Winthrop 2004[288]	2002	Recent arrival in the United States from Guatemala	<1	None (detected during scheduled BAL specimen collection)	31	No	No	No
	Wong 2008[289]	2002	None	<12	Not reported	Not reported	No	No	Yes
	Lee 2003[290]	1999	Recent arrival in Hong Kong from China	3[b]	Malaise	36	Yes	No	No

TABLE 29. (Continued)

Transplanted organ	Reference	Year of transplant	Donor risk factors	Time from transplantation to diagnosis, mo	Presenting symptoms	Follow-up interval, mo	Drug resistant	Recipient died at end of follow-up	Treated for rejection during follow-up
	Shitrit 2004[291]	1999	Close family contact with TB	2.5[b]	Fever, cough	18	No	No	No
	Schulman 1997[292]	1997	None	3	Fever	Not reported	No	No	Yes
	Miller 1995[293]	1993	None	3	Shoulder pain	3	No	Yes (week 12)	Yes
	Ridgeway 1996[294]	1993	None	1.5	Fever	Not reported	No	No	No
	Carlsen 1990[295]	1990	Not reported	5	Dyspnea	6	No	Yes (week 31)	Yes
Pancreas	No reports								

[a] Death was from causes unrelated to *M. tuberculosis* infection.
[b] Case of possible transmission—no pathology confirming the presence of tuberculosis in the donor, but donor risk profile and the timing of symptom onset in the recipient strongly suggest donor-derived transmission.
TB, tuberculosis; BAL, bronchoalveolar lavage.

history: in a recent Australian case of donor-derived tuberculosis in a lung transplant recipient, further investigation into the donor revealed a history of latent tuberculosis 5 years before death, which had been treated with 9 months of preventive isoniazid therapy despite the index case demonstrating *M. tuberculosis* resistance to isoniazid.[16]

A retrospective Spanish study of deceased donors used between January 1998 and June 2011 found that, of 11 deceased organ donors with active *M. tuberculosis* infection at the time of transplantation, tuberculosis was transmitted to the recipients in 2 cases (transmission rate of 18.2%).[275] The risk of tuberculosis is greater for lung transplant recipients than for recipients of other organs. Of cases of unexpected donor-derived *M. tuberculosis* transmission identified from the published literature, 15 (52%) of 29 were in single or bilateral lung transplant recipients. Moreover, in several cases of donor-derived *M. tuberculosis* transmission to lung recipients, it was reported that none of the same-donor organ recipients developed evidence of tuberculosis after several months of observation.[285,286] Based on a literature review of donor-derived tuberculosis in lung transplant recipients reported by Mortensen et al in 2014, the median time to tuberculosis diagnosis was 88.5 days (range, 21–153 days).[286] The most common presenting symptoms among reported cases were fever and dyspnea; however, in a large proportion of cases (>30%) *M. tuberculosis* was detected by protocol acid-fast bacilli smear or culture of respiratory specimens before the onset of symptoms (in these cases the median time to diagnosis was 68.5 days).[286] Of the identified cases of donor-derived tuberculosis in lung transplant recipients, 3 (20%) of 15 were fatal. Another lung recipient died from causes unrelated to tuberculosis.[286]

In recipients of nonlung organs, *M. tuberculosis* infection is more likely to present as extrapulmonary disease that is frequently difficult to diagnose. The most common presenting symptom is fever, though some patients may also experience nausea, cough, headache or a deterioration of renal function (see Table 29). Of the reported cases of donor-derived tuberculosis in kidney transplant recipients, 3 (27%) of 11 were fatal, with 1 additional death from unrelated causes.

Recipient Management and Outcomes

Table 30 summarizes the 2012 recommendations of the Donor-Derived Infections Consensus Conference on *M. tuberculosis* with regard to clinical management of solid organ transplant recipients under different deceased donor scenarios. In summary, potential donors with a history of tuberculosis may be considered on a case-by-case basis only if they have received active treatment for at least 6 months. Donors with latent tuberculosis need active tuberculosis to be ruled out as far as possible and may be considered on a case-by-case basis with ongoing surveillance for the appearance of tuberculosis in the recipient and consideration of recipient tuberculosis prophylaxis. Prophylaxis should also be considered where the donor has a history of latent tuberculosis that has not been sufficiently treated or in the circumstance of unexplained pulmonary apical fibrosis in the donor without cavitation and without additional testing.[277] At this time, IGRA testing in donors is not suggested. Active tuberculosis in the donor needs to be considered and investigated based on clinical and epidemiological features and the decision to proceed to

TABLE 30.

Recommendations for clinical management of recipients under different scenarios of tuberculosis risk—deceased donors[277]

Clinical scenario	Treatment history	Risk for transmission	Recommendations for deceased donor transplant recipients
Latent tuberculosis			
History of tuberculosis exposure or significant risk factors for tuberculosis, not tested		Variable	Insufficient data, monitor clinically
History of latent tuberculosis	Treated effectively	Low	Monitor recipient clinically
	Treated insufficiently, not treated, or treatment details unclear OR new diagnosis of latent tuberculosis*	Moderate	Monitor recipient clinically, consider chemoprophylaxis of recipient with clinical monitoring. Recommend chemoprophylaxis for lung transplant recipient
Unexplained pulmonary apical fibrosis in donor without cavitation and without additional testing		Variable	Consider testing donor—if tests are pending, consider whether donor is high or low risk for tuberculosis before deciding whether to proceed. If all definitive tests for tuberculosis are negative, accept as organ donor but consider other possible causes of apical fibrosis (endemic mycoses, malignancy etc). Consider chemoprophylaxis and/or clinical monitoring in higher-risk tuberculosis donors
History of active tuberculosis			
History of active tuberculosis, site of infection remote from the organ to be transplanted (ie, pulmonary tuberculosis in a kidney donor)	Treated appropriately over 2 years ago	Low to moderate	Monitor recipient clinically, consider cultures of previous tuberculosis sites if possible. Verify adequate treatment. May consider tuberculosis prophylaxis of recipient
	Treated appropriately within the past 2 years	Low to moderate	Monitor recipient clinically, consider cultures of previous tuberculosis sites if possible. Consider chemoprophylaxis of recipient, particularly if adequacy of prior donor treatment cannot be verified
	Treated insufficiently and/or with other than standard regimen	High	Monitor clinically, recommend chemoprophylaxis (as per national guidelines), recommend cultures of previous tuberculosis sites, consult ID specialist
History of active tuberculosis, same site as transplant (ie, renal tuberculosis in a kidney donor)	Treated appropriately	Moderate	Verify treatment, monitor clinically, recommend chemoprophylaxis for recipient (as per local guidelines), recommend cultures of previous tuberculosis sites, consult with ID specialist (NB organ should be carefully evaluated for function, as tuberculosis lesions may result in scarring and be inappropriate for transplant)
	Treated insufficiently and/or with nonstandard treatment	High	Recommend rejecting, in dire circumstances accept and treat recipient for active tuberculosis with informed consent and involvement of ID specialist
Active tuberculosis—microbiologic or pathologic diagnosis			
Active tuberculosis at the time of proposed donation OR positive tuberculosis culture or positive NAT recognized pretransplant		High	Strongly recommend rejecting, particularly if tuberculosis is in the same site as the transplant organ. In dire circumstances accept and treat recipient for active tuberculosis with informed consent and involvement of ID specialist
Findings consistent with possible active tuberculosis but no special cultures or NAT available pretransplant		High	Recommend rejecting, in dire circumstances accept and treat recipient for active tuberculosis with informed consent and involvement of infectious disease specialist. Strongly recommend additional testing of donor, consider including IGRA, biopsy of affected organ can be taken for pathologic examination and NAT during organ procurement. Decision regarding recipient treatment vs chemoprophylaxis will depend on final outcome of donor cultures.
Positive acid-fast bacilli stain, NAT or tuberculosis culture, only known posttransplant		High	Treat recipient for active tuberculosis, and report test results to the OPO immediately; consult with an ID specialist
Findings consistent with tuberculosis but no cultures available, data only known posttransplant		High	Favor treating recipient for active tuberculosis. Pursue molecular testing where possible, consult with an infectious disease specialist

NAT, nucleic acid testing; IGRA, interferon-gamma release assays; OPO, organ procurement organization.

organ transplantation based on the likelihood of active tuberculosis, the results of rapid tests (AFB microscopy and NAT testing from donor samples), and the likelihood of the recipient receiving another donor offer. The location of the infection in the donor is also relevant to the decision to proceed with transplantation and subsequent recipient management,

as risk of transmission is lower when the donor infection is at a site other than the allograft (ie, pulmonary tuberculosis in a kidney donor). If donation proceeds, there should be ongoing surveillance for tuberculosis in the recipient and consideration of recipient tuberculosis prophylaxis.

Treatment protocols are informed by drug susceptibility, local drug resistance patterns, and possible drug interactions with immunosuppressant medications (particularly rifampin/rifampicin and rifabutin). A recent systematic review assessed the benefits and harms of antibiotic prophylaxis to prevent tuberculosis in solid organ transplantation, concluding that prophylactic administration of isoniazid reduced the risk of developing tuberculosis posttransplant by more than half (risk ratio (RR), 0.35; 95% confidence interval [CI], 0.14–0.89).[296] There was, however, no significant on all-cause mortality (RR, 1.39; 95% CI, 0.70–2.78), whereas the risk of liver damage was significantly increased (RR, 2.74; 95% CI, 1.22–6.17). The 3 primary studies included in this systematic review were conducted in India and Pakistan—countries with a high prevalence of tuberculosis—therefore, there remains an absence of evidence regarding the benefits and harms of tuberculosis chemoprophylaxis for transplant recipients in area of low tuberculosis prevalence.

When donor-derived, reactivated, or de novo *M. tuberculosis* infection is suspected in solid organ transplant recipients, clinicians will need to test for disease in the graft as well as other sites, using microscopy, NAT, radiology, pathology (acid-fast bacilli stains), as well as clinical judgment.[277] Notably, the tuberculin skin test and IGRAs have poor sensitivity in immunosuppressed persons after solid-organ transplantation, and in any case are not recommended tests in the diagnosis of active tuberculosis.

Multidrug-resistant Bacteria

Epidemiology

In cases where bacterial infections are transferred from donor to recipient, these cases frequently involve resistant bacteria—in particular MRSA, VRE, and multidrug-resistant Gram-negative rods—that were not cleared by standard antibiotic prophylaxis.

Staphylococcus aureus

Staphylococcus aureus is common in hospital environments, and potential donors may become infected with a resistant strain while in the intensive care unit (ICU). The Australian Group on Antimicrobial Resistance (AGAR) has conducted antimicrobial resistance surveillance since 1986, and surveillance among hospital inpatients since 2005. Laboratories participating in the surveillance network collect *S. aureus* isolates from hospital inpatients and test then for antimicrobial susceptibility. Epidemiological typing is then performed for isolates identified as MRSA. These surveys have shown a substantial burden of MRSA in Australian hospitals overall, with significant interstate variation in the proportion *S. aureus* isolates that were MRSA and in the specific MRSA clones circulating in a given region.

In 2011, the proportion of *S. aureus* isolates that were MRSA was 30.3% nationwide, ranging from 19.9% in Western Australia to 36.8% in New South Wales/ACT.[297] There was wide variation between institutions in the proportion of *S. aureus* that was MRSA, from 7% to 56%.[297] The overall proportion of *S. aureus* isolates that were identified as

healthcare-associated MRSA was 18.2%, ranging from 4.5% in Western Australia to 28.0% in New South Wales/ACT. In 2011, the predominant hospital-acquired MRSA clone in Australia was ST22-IV [2B] (EMRSA-15), although there was significant interstate variation in the circulating clones and in their susceptibility profile.[297]

Based on the 2011 AGAR survey data, resistance to the non–β-lactam antimicrobials was common in MRSA isolates, with the exception of fusidic acid, rifampicin, mupirocin, daptomycin, vancomycin and linezolid (resistance levels below 4% nationally). Ceftaroline is also expected to be active.

More recently, the Staphylococcal Sepsis Outcome Program looked at the proportion of *S. aureus* bacteremia isolates in Australia that are antimicrobial resistant, reporting that 18.8% of *S. aureus* bacteremia cases were MRSA—a high relatively high proportion compared with several European countries.[298]

Enterococcus

Enterococci are among the leading causes of bacteremia, and are intrinsically resistant to a broad range of antimicrobials. Moreover, their ability to acquire resistance through plasmid transfer and transposons has allowed them to rapidly evolve additional resistance in the hospital environment. Although historically enterococcal infections were primarily caused by *Enterococcus faecalis*, there has been a worldwide increase in nosocomial infections with *Enterococcus faecium*, which not only is innately resistant to many classes of antibiotics but also extremely good at evolving new antimicrobial resistances.[299]

AGAR commenced the Australian Enterococcal Sepsis Outcome Program (AESOP) in 2011 for the surveillance of *E. faecalis* and *E. faecium* bacteremia and to monitor evolving patterns of antimicrobial susceptibility. Of the enterococcal bacteremia cases identified by AESOP in 2014, 54.9% of isolates were *E. faecalis* and 39.9% were *E. faecium*. Of the *E. faecalis* bacteremia cases, 36.5% were hospital-acquired; however, of the *E. faecium* cases, 71.8% were hospital-acquired.[299] For *E. faecalis*, acquired resistance was rare with the exceptions of erythromycin (87.4%), tetracycline (72.5%), ciprofloxacin (25.6%), and high-level gentamicin (38.2%). In contrast, the majority of *E. faecium* isolates were nonsusceptible to multiple antimicrobials, including ampicillin (90%), erythromycin (95%), tetracycline (53%), ciprofloxacin (92%), nitrofurantoin (77%), and high-level gentamicin (62%), and 46.1% were nonsusceptible to vancomycin.[299] By comparison, the population-weighted mean percentage of *E. faecium* resistant to vancomycin in Europe is 9% (ranging from 0% in Sweden, to 43% in Ireland).

Thus, not only is *E. faecium* a frequent cause of bacteremia in Australia, the proportion of *E. faecium* that is resistant to vancomycin is high by international standards.[299] Vancomycin resistance is usually acquired through the acquisition of either the vanA or vanB operon. The first VRE case detected in Australasia occurred in 1994 in a liver transplant patient at Austin Health in Melbourne.[300] Although this first case was a vanA-positive *E. faecium*, the majority of VRE subsequently detected between 1994 and 2011 was vanB.[300,301] In late 2013, however, a shift from vanB to vanA *E. faecium* occurred across Australia.[301] In contrast to the vanB gene, which usually integrates into the *E. faecium* chromosome, the vanA gene is often located on a plasmid, permitting easy

horizontal transfer of resistance.[302] In certain centers dramatic shifts occurred, with vanA almost entirely replacing vanB between 2013 and 2014.[301] A retrospective molecular epidemiological study of VRE among patients admitted to the ICU of Royal Prince Alfred Hospital, Sydney, between January and November 2014 confirmed an increasing incidence of VRE, attributed to multiple concurrent clonal outbreaks of vanA VRE, with reusable medical equipment demonstrated to be an important source of infection.[302] Of 1729 patients admitted over the study period, 5.3% were colonized with VRE on admission (60% with vanB, 39% with vanA, and 1% with both). VRE acquisition rates in the ICU rose from 3.1 per 1000 patient days in 2013 to 7.0 per 1000 patient days in 2014, driven by an increase in vanA acquisition. Overall, 3.6% of patients acquired VRE during their stay in the ICU: 55% acquired vanA VRE, and 45% acquired vanB.[302] The emergence of vanA VRE in Australian hospitals will likely lead to a larger overall burden of VRE in Australia and New Zealand.[302] Recently, the rapid dissemination of novel clone of vanB VRE (ST796) was also reported, first recognized at Austin Health at the beginning of 2012, then almost simultaneously appearing in Auckland, then appearing in South Australia, Tasmania and then New South Wales.[300]

Drug-resistant Gram-negative Bacilli

AGAR has been monitoring sepsis due to *E. coli* and Klebsiella since 1992, with the addition of *Enterobacter* species to the surveillance program in 2004. The 2014 survey reported moderately high levels of ampicillin/amoxicillin resistance in *E. coli* isolates (50%), with lower rates of resistance to amoxicillin-clavulanate (8%).[303] Moderate levels of resistance were found in *E. coli* isolates toward cefazolin (21%) and trimethoprim (29%). Multiresistance is on the rise, particularly in *E. coli* and *E. cloacae* isolates, with multiresistance rates of 13% and 12% respectively. Also of concern: approximately 25% of *E. coli* isolates belonged to the ST131 H30-Rx subclone, which is associated with greater antibiotic resistance and greater virulence.

Klebsiella pneumoniae isolates had higher levels of resistance to piperacillin-tazobactam and ceftazidime compared with *E. coli*, but lower rates of resistance to amoxicillin-clavulanate, ticarcillin-clavulanate, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim.

Among *Enterobacter* species, resistance was common to ticarcillin-clavulanate, piperacillin-tazobactam, ceftriaxone, ceftazidime and trimethoprim. Cefepime, ciprofloxacin, and gentamicin resistance, however, were all less than 10%. In 2014, a total of 14 isolates from 14 patients in 9 institutions across 5 Australian states and territories were found to have a carbapenemase gene. Thus, carbapenem resistance attributable to acquired carbapenemases currently remains uncommon in Australia, although 5 difference gene variants were detected in 2014 (IMP, KPC, VIM, NDM, and OXA-181–like).[303]

Compared with other countries in the region, resistance rates in Gram-negative bacteria in Australia are relatively low, but are similar to those observed in Western Europe.[304,305]

Transmission and Recipient Outcomes

With the rise of multidrug-resistant bacteria in hospital environments, an increasing number of potential donors are being exposed to multidrug-resistant bacteria in the ICU, which may then be transmitted to recipients by organ transplantation. Of particular concern are VRE, multiresistant *Pseudomonas aeruginosa*, ESBL-producing enterobacteriaceae, carbapenem-resistant *Acinetobacter baumannii*, *K. pneumoniae*, and other carbapenem-resistant enterobacteriaceae.[5] Lanini et al[306] have described the incidence of carbapenem-resistant Gram-negative bacteria in Italian transplant recipients, reporting 0.63 isolates of carbapenem-resistant Gram-negative bacteria per 1000 recipient days (49 isolates from 887 recipients), and that carbapenem resistance was most frequent among *Klebsiella* spp. isolates (49%). Rates of nosocomial carbapenem-resistant bacterial infection are likely to be higher in Italy than in Australia and New Zealand, given that carbapenemase-producing Enterobacteriaceae are endemic in Italy and are regularly isolated from patients in most hospitals.[307] This study also reported that mortality was 10.23 times higher in recipients who had cultures positive for carbapenem-resistant Gram-negative bacteria after solid organ transplantation compared to those who did not.[306]

Donor-related risk factors for infection or colonization by multidrug-resistant bacteria include prolonged hospital stay (7 days or longer), vasopressor use, and requirement for cardiopulmonary resuscitation or abdominal packing.[308,309] However, the absence of these risk factors does not preclude nosocomial infection/colonization with multidrug-resistant bacteria, as was demonstrated in a case of carbapenem-resistant *A. baumannii* transmission from a donor with a hospital stay of only 2 days.[310] In addition, donor country of origin/prior residence is also a potential risk factor: donors from countries with high rates of gut colonization of multidrug-resistant bacteria such as India pose a higher risk of transmission (personal communication L Grayson).

Donor-derived Transmission of Carbapenem-resistant Gram-negative Bacteria

In an Italian study of the incidence and outcomes of transplantation using organs from donors with unknown carbapenem-resistant Gram-negative bacterial infection, 10.5% of organ donors were discovered posttransplant to be infected or colonized with carbapenem-resistant Gram-negative bacteria, with proven transmission to the organ recipient in 13% (4 of 30) of affected transplants.[311] The recipients in whom transmission did occur all received antibiotic therapy that was late, short, or inappropriate. There was also a higher risk of transmission where the donors were bacteremic and the donor organ was culture-positive. The first 2 transmission cases involved a donor who died of cerebrovascular accident after 4 days in the ICU and developed a fever after brain death; the day after organ transplantation the donor's blood cultures became positive for carbapenem-resistant *K. pneumoniae*. Liver, lungs, and pancreas were donated to 4 recipients. The recipient of an extended right graft of the donor liver received preemptive treatment with meropenem alone for 3 days, starting on day 4 posttransplant. On day 7, samples from abdominal drainage fluid were sent for microbiological testing and cultures were positive for carbapenem-resistant *K. pneumoniae*. The patient was treated with colistin and tigecycline, and the infection was resolved by day 37 posttransplant. The lung recipient was commenced on meropenem alone on day 2 posttransplant; on day 10, cultures from BAL grew carbapenem-resistant *K. pneumonia* and colistin was added to the treatment for 14 days. The patient did not develop infection, but was found

to be colonized by carbapenem-resistant *K pneumoniae* initially in the lung and later in the rectum.[311]

The third case identified by the Italian study involved a donor who had experienced several episodes of fever while in the ICU and was found to be positive for carbapenem-resistant *K. pneumoniae* after organ retrieval and transplantation. The kidney recipient, who received a full, targeted antibiotic treatment regimen (gentamicin and meropenem for 8 days), remained negative for carbapenem-resistant *K. pneumoniae*; however, the liver recipient, who received only 3 days of full antibiotic treatment (gentamicin and meropenem), developed leukocytosis, pleural effusion and an intra-abdominal collection on day 12 posttransplant.[311] On day 24, the liver recipient developed fever and infection of the abdominal wound; cultures from the wound swabs grew carbapenem-resistant *K. pneumoniae*. The wound infection was treated with a few days of oral antibiotics, and on day 60, abdominal ultrasound revealed a per-hepatic collection that had to be drained, with the fluid culture testing positive for carbapenem-resistant *K. pneumoniae*. After complete drainage and antibiotic treatment, the infection was resolved, and the patient was alive and well 18 months posttransplant.

The forth transmission case in this series involved a donor who had been admitted to the ICU for septic cerebral embolization from a methicillin-susceptible *S. aureus* driveline infection and bacteremia, who subsequently died from cerebral hemorrhage. Known to be a rectal carrier of carbapenem-resistant *K. pneumoniae*, urine cultures turned positive 2 days after retrieval; however, this information was not properly communicated.[311] One recipient received both kidneys, and on posttransplant day 15 he was readmitted to hospital due to high-grade fever which was confirmed to be due to carbapenem-resistant *K. pneumoniae* infection of the graft. The patient was treated with meropenem+colistin+tigecyline but blood cultures remained positive so the antibiotic regimen was changed to ertapenem+meropenem+colistin. Despite an initial response, bacteremia returned, and the patient died 2 months later due to persistent carbapenem-resistant *K. pneumoniae* infection of the graft.[311]

In a case reported from Israel, a donor who was an asymptomatic carrier of carbapenem-resistant *K. pneumoniae* in the respiratory tract donated kidneys, liver, and lungs to 5 recipients.[312] The donor had been admitted to hospital in a deep coma after a near drowning. After 5 days on mechanical ventilation, he was declared brain dead. Routine BAL taken at the time of organ donation grew carbapenem-resistant *K. pneumoniae* 2 days after transplantation had taken place, with antibiotic sensitivity limited to gentamicin, colistin, and tigecycline. The recipient of the liver and the 2 kidney recipients did not receive postoperative antibiotic treatment, and none developed infectious complications. The 2 lung recipients both received perioperative antibiotic prophylaxis with piperacillin-tazobactam, and after the donor culture results, both received IV colistin for 5 days. One of the lung recipients developed pneumonia 2 weeks after transplantation; *Proteus mirabilis* was cultured from sputum samples, and after treatment with IV colistin and ciprofloxacin the patient made a full recovery. The second lung recipient was receiving a second transplant due to cystic fibrosis. On day 19 posttransplant, the patient developed tachypnea and dyspnea, and a new infiltrate in the transplanted lung was revealed by radiography. Given the results of donor cultures, the initial empiric antibiotic therapy with piperacillin-tazobactam was changed to colistin and tigecycline; however, the patient continued to deteriorate. One week later, the patient was hypotensive and oliguric, with decreased consciousness. At this time, blood cultures were positive for carbapenem-resistant *K. pneumoniae*, with antibiotic sensitivity profile the same as the donor. Treatment was unsuccessful and the patient died 4 weeks later.

In a 2007 case of carbapenem-resistant *A.baumannii* transmission from a donor to a lung recipient in Brazil, the donor had been in the hospital for only 2 days before procurement, with partial pressure of oxygen/fraction of inspired oxygen greater than 300, normal chest x-ray, and no evidence of bronchial aspiration by bronchoscopy.[310] Perioperative antimicrobial prophylaxis consisted of vancomycin plus cefepime. On day 2 posttransplant, the recipient developed fever, arterial hypotension, and respiratory failure, with a chest x-ray revealing an infiltrate in the lower third of the right hemithorax. The patient was reintubated and norepinephrine infusion was started, and meropenem substituted for cefepime. On the same day, the results of the donor's BAL culture became available, yielding *A. baumannii* susceptible to ampicillin-sulbactam, meropenem, imipenem, and amikacin; the result for carbapenems was, however, incorrect. Although the recipient's lung function improved, she remained febrile and wound site infection was noted. On day 9 posttransplant, carbapenem-resistant *A. baumannii* was isolated from the recipient's BAL and from the surgical wound specimen, and IV polymyxin B was substituted for meropenem, and tacrolimus dosage was reduced. By day 29 posttransplant, the patient's serum creatinine had risen to 2.1 mg/dL and the decision was made to stop polymyxin B therapy. Serum creatinine level returned to baseline; however, on day 46, the patient presented with pneumonia and recurrence of infection at the surgical wound; a transbronchial lung biopsy showed coexistence of CMV pneumonia. Resumption of polymyxin B together with inhaled amikacin produced transient improvement, but the fever returned and respiratory function progressively worsened. Empiric amphotericin B therapy was started on day 57 and immunosuppression stopped on day 61; however, the patient died on day 65 posttransplant.

Donor-derived Transmission of Other Multidrug-resistant Bacteria

Deceased donors who have undergone traumatic injury requiring abdominal packing to control major hemorrhage are at particularly high risk of nosocomial infection with bacterial or fungal pathogens, including multidrug-resistant bacteria. In a case report published in 2012, a 21-year-old man with a gunshot wound to his abdomen underwent damage control laparotomy and abdominal packing, but subsequently deteriorated and was declared brain-dead 3 days after admission.[309] He donated organs to 4 separate recipients; all 4 of whom subsequently developed infections with MDR *P. aeruginosa*. The donor had received piperacillin-tazobactam and fluconazole before the laparotomy and packing, and at the time of organ procurement showed no signs of active infection. Blood, urine, and wound cultures from swabs taken the day before procurement were all negative. Nonetheless, preprocurement broad-spectrum empiric antibiotics (vancomycin, piperacillin-tazobactam and fluconazole) were

administered, and during the procurement surgery the donor was checked for and cleared of any signs of intra-abdominal infection.

Despite these precautions, the day after transplantation cultures from peritoneal swabs obtained during procurement was positive for Gram-negative rods. The relevant transplant centers were contacted, and imipenem or meropenem were added to the regimens of the recipients. On the fourth day after transplantation, the pathogen isolated from the donor was confirmed to be MDR *P. aeruginosa*, with resistance to extended spectrum penicillins, ceftazidime, fluoroquinolones, and tobramycin.[309]

The heart recipient was hospitalized for dyspnea approximately 6 weeks posttransplant and was found to have a loculated right pleural effusion requiring tube thoracostomy. Culture of the drained fluid showed presence of *P. aeruginosa* with the same resistance pattern as observed in the donor. After treatment with IV meropenem for 2 weeks, the patient recovered well and had no further MDR infections. The liver recipient experienced coagulopathy at the time of transplantation and required vasopressor support due to persistent hypotension and low systemic vascular resistance. On day 8 posttransplant, a hepatojejunostomy leak was discovered requiring debridement and reconstruction, and intraoperative abdominal cultures taken at this time grew MDR *P. aeruginosa* and vancomycin-resistant *E. faecalis*. The patient progressed to multiple organ dysfunction syndrome and died on day 38 posttransplant. The recipient of the first kidney developed purulent drainage at the incision site approximately 2 weeks posttransplant, and ultrasound revealed a complex subcutaneous collection requiring the wound to be opened and treated. Cultures from the abdominal wound grew MDR *P. aeruginosa* and vancomycin-resistant *E. faecalis*. The patient was due to be discharged; however, it was discovered that asystolic and resuscitation was not successful. A postmortem showed multiple fresh thromboemboli in the left pulmonary artery. The recipient of the second kidney had positive perioperative blood cultures for MDR *P. aeruginosa* and vancomycin-resistant *E. faecalis*, and subsequently developed a perinephric collection requiring percutaneous drainage. The patient was discharged with home IV polymixin and amikacin, but no further follow up information was available.

In a second case report of MDR *P. aeruginosa* transmission, the donor was admitted to the ICU for intracranial bleeding, and 6 days later, developed bilateral pneumonia with cultures showing presence of *P. aeruginosa*.[313] Meropenem was administered, and 11 days later endotracheal, blood, and urine cultures were all negative. The donor then deteriorated, and died from severe intracranial hypertension 18 days after ICU admission. Both kidneys were retrieved and transplanted into 2 recipients who were given prophylaxis consisting of cefotaxime, amphotericin B, and trimethoprim-sulfamethoxazole; *P. aeruginosa*–specific antibiotics were not administered. MDR *P. aeruginosa* was detected in both recipients approximately 1 week posttransplant, and both recipients died within 2 weeks of transplantation from massive hemorrhage as a result of arterial anastomotic rupture.[313]

In a third case of donor-derived MDR *P. aeruginosa* infection, the donor was a 21-year-old male gunshot victim who died after a prolonged hospital course.[314] The donor had developed pulmonary infiltrates and before procurement a

bronchoscopy was performed. Cultures from the BAL grew MDR *P. aeruginosa*; however, results were not available at the time of organ procurement. Urine and peritoneal cultures taken during procurement also grew MDR *P. aeruginosa* 3 days after organ retrieval, at which point the recipients of the donors organs were informed. The recipient of one of the kidneys died from pseudomal infection shortly after; however, the recipient of the second kidney was successfully treated with 6 weeks of polymyxin B and amikacin, consistent with the drug susceptibility profile of the isolated bacteria, and 1 year later was alive with normal kidney function. The heart recipient did not develop infection and the liver recipient died from complications of the transplant surgery.

These cases highlight the risk of transmission of multidrug-resistant pathogens from donors with undetected nosocomial infections and also from donors with traumatic injuries involving major blood loss and abdominal packing. In open-abdominal cases, the injuries sustained typically require significant volume and blood product replacement, which may result in a washout effect of prophylactic antibiotics and ineffective antibiotic coverage, leaving the potential donor susceptible to infection with multidrug-resistant bacteria.[309] Alternatively, antibiotic therapy may reduce the bacterial load to a level that is undetectable by standard culture protocols but is still able to transmit infection to an immunosuppressed individual.[313] Negative cultures before organ retrieval and the absence of physical evidence of infection do not rule out the presence of pathogens capable of transmitting infection: in the 2 cases above, the donor received appropriate antibiotic therapy, cultures were negative, and there was no evidence infection at the time of organ retrieval. In cases of traumatic injury, the type of packing used and its duration may further increase the risk of nosocomial infection, abscess formation, and/or sepsis in the potential donor.[315,316] Temporary VAC closure for example may be associated with lower risk of infection than intra-abdominal packing with lap sponges or towel clip closure.[315,317]

Methicillin-resistant *S. aureus* is another drug-resistant organism that has been transmitted by solid organ transplantation. In a 2012 case, the donor—who had a history of IVDU—was admitted to the emergency department after 2 days of progressive confusion and somnolence.[318] He was minimally responsive and had a fever, and was treated with broad-spectrum antimicrobial therapy for presumed bacterial meningitis. A CT scan showed a large right parietal intracranial hemorrhage, and within 24 hours the donor was declared brain dead. Peripheral blood cultures taken during the emergency department evaluation revealed the presence of MRSA, and by the time of organ donation 36 hours after brain death, the donor had been treated with vancomycin and had remained afebrile for 48 hours. Lungs, kidneys, pancreas, and liver were recovered and transplanted into 4 recipients. The kidney and pancreas recipients received 5 doses of vancomycin prophylaxis posttransplant and subsequently showed no signs of MRSA infection. The liver recipient was receiving daptomycin 4 mg/kg for cellulitis at the time of transplantation; however, MRSA growth was observed on blood cultures collected 3 hours after transplantation. Daptomycin was continued at 6 mg/kg for 14 days, after which blood cultures were negative for MRSA. However, on day 58 posttransplant, the patient was readmitted with fever and chills. Blood cultures were positive for MRSA, and a

6-week course of vancomycin was initiated, after which symptoms resolved. The lung recipient was initiated on vancomycin therapy at the time of transplantation given the donor history; however, blood cultures collected 6 days posttransplant revealed MRSA growth. Despite continued appropriate antibiotic therapy, MRSA continued to be detected on BAL cultures until 99 days posttransplant. Six months posttransplant, the patient was readmitted due to dyspnea on exertion, and a chest CT suggested extensive right-sided multifocal consolidation. Bronchoalveolar lavage cultures revealed MRSA, and vancomycin therapy was resumed for another 4 weeks, after which time symptoms resolved.

European guidelines recommend that organs from donors returning positive cultures for multidrug-resistant bacteria may be considered for transplantation in well-defined circumstances provided there is close recipient follow-up, unless the organ to be transplanted is itself colonized.[5]

At this time, it is uncertain whether organ donors should have enhanced microbiological screening for MDR bacteria, over and above what is standard practice in most ICUs. Routine rectal/fecal screening with results made available before transplantation should be considered where not already performed. If MDR bacteria are identified before transplantation, the risks are highest for the bacteremic donor or where the positive culture is taken from the organ that is to be transplanted: in these cases transplantation should be avoided. In all other circumstances, transplantation can be considered in consultation with an infectious diseases physician, provided that the recipient receives a course of active antimicrobials.

Recipient Management

Directed antimicrobial prophylaxis in recipients has been shown to be effective in preventing transmission of multidrug-resistant Gram-negative pathogens.[312,319] In a case report from the United States, Ariza-Heredia et al[319] describe the use of organs from a donor known to be infected with carbapenem-resistant *K. pneumoniae* before organ procurement. The donor was a 21-year-old man who sustained multiple injuries in a motor vehicle accident and was hospitalized for approximately 3 weeks before being declared brain dead. He developed pneumonia during treatment, an infected subdural hematoma, and meningitis due to carbapenem-resistant *K. pneumoniae*, although blood cultures remained negative. The donor was treated with IV tigecycline for 9 days and received 3 doses of intrathecal gentamicin at the time of death. As cultures were still positive for carbapenem-resistant *K. pneumoniae* at the time of death, the transplant teams were informed and specific consent sought from the potential recipients and their families. The liver, kidneys, heart, and a vein graft were retrieved. The recipient of the right kidney received pretransplant doses of IV gentamicin (4 mg/kg) and tigecycline (100 mg), and posttransplant received a 10-day course of IV tigecycline (50 mg every 12 hours). Surveillance cultures of the preservation fluid were negative, and 5 months posttransplant, the recipient was doing well. The heart recipient received perioperative IV cefepime (2 g every 12 hours) and tigecycline (100 mg loading does then 50 mg twice daily). Antimicrobial prophylaxis received posttransplant included valacyclovir, trimethoprim-sulfamethoxazole, and inhaled amphotericin B, and cultures remained negative for carbapenem-resistant *K. pneumoniae*.

The recipient of the liver and kidney in the case reported by Ariza-Heredia developed a postoperative infected hematoma and peritonitis due to carbapenem-resistant *K. pneumoniae*, despite receiving prophylaxis with IV tigecycline (initial loading dose of 100 mg, followed by 50 mg every 12 hours planned for 2 weeks).[319] On posttransplant day 10, the patient developed severe abdominal pain, tenderness and leukocytosis, and cultures of the ascetic fluid were positive for carbapenem-resistant *K. pneumoniae*. The patient underwent exploratory laparotomy and washout, and IV amikacin was added to the treatment regimen, along with ciprofloxacin for possible synergy, and fluconazole to treat a concurrent *Candida albicans* infection. On day 24, cultures were still positive for carbapenem-resistant *K. pneumoniae*, and the treatment regimen was changed to meropenem (1 g IV every 8 hours), amikacin (500 mg IV every 12 hourly), ampicillin (1 g IV every 6 hours), and fluconazole (200 mg p.o. daily) for 4 weeks. Five months posttransplantation, the recipient showed no recurrence of infection.

Source control is the first priority in the treatment of multidrug-resistant bacteria, including drainage of collections and the removal of any infected devices. The choice of antimicrobial treatment and dosage should take into account pathogen susceptibility profile and local resistance patterns, predicted drug levels at the site of the infection, cost, method of administration, side-effect profile, severity of infection, and any know multidrug-resistant colonizers in the recipient.[320] Treatment recommendations for multidrug-resistant gram-negative bacteria infections in solid organ transplant recipients are given in Table 31.

Treponema pallidum

Epidemiology

The number of cases of infectious syphilis reported in Australia in 2016 was 3367, of which 87% of diagnoses were in males and 16% were in ATSI persons.[37] In the non-Indigenous population, male-to-male sex is the primary transmission route, and over 90% of all notifications of infectious syphilis are in males (see Figure 13). In contrast, only 54% of infectious syphilis notifications in ATSIs in 2006 were in males. The infectious syphilis notification rate in Australia increased 107% from 2012 to 2016 (from 6.9 to 14.3 cases per 100 000), driven largely by increased transmission among MSM and by an ongoing outbreak of infectious syphilis among ATSI people living in northern Australia.[37,321] This outbreak began in northern Queensland in January 2011, spread to the Northern Territory in July 2013, and to the Kimberley region of Western Australia in June 2014.[321] An outbreak in the western, Eyre and far north regions of South Australia was declared in March 2017.[321] By 2016, the infectious syphilis notification rate in the ATSI population living in remote and very remote areas was 135.4 per 100 000—50.1 times higher than the rate in the non-Indigenous population.[37] Also of note, this outbreak has primarily affected young ATSI people—in 2016, 21% of infectious syphilis notifications in the ATSI population were in the 15- to 19-year age group, compared to only 2% of the non-Indigenous population.[37]

In New Zealand there has also been a steady increase in infectious syphilis cases since 2002, with a notable jump in notifications from 2013 to 2014 (from 82 to 140 cases).[322] As in Australia, the vast majority of cases (>90%) are in males,

TABLE 31.

Treatment recommendations for multidrug-resistant gram-negative bacteria infections in solid organ transplant recipients[320]

Pathogen	Recommendation	Evidence level
ESBL-producing *Enterobacteriaceae*	Carbapenems	I
	Alternative: cefepime or piperacillin/tazobactam (if susceptible and low inoculum infection)	III
Carbapenem-resistant *Enterobacteriaceae*	Systemic infections: individualized combination regimen with 2 or more of Colistin, Tigecycline, Aminoglycosides or high-dose prolonged-infusion carbapenems	II-3
	Uncomplicated UTI: oral fosfomycin or IV aminoglycosides	
MDR Acinetobacter	Carbapenems (except ertapenem) if susceptible	II-3
	If carbapenem resistant, consider combination therapy with Colistin, Ampicillin/sulbactam, tigecycline (if susceptible and no bloodstream or urinary infection), or rifampicin	
MDR *P. aeruginosa*	Individualized combination regimen with 2 or more of antipseudomonal beta-lactam (consider high doses of prolonged or continuous infusion), aminoglycoside, ciprofloxacin, adjunctive aerosolized colistin or tobramycin[a]	II-2
Pan-resistant *P. aeruginosa*	Individualized combination regimen with 3 or more of IV colistin, doripenem or another antipseudomonal beta-lactam, aminoglycosides, fosfomycin, rifampicin, adjunctive aerosolized colistin or tobramycin[a]	II-2
MDR *B. cepacia* complex	High-dose TMP/SMX	II-2
	Alternatives if susceptible: meropenem, ciprofloxacin	
Trimethoprim/sulfamethoxazole-resistant or pan-resistant *B. cepacia* complex	Combination therapy with meropenem, aminoglycoside, ceftazidime (or trimethoprim sulfamethoxazole)	II-2
MDR *A. xylosoxidans*	Combination therapy with piperacillin/tazobactam, carbapenems (except ertapenem), trimethoprim/sulfamethoxazole	III
MDR *S. maltophilia*	High-dose trimethoprim/sulfamethoxazole	II-2
	Alternatives: ticarcillin/clavulanate, moxifloxacin, doxycycline, tigecycline (consider combination therapy)	

[a] Ceftolozane-tazobactam has become an option since this article was published.

UTI, urinary tract infection.

and male-to-male sex is the primary transmission route (approximately 90% of cases). The majority ethnicity reported in MSM cases was NZ European (57% in 2014), followed by Asian (13%), Māori (13%), other (12%), and Pacific Islanders (3%).[322] Cases are concentrated among males aged 20 to 34 years, with the biggest increase in cases since 2011 occurring among males aged 20 to 24 years. The Auckland region reported the highest number of infectious syphilis notifications in 2014 (61% of the total).[322]

Donor Screening and Risk Minimization

Historically, syphilis screening has been based on nontreponemal serological tests—either the RPR or Venereal Disease Research Laboratory (VDRL) test—which are sensitive in newly infected individuals but can produce false-positive results due to factors such as other infections (eg, HIV), autoimmune conditions, injecting drug use, or other causes of inflammation or immunological reactivity. In a retrospective study of RPR-positive deceased donors, Theodoropoulos et al demonstrated a false-positive rate of 40.6% for RPR tests.[51] Treponemal-specific tests have greater specificity but continue to yield positive results after successful treatment.[323] The United States Centers for Disease Control specify that a diagnosis of syphilis requires positive results on both a nontreponemal test and a treponemal-specific test.[324] Treponemal-specific tests include FTA-ABS tests, the TP-PA) assay, various EIAs, chemiluminescence immunoassays, immunoblots, or rapid treponemal assays. Test performance characteristics of available syphilis tests, versus TP-PA as the gold standard, are given in Table 32.
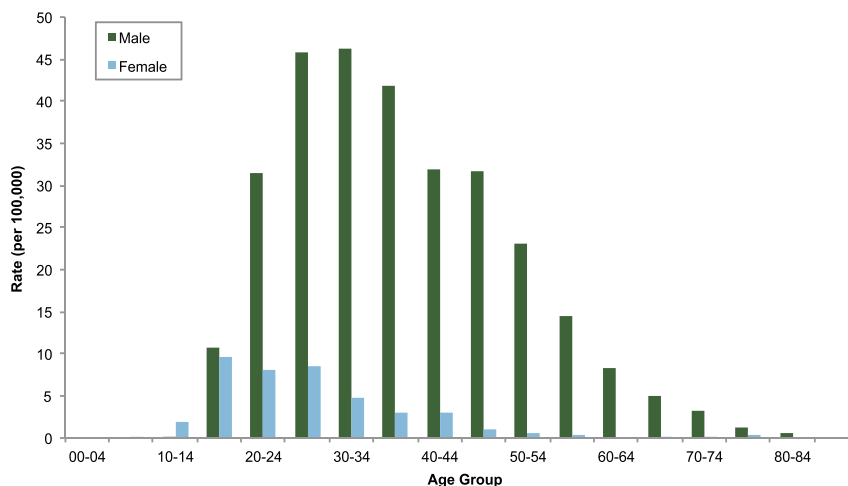
FIGURE 13. Age and sex distribution of the syphilis notification rate (syphilis of <2 years duration), in Australia in 2016 (Source: http://www9.health.gov.au/cda/source/cda-index.cfm).

TABLE 32.

Test performance characteristics of various syphilis tests as compared to TP-PA[51]

Test	Sensitivity	Specificity
RPR*	79.2% (95% CI, 57.8–92.8%)	81.2% (95% CI, 69.9–89.6%)
FTA-ABS	87.5% (95% CI, 67.6–97.2%)	84.1% (95% CI, 73.3–91.8%)
MHA-TP	91.7% (95% CI, 73.0–98.7%)	100% (95% CI, 94.7–100%)
CLIA	100% (95% CI, 85.6–100%)	100 (95% CI, 94.7–100%)

RPR, rapid plasma reagin; FTA, fluorescent treponemal antibody.

The conventional approach to screening has been to test first with a nontreponemal test and then confirm positive results with a treponemal-specific test, though more recently there has been a shift to a "reverse-sequence" approach, whereby an initial treponemal-specific test is followed by a nontreponemal test to confirm positive results.[51] Current international guidelines and state-based guidelines in Australia recommend routine screening of deceased donors for syphilis infection using a treponemal-specific EIA, with confirmation by a nontreponemal serological test. If the nontreponemal test is negative, then a second treponemal test based on different antigens to the original test should be performed. This reverse sequence approach has the advantage of being able to distinguish potential donors who have been previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with a false-positive result.[324] Treponemal test results should be interpreted in the context of what is known about the donor's history of treatment for syphilis and their sexual history, because there is always the possibility that previously treated persons may have a new, recently reacquired syphilis infection.

A positive syphilis test does not necessarily preclude organ donation; however, newly diagnosed syphilis indicates that the donor is also at increased risk of having recently acquired HIV, HBV, or HCV, and decisions regarding utilization should be made accordingly.[51] If the decision is made to proceed with transplantation, then the recipient will require appropriate treatment.

Transmission Risk and Recipient Management

Only 4 cases of syphilis transmission via organ donation have been reported—1 confirmed transmission reported to the United States OPTN, and 3 reports in the published literature.[1,325,326] In a 2003 case, a homosexual male with a history of treated syphilis donated kidneys to 2 recipients.[325] Donor syphilis serology, available only after transplantation had taken place, was reactive on TP-PA (titer, 1:1280) and RPR (titer, 1:2), which was interpreted as consistent with a history of treated infection. The 2 recipients were informed and were administered a single dose of 2.4 g IV benzyl penicillin instead of the recommended benzathine penicillin 2.4 MU administered intramuscularly. Recipient serum samples collected on day 5 posttransplant were reactive on treponemal EIA, and both recipients were then treated for early latent syphilis according to the 2002 UK guidelines. After 2 years of follow up, both recipients had excellent kidney function, and 3 monthly RPR tests remained negative.

In 2011, a 55-year-old woman underwent liver transplantation with a graft from a deceased donor whose medical history included schizophrenia and a 2-week history of ear infection, which progressed to meningitis precipitating brain death.[326]

Results of donor syphilis serology became available 24 hours after the transplant had taken place, and showed reactivity in the treponemal EIA with a negative VDRL test—consistent with latent syphilis infection. The recipient was immediately prescribed treatment for latent syphilis as recommended by UK national guidelines. Due to an allergy to penicillin, doxycycline 100 mg BID was introduced for 28 days. There was evidence of recipient seroconversion for syphilis at 1 month posttransplant; however, syphilis treatment was successful, and the patient was well with stable graft function at 9 months posttransplant.[326]

The fourth reported case of donor-derived syphilis transmission was in a lung transplant recipient whose donor, a 38-year-old woman who died of subarachnoid bleeding, returned serology test results indicating past syphilis infection 1 day after transplantation had occurred.[327] The recipient received penicillin G intravenously 3 times per day for 10 days, starting on day 1 posttransplant. Although immunoblot testing detected T. pallidum–specific newly synthesized IgG antibodies on day 29 posttransplant, the patient developed no clinical signs of syphilis infection, and by 3 months posttransplant, the T. pallidum hemagglutination titer had returned to negative. The recipient recovered well over long-term follow-up and graft function was normal.

In addition to these cases, there have been 4 cases of organ transplantation involving a syphilis-positive donor that did not result in transmission to the recipient after appropriate therapy.[328-331] Transplanted organs included kidney, heart, lung, and liver, and in each case, there was no evidence of infection in the recipients, who had all received treatment with benzathine penicillin G.[324] In the most recent of these cases, the EIA results showing that the donor was seropositive for syphilis were available only after transplantation had occurred.[331] Based on negative results on TP-PA and VDRL confirmatory testing, it was not possible to differentiate between treated syphilis and late syphilis, and the decision was made to treat the recipient. Three doses of benzathine penicillin 2.4 MU were administered intramuscularly weekly for 3 weeks, and repeated serology at regular intervals posttransplant showed that the recipient remained free of syphilis infection at 3 months posttransplant.

These case reports suggest that, where the donor is found to have latent syphilis, clinical manifestations of T. pallidum can be successfully prevented with treatment of the recipient. However, a donor with secondary syphilis may be bacteremic with the involvement of many organs; hence, caution should be taken if clinical manifestations of secondary syphilis are present. The treatment regime of the recipient should be discussed with an infectious diseases physician and may include use of benzathine or IV penicillin (P Boan, personal communication).

Bacteremia and Meningitis

There is substantial evidence that organs from bacteremic donors and donors with proven bacterial meningitis can be safely used for transplantation provided that the bacteria are confirmed to be susceptible to antibiotics and the donor and recipient receive appropriate treatment pretransplantation and posttransplantation.[5,332] However, it is not uncommon for bacteremia in the donor to be unrecognized until after transplantation has occurred: in 1 study, 60% of bacteremic donors were afebrile in the 24 hours before organ procurement.[333]

A retrospective study of organ donors in Spain found that 5% of liver and heart donors had bacteremia at the time of

organ donation (including recognized and unrecognized infections).[333] The most common microorganisms isolated from donors with bacteremia in were *S. aureus*, *E. faecalis*, *A. baumanni*, and *S. viridans*. There were no documented incidents of transmission of the isolated bacteria to recipients in this study nor was there evidence of any negative clinical impact on the outcomes of transplantation. The authors note, however, that bacteremic donors may not be safe in all circumstances, and their findings may in part be attributable to a degree of selection bias, whereby patients with positive blood cultures and evident sepsis were never considered as potential donors. It should also be noted that the risk of transmission varies according to the type of bacteria causing the infection—for example, Gram-negative bacilli (eg, *E. coli*) pose a greater risk than Gram-positive bacteria.[334] Given the high rates of graft loss, morbidity and mortality associated with transmission of bacteremia—especially in the case of infection caused by Gram-negative bacilli—susceptibility testing in the donor is important.[335]

Numerous other studies have demonstrated that transplant outcomes in recipients of organs from bacteremic donors are equivalent to outcomes from nonbacteremic donors, provided that the donor is treated with appropriate antibiotic therapy for at least 24 to 48 hours and shows some degree of clinical response (eg, improved white cell blood count, improved hemodynamics, defervescence), and tailored antibiotic treatment is initiated in the recipient in a timely manner.[49,332,335] Recipients should be treated with tailored antibiotic therapy for at least 7 days posttransplant, or longer if the organism is difficult to treat (eg, *S. aureus*) or if there is the potential for infection to disrupt an anastomosis or seed an endovascular source.[332] Based on existing evidence, no particular organ from a bacteremic donor is more likely to transmit infection to the recipient than another.[335]

There are also numerous published studies describing successful transplantation using organs from donors who died from microbiologically proven bacterial meningitis caused by *N. meningitidis*, *S. pneumoniae*, *Haemophilus influenzae*, and *E. coli*.[336-340] A contributing factor to the low rate of transmission of infection from donors with bacterial meningitis is that the most common meningeal organisms do not survive at the low temperatures maintained during cold perfusion and storage before transplantation.[336] Before organ acceptance, meningitis should be confirmed as the sole site of infection, and the donor should ideally receive 48 hours of appropriate treatment with evidence of clinical improvement before organ retrieval, although successful outcomes have been reported after only 24 hours of antibiotic therapy where blood cultures were negative on the day of donation.[337] Tailored antibiotic therapy in the recipient is recommended for at least 7 days posttransplant.[336,341]

Exceptions exist; however, for example, meningitis caused by *Listeria* species may cause disseminated infection that is difficult to treat in the immunosuppressed patient, with a high risk of relapse.[5,342] Similarly, meningitis caused by disseminated *M. tuberculosis* infection may be transmitted to the recipient with fatal consequences and is a contraindication to transplantation.[284] Other organisms that are rare causes of meningitis but are notable for establishing metastatic infection, adherence to endothelial surfaces, or for having other markers of virulence—for example, *S. aureus*, *P. aeruginosa*, *Salmonella* spp.—are contraindications to organ donation.[343] Lastly,

the time course of infection is relevant: persistent bacteremia caused by any organism increases the risk of metastatic infection, and in such cases, organ transplantation may carry a higher risk of disease transmission.[343]

European guidelines recommend that, in general, organs from donors with bacteremia or bacterial meningitis should only be considered for use after 48 hours of targeted and effective antibiotic therapy and with clinical evidence that the infection has been cleared. Utilization of donors with ongoing sepsis and positive blood cultures is not recommended, especially if effective therapy cannot be confirmed. If the results of blood cultures are not available before transplantation but clinical data indicate that antibiotic treatment has been effective, then it is recommended that a transplant infectious disease specialist be consulted before organs are discarded.[5] Any meningitis caused by an unknown pathogen is an absolute contraindication for organ donation. A brain abscess is not a contraindication per se; however, the potential causes of the brain abscess should be evaluated before accepting the organs. Extreme precaution should be used for donors with presumed bacterial meningitis with negative cultures, especially when no pathogen can be identified by culture or PCR—in this case, organs should not be used for transplantation. In the case of a nonreactive culture but where the bacteria are confirmed by PCR as the pathogen causing the meningitis, it can be assumed that after 48 hours of antibiotic treatment, infection will not be transmitted.[5]

UK guidelines state that where an organ donor has been diagnosed with bacteremia in the 5 days preceding the donation but there is no visible damage or local infection in the organ at retrieval, donation of an organ is acceptable with appropriate recipient antibiotic prophylaxis.[29] Similarly, if bacterial meningitis has been confirmed, but there is no visible damage or local infection in the organ or tissues required at retrieval, the donation of the organs, tissues, and cells are acceptable. Appropriated antibiotic prophylaxis covering any organism from the donor should be considered for identifiable recipients, especially in the case of organs. However, organs from meningitis cases from whom no organism is cultured should not be used.

Summarizing these international guidelines, organs from bacteremic donors may be used provided the organism is readily treatable (not MDR), the donor has received at least 24 hours effective antibiotic therapy with some improvement, and a treatment course is administered to the recipient. Organs may be used from donors with bacterial meningitis with a treatment course given to the recipient, although caution is advised where the pathogen has not been confirmed.

Pulmonary Infections

Bacterial colonization of donor lungs is common as (1) the lungs are in constant contact with the external environment and the airways are normally colonized with multiple organisms; (2) most donors require emergency intubation, which may result in aspiration and pneumonia; and (3) the rate of bronchopulmonary infections increases in proportion to the length of time spent in the ICU (as does the rate of infection with antibiotic-resistant organisms).[5] Before donation, aspiration and consequent pneumonia must, therefore, be ruled out/treated.[5] In particular, the potential transmission of any MDR pathogens must be ruled out. European guidelines state that, in the case of pneumonia without bacteremia, all

other organs can be used safely. After at least 48 hours of effective antibiotic treatment and unimpaired pulmonary function, lungs may be considered for donation.[5] In cases where bacterial infection in the donor lungs is not detected before transplantation, lung recipients should not suffer complications due to donor-derived bacteria as long as the transmitted pathogens are not MDR and provided appropriate prophylaxis is given.[344]

A recent significant discovery has been the role of disseminated Ureaplasma infection in hyperammonemia syndrome after lung transplantation.[345,346] Hyperammonemia syndrome is a fatal complication of immunosuppressed patients in which serum ammonia levels progressively increase, leading to cerebral edema and death. It has been described in bone marrow, lung, heart-lung, kidney, liver, intestinal, and islet cell transplant recipients; however, it has most frequently been reported in lung transplant recipients.[347] A large retrospective case series performed at Barnes-Jewish Hospital in St. Louis, Missouri, between 2000 and 2013 found an incidence of hyperammonemia syndrome after lung transplantation of 1% (n = 8/807), with a mortality rate of 75%.[347] A smaller retrospective cohort study of 145 lung transplant recipients found an incidence of hyperammonemia syndrome of 4%.[348]

Hyperammonemia syndrome was first described in 1991 in a recipient of a bone marrow transplant.[349] The cause of the syndrome remained unknown, however, until 2015 when Bharat et al[346] published preliminary evidence that the syndrome may be caused by donor-derived infection with Ureaplasma species.[346] Ureaplasma species are mollicutes that depend on urea hydrolysis to ammonia and carbon for energy production, and are part of the normal microbiome of the urogenital tract. Although the hydrolysis of urea and the generation of ammonia in the urine do not cause harm, disseminated ureaplasma infection might pose a severe threat by releasing free ammonia into the circulation. The released ammonia is then converted back into urea in the liver, which provides more substrate to Ureaplasma, and thus a cycle of urea hydrolysis and hepatic urea production is established.[346]

In their initial study, Bharat et al[346] performed microbiologic examination (PCR, specialized culture, and molecular resistance profiling) of specimens taken from 6 lung transplant recipients who developed hyperammonemia syndrome posttransplantation. They found evidence of systemic infection with *U. urealyticum* or *U. parvum* in all 6 cases, but they found no evidence of infection in 20 control lung transplant recipients with normal ammonia concentrations.[346]

Ureaplasma is not known to colonize normal healthy lungs, and why hyperammonemia is reported more frequently in lung transplant recipients than recipients of other solid organ transplants is not known. One theory relates to aspiration at the time of injury causing death.[345] Ureaplasma is able to colonize the oral cavity, with possible routes of transmission, including sexual transmission from the genitourinary tract of a partner.[350] An aspiration event at the time of injury could then cause the organism to be drawn down into the lungs, and given that *Ureaplasma* does not grow in routinely performed bacteriological cultures, it would not be detected on standard BAL culture.[345]

NAT is the fastest detection method if *Ureaplasma* is suspected, and culture is also available. Bharat et al reported that *Ureaplasma* species are susceptible to macrolides, fluoroquinolones, and tetracyclines; however, they also observed the emergence of resistance in their case series of 6 patients. At this time, routine donor testing for *Ureaplasma* is not suggested.

Urinary Tract Infections

Urinary tract infections (UTIs) and pyelonephritis are common among potential donors due to bacteria ascending along the urethral catheter. Any suspected UTIs in potential donors should be confirmed by urine culture, and potential kidney donors with UTI should be investigated to rule out upper tract infection. In case of a UTI restricted to the lower urinary tract, kidneys may be used as they are not infected. All other organs can be safely used for transplantation.

Before organ retrieval, the donor should be treated with antibiotics for 24 to 48 hours or until there is documented resolution of the infection.[49] The final decision about organ utilization should be made at the time of organ recovery.[5] Posttransplant treatment of the recipient may reduce the risk of donor-derived infection. In general, however, there is no need to treat the recipient of a nonkidney organ from a deceased donor with nonbacteremic, localized infection that does not involve the transplanted organ (excluding meningitis cases).[49]

European guidelines state that in the case of UTI without bacteremia, all nonkidney organs can be used safely for transplant, and that uncomplicated UTI/bacteriuria is in most cases not a contraindication for the utilization of kidneys, provided adequate antibiotic treatment is given to the donor and recipient.[5]

FUNGAL, PARASITIC, AND OTHER INFECTIONS

Toxoplasma gondii

Epidemiology

Toxoplasma gondii is a protozoan (coccidian) parasite of mammals, which reproduces in cat species but has a wide intermediate host range.[351] It is one of the most common parasitic infections of humans and other warm-blooded animals.[351] Exposure is extremely common in all regions of the world, although there is substantial geographical variation in rates of *T. gondii* (see Table 33). It is estimated that 16% to 40% of the populations of the United States and United Kingdom are infected, whereas in Central and South America and parts of Europe, infection rates are as high as 80%.[353] A study of pregnant women in Australia found 35% had IgG antibodies to *T. gondii*.[354] Transmission can occur due to:

- ingestion of undercooked meat containing Toxoplasma cysts;
- ingestion of contaminated soil (eg, via unwashed fruit or vegetables) containing cat feces;
- ingestion of cat feces via cleaning a cat's litter box, gardening, contact with sandpits, and so on;
- transplacental transfer from mother to fetus.

It is believed that the majority of infections that occur globally are due to ingestion of cysts in infected meat, or oocysts in food or water contaminated with cat feces.[351] Geographical variation in *T. gondii* infection is hypothesized to be due to (i) the relative level of contamination in the environment with oocysts, and (ii) local culinary traditions with respect to meat preparation (eg, a preference for raw or undercooked

Median rate of acquired *T, gondii* per 100000 population by WHO region with 95% CIs, 2010[352]

Region	Africa	Americas	Eastern Mediterranean	Europe	South East Asia	Western Pacific Region
Rate (95% CI)	229 (132–386)	159 (92–261)	195 (118–292)	119 (79–180)	137 (55–244)	116 (63–176)

meat).[353] When ingested, bradyzoites from tissue cysts or sporozoites from fecal oocysts transform into tachyzoites and penetrate intestinal epithelial cells and divide rapidly in the intestine. *T. gondii* is then spread to organs and tissues by invasion of the lymphatics and blood, and is able to multiply in almost any cell in the body.[351] In immunocompetent hosts, symptoms are usually either absent or mild, such as swollen lymph nodes, headache, fever, and fatigue.

The immune response to *T. gondii* infection involves both humoral and cellular factors; however, immunity does not eradicate infection as cysts can persist for years after acute infection. After proliferating, tachyzoites transform into bradyzoites, which are less susceptible to proteolytic enzymes and form latent intracellular cysts mainly in muscle tissues and the brain (although visceral organs including lungs, liver, and kidneys may also be affected).[351] Intact cysts may persist for the life of the host, and can, therefore, be transmitted directly by solid organ transplantation. Intact cysts are unlikely to cause harm in immunocompetent persons; however, in immunocompromised persons, the rupture of a tissue cyst may result in bradyzoites being transformed into tachyzoites, followed by renewed replication. Alternatively, if the donor has an acute *T. gondii* infection at the time of donation, then tachyzoites transmitted to the recipient may persist and continue proliferating, resulting in severe symptoms, complications, and death.

Donor Screening and Risk Minimization

Organs which contain tissue cysts infected with *T. gondii* carry the risk of primary infection in a naive and immunosuppressed recipient. Hearts are at higher risk of containing *T. gondii* cysts compared with other organs, and serological tests for toxoplasma are usually included among standard screening tests for heart donors in most jurisdictions.[5,355] Although a positive serological test for *T. gondii* is not a contraindication to donation, it may inform the need for prophylaxis in heart recipients.

Numerous serological tests exist for the detection of *T. gondii* antibodies, including both IgM and IgG. IgM antibodies appear sooner after infection than IgG, and disappear faster after recovery. NAT can be used to diagnose active infection[356,357]; however, given that active infection is rare and the goal of donor screening is primarily to detect latent toxoplasma in the heart and other organs resulting from past infection, international guidelines recommend serological testing only for pretransplant screening of potential organ donors.[5,29,32] Donor and recipient toxoplasma IgG are generally recommended as routine for cardiac transplant recipients, with donor testing for acute toxoplasma (IgM, NAT) used only in an appropriate clinical context (ie, where there is clinical suspicion of acute toxoplasmosis).

Transmission

Toxoplasma gondii transmission by organ transplantation has been reported multiple times in the literature, most commonly by heart transplantation, followed by kidney and liver transplantation.[19,358-362] Cases of toxoplasmosis after bowel and pancreas transplantation have also been reported.[362,363] Presenting symptoms typically are nonspecific, including fever, respiratory distress, neurological manifestations, and bone marrow suppression.[362] Cerebral toxoplasmosis, although a well-known complication in HIV patients, is extremely rare in transplant recipients.[363] The majority of cases are diagnosed within 90 days of transplantation, although the median time to onset of symptoms in cases of donor-acquired primary toxoplasmosis is shorter—approximately 15 to 25 days posttransplant—than for reactivation of latent infection.[19,359,361,362,364] Primary toxoplasmosis is also significantly more lethal: a review of published cases of primary toxoplasmosis after kidney transplantation found a mortality rate of 50%, with fatal outcomes confined to those patients who developed clinical evidence of toxoplasmosis less than 90 days posttransplant.[364]

Mortality from toxoplasmosis posttransplantation is highest in those patients with disseminated disease, or where there is a delay in diagnosis and targeted treatment.[361] In 1 such case of fatal disseminated toxoplasmosis after liver transplantation from a seropositive donor to a seronegative recipient, the recipient developed symptoms 12 days posttransplant and was initially treated for MRSA and then for CMV after this was detected on BAL performed on day 26 posttransplant.[365] The patient's condition did not improve, and on day 40, she developed acute respiratory failure with shock. On admission to the ICU, a second BAL was performed and direct microscopy revealed *T. gondii* tachyzoites, at which point, therapy with pyrimethamine and sulfadiazine was initiated. The patient, however, died 5 days later. The recipients of the other organs from the same donor (heart, lungs, kidneys and cornea) showed no evidence of *T. gondii* infection more than 9 months posttransplant: all of these recipients were seropositive for toxoplasmosis before transplantation.[365]

In a similar case of a fatal outcome after delayed diagnosis and treatment, a 10-year-old recipient of a small bowel transplant developed fever, bilateral frontotemporal headaches, abdominal pain, vomiting, and diarrhea 3 months posttransplant.[362] Blood and CSF bacterial, viral, and fungal cultures were all negative, and CMV and EBV were not detectable by PCR. She was treated with beta-lactam antibiotics and briefly improved before deteriorating again. Treatment for steroid-resistant rejection on day 23 of hospitalization precipitated respiratory distress and acute deterioration 2 days later. Her antimicrobial regimen was changed to imipenem, fluconazole, liposomal amphotericin, amikacin, trimethoprim-sulfamethoxazole, and cidofovir, but she died of multiorgan failure on hospital day 27. Autopsy showed severe diffuse pulmonary edema for the lungs and patchy recent hemorrhages, and microscopic examination demonstrated small numbers of encysted *T. gondii* organisms.[362] Fatal cases of toxoplasmosis after delayed diagnosis and treatment have also been reported in heart and multivisceral transplantation.[363,366]

Two cases of *T. gondii* transmission have been reported in Australia after kidney transplantation from a common donor.[19] Both of the Australian cases died 5 weeks after transplantation, within a few days of each other; neither was on active toxoplasma prophylaxis.[19] The first kidney recipient experienced a rise in serum creatinine, liver function tests, and lactate dehydrogenase on day 23 posttransplant, and a MAG3 scan showed a lower pole infarct. He deteriorated on day 29, becoming agitated and tachypneic, hypoxic, and hypotensive. A chest x-ray revealed lower zone opacities and broad-spectrum antibiotics were commenced, but the patient's condition worsened, and he died on day 30 posttransplant from cardiogenic shock. Post mortem examination showed intracytoplasmic inclusions in the heart, liver, and lungs, but not in the transplanted kidney. The second kidney recipient presented on day 28 with a fever, hypotension, thrombocytopenia, abnormal liver function tests, and widespread, bilateral interstitial infiltrates were observed on chest x-ray. Broad-spectrum antibiotics were commenced but the patient developed multiorgan failure and died on day 32 from cardiogenic shock. Post mortem examination showed presence of *T. gondii* in the lungs, heart, liver and brain, but not in the transplanted kidney.

The donor in the cases above was a 45-year-old woman with a history of major depression, alcohol abuse and multiple suicide attempts, who was found collapsed at home, unresponsive and cyanosed: there was no clinical suspicion that the donor had died from acute toxoplasmosis. Retrospective testing of donor serum showed positive IgG but indeterminate IgM antibodies; analysis of sections of renal tissue from the donor did not show signs of *T. gondii* infection and NAT testing on post mortem liver tissue from the donor was negative for *T. gondii*. The authors concluded that the donor most likely had an acute infection at the time of death, and that—because *T. gondii* may reside inside leukocytes or mononuclear cells—transmission probably occurred at the time of transplantation via transfer of these cells.[19] Subsequent to this unexpected transmission event, the center where these cases occurred introduced trimethoprim-sulfamethoxazole prophylaxis for 6 months posttransplant as standard practice.[19]

Recipient Management and Outcomes

Prophylactic use of trimethoprim-sulfamethoxazole (co-trimoxazole), atovaquone, or combinations, including pyrimethamine dapsone and folinic acid, or pyrimethamine-sulfadiazine have been demonstrated to be effective against *T. gondii* by multiple studies, and European guidelines recommend their use for recipients at risk of *T. gondii* infection—usually recipients of heart and vascularized composite allografts where muscle tissue is involved.[5,41,355] Trimethoprim-sulfamethoxazole is additionally effective against *Listeria monocytogenes*, *Nocardia asteroids*, and *P. jeroveci*. Trimethoprim-sulfamethoxazole prophylaxis for at least 3 months posttransplant (but usually 6 months or longer, depending on the organ) is currently standard international practice for recipients at risk of *T. gondii* transmission.[367]

Serological tests have poor sensitivity for toxoplasma antibodies in immunosuppressed patients; therefore, in patients with a clinical suspicion of primary toxoplasmosis posttransplant, NAT is the best diagnostic strategy.[364,365] A positive toxoplasmosis PCR of the BAL or CSF can make an early diagnosis of disease; however, a positive PCR from a blood sample without evidence of organ involvement does not confirm diagnosis of acute disease: definitive diagnosis of toxoplasmosis requires the identification of parasites in biopsy samples.[367]

Combination therapy with oral sulfadiazine and pyrimethamine or IV trimethoprim-sulfamethoxazole is the preferred treatment for acute toxoplasmosis. These drugs are beneficial when administered in the acute stage of infection when there is active replication, and synergistically act against the tachyzoites during active infection or reactivation. Alternative drugs for the treatment of clinical *T. gondii* infection include diaminodiphenylsulfone, atovaquone, spiramycin, and clindamycin.[351]

Malaria

Epidemiology

There were 266 notifications of malaria in Australia in 2016, compared with 373 in the 2013/2014 season (June-July), and compared to an average annual number of cases of 434 over the 5 years from 2008/2009 to 2012/2013.[257] This is consistent with a significant decline in malaria notifications overall in Australia since 2004 to 2005, corresponding to a global decline in malaria incidence over the period from 2000 to 2015.

Australia remains free of endemic malaria: all cases were reported in travellers or military personnel returning from endemic areas or in refugee arrivals. Despite the current absence of endemic malaria, suitable vector mosquitos are present in northern Australia and the area is "malaria receptive". Limited transmission does also sometimes occur in the Torres Strait after importation. There was 1 case of malaria acquired on Saibai Island in 2013, and 7 locally acquired cases in the Torres Strait in 2011.[257]

The number and rate of malaria notifications in 2016 was highest in the 35- to 39-year age group (23 cases, 2.9 per 100 000 population), and the majority of cases (64%) were in males. Figure 14 shows the malaria notification rate in Australia in 2016 by age and sex.

New Zealand is also free of endemic malaria. There were 42 notifications of malaria in New Zealand in 2017, the vast majority of which were in the 20- to 39-year age group.[368] By comparison there were 26 malaria notifications in 2016, and 38 in 2015.[368] All cases were acquired overseas, most commonly in sub-Saharan Africa countries, followed by India, then Papua New Guinea, Solomon Islands and Vanuatu.[39]

Donor Screening and Risk Minimization

The possibility of malaria infection should be considered for donors with previous residence in or travel to endemic areas, especially if the potential donor has unexplained febrile illness. All 4 of the main plasmodia species that infect humans—*P. ovale*, *P. vivax*, *P. malariae*, and *P. falciparum*—have been described in solid organ transplantation.[355]

US guidelines recommend donor testing for malaria with thick and thin blood smears if the donor is epidemiologically at high risk for infection.[355] This includes donors who have spent time in malarious regions within the previous 3 years. UK guidelines state that febrile donors with a recent travel history (<1 year) require a malarial screen (blood film and PCR) before donation.[29] If a donor was born or has lived
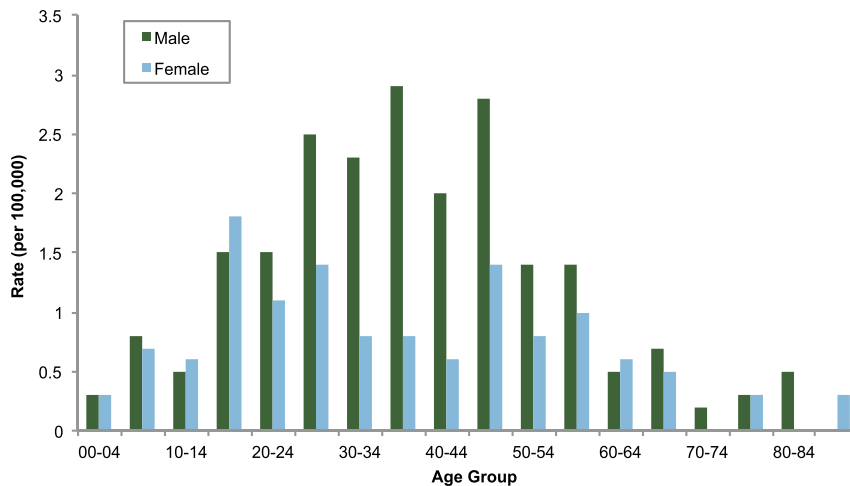
FIGURE 14. Notification rate of malaria in Australia in 2016, by age group at sex (source: http://www9.health.gov.au/cda/source/cda-index.cfm).

in a malarious area for more than 6 months at any time of life, a validated antimalarial antibody test should be performed, but donation may proceed pending the results. When a recipient has been found to have received an organ from a donor whose serum contains malarial antibody, a risk analysis must be undertaken with the assistance of the HPA Malaria Reference Laboratory. This will require testing for the presence of malarial parasitemia in both the donor and the recipient. Follow-up of the recipients of organs from high-risk donors for appearance of malarial symptoms is recommended, irrespective of the donor antibody status.

Because Australia and New Zealand are not endemic for malaria, malaria antibody testing is not routinely available. Donors with fever and a history of recent travel to an endemic country should have malaria excluded by thick/thin films and PCR. Asymptomatic donors should be screened by thick/thin films and PCR if there is a history of previous residence in an endemic country. The decision to proceed to transplantation will likely be made on the basis of negative blood films as PCR is usually delayed. The recipient can be treated routinely for malaria if the donor result returns positive.

Transmission

Although malaria is a rarely reported complication of organ transplantation outside of nonendemic countries, there have been several documented cases of donor-derived malaria transmission including recipients of kidneys (6 cases), livers (4 cases), and hearts (4 cases).[369-375] A donor history of recent travel to or prior residence in an endemic country should prompt suspicion of malaria in recipients with unexplained fever after transplantation.[367]

Based on published case reports, recipients of livers and hearts with donor-derived malaria tend to have worse outcomes compared to kidney recipients, which is thought to relate to the higher intensity of immunosuppressive regimen in liver and heart transplantation.[367] Additional hypotheses for why kidney recipients fare better include longer cold ischemia times for kidneys than other organs, which may decrease the amount of active transmitted Plasmodium; similarly, as kidneys are retrieved at the end of the surgical procedure, they may have been more thoroughly flushed than other organs,

removing more of the before retrieval.[369] Donor-derived malaria is particularly fatal to liver recipients, as parasitized hepatocytes are transplanted with the allograft, resulting in high-level parasitemia; moreover, antimalarial therapy can be hepatotoxic, contributing to graft failure.[367] For example, in a case of fatal *P. falciparum* transmission from a donor to a liver recipient, the recipient became febrile day 20 posttransplant and blood films revealed high-level parasitemia.[372] Quinine therapy resolved the fever and parasitemia; however, the recipient died on day 51 posttransplant. The donor in this case was an 8-year-old child from the Ivory Coast who had arrived in France 2 months before death. Retrospective examination of donor sera, liver and spleen samples showed high antibody titers against *P. falciparum*, malarial pigment in both organs, macrophage reactions in the spleen and a suspected intraerthrocytic trophozoite in the liver.[372]

Demonstrating the different outcomes of malaria infection for kidney versus heart and liver recipients, Chiche et al[369] describe the outcomes for 4 recipients of organs from a donor who was retrospectively confirmed to be infected with *P. falciparum*. Eight days posttransplantation, schizonts were observed on a routine blood sample taken from the liver recipient, and diagnosis of malaria was confirmed by thin and thick blood smears, which demonstrated high-level parasitemia. The patient was treated with 25 mg/kg per day of quinine; however, an alteration of neurological status occurred, and they went into a deep coma within 3 days. Vibramycin was added to quinine, but immunosuppressive therapy was not altered. There was an improvement in status 5 days after starting quinine and parasitemia disappeared, but there was a corresponding elevation of liver function tests. Liver enzymes began to improve 1 month later, and after 3 months, the patient had recovered. The heart recipient developed fever and neurological disorders on day 5 posttransplant, along with acute renal failure with severe acidosis, abnormal liver tests, cytolysis, anemia, and thrombopenia. At this point, information about suspicion of malaria in the donor became available, and the patient was rapidly treated. However, the patient died from multiple organ failure caused by active malaria infection 17 days posttransplant. The 2 recipients of the donor's kidneys showed no signs of infection when diagnosis was made in the liver and heart recipients. Prophylactic

antimalarial chemotherapy was given, and both patients remained in good health.[369]

Plasmodium vivax infection tends to be less severe than *P. falciparum* infection.[367] In a case of *P. vivax* transmission from a donor originally from Zaire to 2 Swiss kidney recipients, both recipients recovered quickly after treatment.[370] The donor had been in good health before death from an intracerebral hemorrhage 2 months after entry to Switzerland. Blood smear was negative for parasites, and the donor's red cells were Duffy-negative. Despite no indications of malaria in the donor at the time of organ retrieval, the 2 kidney recipients became febrile on days 9 and 16 posttransplant respectively, with *P. vivax* detected on day 25. Both recipients received chloroquine treatment for 3 days and subsequent smears were negative.[370] In a case of *P. vivax* transmission by liver transplantation, parasitemia was successfully cleared after antimalarial treatment; however, the patient died several months later from graft failure as a result of hepatotoxicity from chloroquine and primaquine therapy.[371] The donor in this case was originally from Cameroon, having immigrated to Germany 18 months before, with no clinical signs of active malaria infection at the time of death. Retrospective serological testing showed antibody titers against *P. vivax* and *P. falciparum*. Both kidneys, the heart, and the liver were transplanted: only the liver recipient and the recipient of one of the kidneys developed febrile illness. The heart recipient was suspected to have a subclinical malarial infection on the basis of a positive titer for *P. vivax* 12 months after transplantation, and again at 22 and 25 months posttransplant, though without symptoms of infection. The liver recipient developed a high-grade fever on day 28 posttransplant, at which point, *P. vivax* were found in a Giemsa-stained thin smear taken for blood count. The patient was treated with 8 days of oral chloroquine, followed by 14 days of oral primaquine, which resolved the fever within 4 days although a slow rise of bilirubin and liver enzymes was noted in parallel with antimalaria therapy. Elevation of liver function tests was progressive, and liver biopsies showed increasing centrolobular toxic parenchymal cell damage and persisting malaria pigment deposits. After progressive cholestasis, the patient died of liver failure 6 months posttransplant.[371] The kidney recipient who developed malaria infection was treated with a 1-day course of mefloquine (total dose, 1500 mg), after which the patient was no longer febrile, and there was no further evidence of malaria infection.

Recipient Management

Although malaria can be fatal in transplant recipients, early detection and appropriate specific therapy will usually result in prompt recovery. Patient outcomes will depend on the species (*P. falciparum* is associated with worse outcomes), the presence of any other infections, and any issues with drug toxicity.[355] Quinine can interact with cyclosporine metabolism, lowering cyclosporine blood levels.[376]

Treatment of malaria requires the identification of the specific plasmodium species and knowledge of the geographical distribution of sensitivity patterns.[355] Chloroquine can be used to treat *P. vivax*, *P. malariae*, *P. ovale*, and uncomplicated *P. falciparum* from chloroquine-susceptible regions. Uncomplicated *P. falciparum* originating from a chloroquine-resistant region may be treated with an artemisinin combination

therapy, atovaquone-proguanil, quinine-based regimen, or mefloquine.[355] Quinine and mefloquine, however, significantly interact with calcineurin inhibitors.[367] Severe cases of *P. falciparum* should be treated with IV artesunate, followed by doxycycline, tetracycline, or clindamycin. In cases of *P. vivax* and *P. ovale* infection, primaquine should be administered to prevent relapse (after excluding G6PD deficiency).[355] *P. vivax* resistant to chloroquine has been observed in Oceania.[355]

Strongyloides stercoralis

Epidemiology

Strongyloides is an intestinal nematode that is endemic to tropical or subtropical regions of the world. Infection is transmitted by skin contact with soil contaminated with human waste, and prevalence is, therefore, directly related to sanitation and hygiene conditions. Outside of the endemic regions of Southeast Asia, Central and South America, and Africa, *Strongyloides* infection is also found in poor communities, former war veterans, refugees, immigrants and travelers, and people occupationally exposed to soil (eg, farmers and miners) in parts of the United States, Europe, United Kingdom, and Australia.[377,378] A study of Vietnam veterans resident in South Australia found *Strongyloides* seropositivity of 11.6% in this cohort.[379] Similarly, a high prevalence (27.5%) of *Strongyloides* larvae in stool samples from Australian ex-prisoners of war held in Southeast Asia during World War II has been reported.[380] Cross-sectional surveys of selected immigrant/refugee groups in Australia has found positive or equivocal serology for *S. stercoralis* of 11% among East Africans, 42% among Cambodians, and 24% among Laotians.[381,382] Additional risk factors for *Strongyloides* infection include individual-level low socioeconomic status, institutionalization, and alcoholism.[367]

In a retrospective review of clinical records from Royal Darwin Hospital conducted in 1993, a total of 68 cases of *Strongyloides stercoralis* confirmed by stool microscopy were identified, of which 64 were aboriginal persons, and more than half of which were children younger 5 years.[383] A similar retrospective analysis conducted in Queensland found an overall infection rate between 1972 and 1991 of 1.97%, although there was wide geographic variation in prevalence. Prevalence was highest in northern regions of Queensland with summer wet seasons: the highest average prevalence was observed at Doomadgee (12%), with a peak of 27.5% in the wet season. As was observed in the Northern Territory, children were the major reservoirs of *Strongyloides* infection in this study.[384]

The *Strongyloides* life cycle has both free-living and parasitic stages. Adult female worms infecting the human small intestine lay eggs in the intestinal mucosa that hatch into rhabditiform larvae, which are then excreted in the stool.[385] In moist, warm conditions, environmental rhabditiform larvae can molt into infective filariform larvae or develop into free-living adult worms. Infection in humans generally occurs through dermal penetration by filariform larvae, which enter the blood stream and then migrate to the small intestine. This migration frequently occurs via the pulmonary route: larvae are carried by the bloodstream to the lungs, where they penetrate the alveolar spaces and then ascend the tracheobronchial tree migrate to the pharynx/trachea where swallowing allows them to enter the gastrointestinal tract.[385] Hence, in acute strongyloidiasis, the first sign of infection is typically

a local reaction at the infection site, followed by pulmonary symptoms (cough, tracheal irritation, dyspnea) several days later, then gastrointestinal symptoms (abdominal pain, diarrhea, constipation, nausea and vomiting, and anorexia) approximately 2+ weeks after infection as larvae migrate to the gastrointestinal tract.[385] As some rhabditiform larvae transform into invasive filariform larvae before they are excreted in the stool, *Strongyloides* has the ability to reinfect the host by invading the intestinal wall or perianal skin. This cycle of autoinoculation allows *Strongyloides* infection to persist in the host indefinitely.

Although most chronically infected individuals are asymptomatic, in immunocompromised patients the rate of molting of rhabditiform larvae into filariform larvae is increased such that the autoinoculation cycle can accelerate to the level of life-threatening hyperinfection.[385,386] In solid organ transplant recipients, *Strongyloides* infection may initially present with vague gastrointestinal symptoms. Hyperinfection symptoms include pyrexia, gastrointestinal pain, bloody diarrhea, ileus, anorexia, nausea, vomiting, sore throat, difficulty swallowing, dyspnea, pneumonitis with bilateral infiltrates, and in rare cases, intestinal or pulmonary obstruction.[367,385] The numerous larvae may cause mucosal ulceration at any level of the gastrointestinal tract, and esophagitis, gastritis, duodenitis, jejunitis, ileitis, colitis, and proctitis have all been reported in association with hyperinfection.[385] Purpuric rash may be present, and eosinophilia may be a clue to *Strongyloides* infection in some cases; however, it is usually absent with steroid therapy.[367] The defining characteristic of hyperinfection is a huge increase in the numbers of larvae in the stool or sputum. Disseminated infection occurs when the larvae migrate to organs outside of those normally involved in the pulmonary autoinfective cycle (gastrointestinal tract, peritoneum, lungs).[385] Organs affected in reported cases of disseminated *Strongyloides* infection include mesenteric lymph nodes, gallbladder, liver, heart, pancreas, skeletal muscle, kidneys, ovaries, and brain.[385] Disseminated *Strongyloides* may be complicated by bacteremia and meningitis resulting from gram-negative bacteria migrating outside of the intestinal tract by attachment to filariform larvae or via disrupted intestinal mucosa.[385] Gram-negative sepsis is also life-threatening—moreover, it may obscure the underlying diagnosis of strongyloidiasis.[387] Hyperinfection is fatal in approximately 50% of cases; the mortality rate in disseminated strongyloidiasis is up to 80%.[385]

Glucocorticoids, at any dosage, are directly associated with the transformation of chronic strongyloidiasis to hyperinfection.[385,388] The majority of cases of *Stongyloides* hyperinfection in organ transplant recipients appear to have been precipitated by increased glucocorticoid doses in response to rejection.[385,389] Donor preconditioning with high-dose steroids may also reactivate *Strongyloides* in the latently infected donor, causing disseminated disease that may then be transmitted by solid-organ transplantation.[390]

Infection with HTLV-1 is associated with increased prevalence of *S. stercoralis* infection, and with a greater likelihood of hyperinfection syndrome.[391,392]

Donor Screening and Risk Minimization

US guidelines recommend routine screening of donors coming from endemic regions for *Strongyloides* IgG and that recipients of organs from deceased donors testing positive for *Strongyloides* antibodies should receive ivermectin posttransplant.[393] Because of the longevity of the parasitic infection, screening is warranted even for very remote histories of travel to endemic regions or for residence in places where the disease was considered endemic decades ago should prompt screening.[385] Eosinophilia is a common marker of helminth infections, and thus donors with unexplained eosinophilia or with gastrointestinal symptoms should also be evaluated for *Strongyloides*.[355,387]

The CDC guidelines recommend testing with *Strongyloides* IgG ELISA; stool screening is recommended only when serological testing is unavailable or when serological findings are negative in a patient with symptoms, eosinophilia, or a known history of exposure.[387] Stool testing has poor sensitivity as larvae are excreted intermittently and in small quantities; the sensitivity of a single specimen is only 15% to 30%, although this increases to nearly 100% if stool specimens are collected and examined in an expert laboratory on seven consecutive days (obviously unfeasible in the context of organ donation).[394] Although useful for detecting chronic/latent infections, serological testing is less sensitive in the detection of new infections (~85%)[367] Negative serology results should be interpreted with caution in the context of the potential donor's medical and social history.[387]

The New York Organ Donor Network commenced targeting screening for Stronglyoides in 2010.[395] From 2010 to 2013, of 1103 potential donors, 233 (21%) were identified as being at increased risk and were tested for Stronglyoides antibody before procurement. Of this number, 10 (4.3%) tested positive, of which 7 became organ donors, with organs transplanted into 18 recipients. Fourteen recipients received prophylaxis; none developed strongyloidiasis.[395]

Transmission

In the context of transplantation, *Strongyloides* is most commonly seen as reactivation of dormant disease in the recipient. Although donor-derived *Strongyloides* transmission is rare, cases have been reported involving kidney, kidney-pancreas, liver, heart, and intestinal allografts (though it should be noted that several of these cases the attribution of transmission as donor-derived was not proven).[387,389,390,395-400] One of the reasons that cases of donor-derived *Strongyloides* transmission are not reported more commonly—which is surprising given the high rates of chronic infection in endemic regions and the difficulties of screening—is that cyclosporine is strongly parasiticidal against *Strongyloides*. After cyclosporine became a standard part of immunosuppressive regimens in the 1990s, a corresponding decline in case reports of *Strongyloides* hyperinfection was noted; there is also experimental evidence to support an anthelmintic effect of cyclosporine A on *S. stercoralis*.[385] A case of *Strongyloides* hyperinfection occurring in a kidney transplant recipient immediately after cyclosporine A withdrawal due to an episode of acute rejection provides further evidence of an anthelmintic effect of cyclosporine A.[397]

Table 34 presents summaries of cases of donor-derived *Strongyloides* transmission reported in the peer-reviewed literature (deceased donors). In the vast majority of reported cases of donor-derived *Strongyloides* infection, the donor was originally from an endemic country and thus was at

TABLE 34.

Reported cases of donor-derived *Strongyloides* transmission (deceased donors)

Reference	Donor characteristics	Transplanted organs	Onset of symptoms (days posttransplant)	Symptoms	Diagnosis (days posttransplant)	Treatment	Hyper-infection	Concomitant infections	Cause of death (day posttransplant)
Hoy, 1981[400]	47-year-old male with no known health problems, born and raised in the northeastern United States who worked for 20+ years as an insulation engineer	Kidney	17	Fever (day 17), pruritic rash (day 33), diarrhea (day 42), epigastric burning, nausea, vomiting, left-sided pleuritic chest pain, acidosis, hypotension	66	Thiabendazole 25 mg/kg twice daily for 5 days	Yes	*Klebsiella, B. fragilis, E. corrodens, P. aeruginosa,* CMV (reactivation)	Pneumonia and respiratory failure (day 97)
		Kidney	18	Fever (day 18), nonpruritic rash (day 26), cough (day 27), vomiting, diarrhea, abdominal (day 64)	68	Thiabendazole 25 mg/kg twice daily for 5 days	No	CMV (primary), *K. pneumoniae*	Recovered
Hamilton, 2011[390]	54-year-old male from the Dominican Republic resident in the United States for 2.5 years before death from a gunshot wound to the head, who received high-dose steroids as part of a preconditioning regimen	Kidney	49	Rash (day 49), diarrhea, nausea, vomiting, intense abdominal cramping (day 63)	70	Ivermectin 200 µg/kg once daily for 5 days, then alternate days for 25 days	Yes	—	Recovered
		—	Severe epigastric pain, hematemesis	70	Ivermectin 200 µg/kg once daily for 2 days, then retreated weekly for 5 weeks	No	—	Recovered	
		—	—	70	Ivermectin 200 µg/kg once daily for 2 days, albendazole 400 mg daily for 7 days	No	—	Recovered	
Abanyie, 2015[395]	45-year-old male from Guyana who had immigrated to the United States; cause of death was subarachnoid hemorrhage[a]	Liver	90	Diffuse abdominal pain, nausea, nonbloody emesis (day 90), altered mental status, hypoxia (day 96)	101	Ivermectin 200 µg/kg once daily for 13 days, albendazole 400 mg twice daily for 12 days	No	*P. aeruginosa,* vancomycin-resistant *E. faecalis*	Recovered
Abanyie, 2015[395]	49-year-old US-born homeless military veteran who died from a subdural hematoma, no known international travel	Kidney	—	Respiratory symptoms	—	Ivermectin for 5 days followed by albendazole for 7 days	No	—	Recovered
		—	Chest pain	—	Ivermectin 200 µg/kg once daily for 2 days, then twice weekly for 2 weeks	No	—	Recovered	
Abanyie, 2015[395]	55-year-old male born in the West Indies and resident in the United States for 21 years, died from head trauma in car accident[b]	Kidney	—	Gastrointestinal	231	—	—	—	Recovered

Reference	Donor characteristics	Transplanted organs	Onset of symptoms (days posttransplant)	Symptoms	Diagnosis (days posttransplant)	Treatment	Hyper-infection	Concomitant infections	Cause of death (day posttransplant)
Abanyie, 2015[395]	58-year-old female born in Honduras, died of respiratory failure due to asthma exacerbation	Kidney	—	—	287	—	—	—	Recovered
Roseman, 2013[401]	46-year-old male from Honduras who had emigrated to the US 7 years before, died after being struck by a car	Kidney	60	Delirium, fever, nausea, vomiting diarrhea (day 60), odynophagia, abdominal pain (day 67)	68	Vancomycin and oral ivermectin, switched to subcutaneous ivermectin 20 µg/kg divided into 6.5 mg per upper extremity every other day for 8 days. Albendazole given concomitantly for 3 days. Tacrolimus was changed to cyclosporine.	—	S. aureus and coagulase-negative Staphylococcus	Recovered
		Kidney	30	Diarrhea (day 30), abdominal pain	68	Oral ivermectin 200 µg/kg daily for 7 days, albendazole 400 mg twice daily for 3 days	No	CMV (primary)	Recovered
Le, 2014[402]	24-year-old Puerto Rico–born man who died from multiple gunshot wounds[c]	Heart	48	Fatigue, sore throat, hemoptysis (day 48), respiratory distress, hypotension (day 49), metabolic acidosis	55	Ivermectin, albendazole	Yes	E. cloacae, K. pneumoniae, vancomycin-resistant enterococci	Gram-negative & enterococcal bacteremia and VRE meningitis (day 77)
		Kidney-pancreas	52	Nausea, anorexia, abdominal fullness, nonpuritic rash	66	Ivermectin, albendazole. Immunosuppression transitioned to cyclosporine	MDR E. cloacae	Recovered	Recovered
		Kidney	72	Fever, vomiting, diarrhea, diffuse petechial rash	72	Cefepime, ivermectin, albendazole. Immunosuppression transitioned to cyclosporine, MMF and prednisone discontinued	—	Recovered	Recovered
Rodriguez-Hernandez, 2009[398]	47-year-old male from Ecuador	Liver	75	Asthenia, anorexia, diarrhea, malaise (day 75), vomiting (day 79), dyspnea, cough, whitish expectoration, fever (day 80)	88	Albendazole 400 mg b.i.d. for 14 d and ivermectin 200 µg/kg per day for 7 days, then intermittent prophylaxis with ivermectin for >3 weeks	Yes	K. pneumoniae, CMV	Recovered
Brügemann, 2010[396]	Donor originally from surname[d]	Heart	42	Abdominal pain, anorexia, nausea, vomiting, rash	49	Ivermectin 200 µg/kg per day for 15 d, albendazol 400 mg twice daily for 10 d	Yes	CMV (primary), novel influenza A/H1N1	Recovered
Patel, 2008[389]	39-year-old Honduran man living in the United States, died from motor vehicle accident	Intestine	40	Nausea, vomiting, constipation, abdominal discomfort, low-grade fever, headaches, photophobia	40	Ivermectin 200 µg/kg daily, thiabendazole 25 mg/kg twice daily, ivermectin retention enemas 15 mg daily	Yes	E. faecium, ESBL-producing K. pneumoniae, carbapenem-resistant P. aeruginosa, CMV	Acinetobacter septicemia (day 425)

[a] The recipients of the donor kidneys were asymptomatic and both tested seronegative for Strongyloides posttransplant. Both were treated with oral ivermectin after notification of the potential disease transmission in the liver recipient.

[b] The recipient of the liver remained asymptomatic posttransplant and was not treated.

[c] A fourth recipient underwent liver transplantation but died on day 4 posttransplant. No evidence of Strongyloides was found on autopsy.

[d] The liver and 1 kidney were also donated. The liver failed 1 week posttransplant due to hemostatic problems; evaluation of the recipient, who received a second graft, 4 months after the original transplant showed evidence of Strongyloides infection. The recipient of the kidney died 6 months posttransplant due to sepsis with E. coli, which could have been a complication of Strongyloides; although antibodies against Strongyloides were not detected.

CMV, cytomegalovirus.

increased risk of latent *Strongyloides* infection. Not all recipients of organs from infected donors go on to have symptomatic *Strongyloides* infection—in a review of US cases reported to the CDC between 2009 and 2013, 11 of 20 recipients was symptomatic, with the most common symptom being gastrointestinal complaints.[395,398] As *Strongyloides* is not commonly seen in high-income countries, symptoms in transplant recipients are often initially misattributed to primary CMV infection or CMV reactivation, to bacterial infection, or to a reaction to immunosuppressive medications, delaying diagnosis and appropriate treatment.[395,396,400] The median time to onset of symptoms for the cases reported in Table 34 is 49 days compared with a median time to diagnosis of 69 days. Of 18 recipients with donor-derived *Stronglyoides* infection, there were 3 reported deaths: 2 from bacteremia/septicemia and 1 from respiratory failure. In each of the fatal cases, the patient had developed *Strongyloides* hyperinfection syndrome.

Where treatment was administered only until parasitological cure, *Strongyloides* infection recurred weeks or months later in some cases.[400] There was also a high risk of *Strongyloides* recurrence after episodes of rejection treated with high-dose steroids, even if microscopic and PCR evidence indicated that the previous infection had been resolved.[396]

Recipient Management

Given the risks of reinfection and hyperinfection associated with *Strongyloides*, the goal of treatment is the total eradication of the parasite, not just symptom management.[385] Ivermectin is the first-line drug of choice against *Strongyloides*. Albendazole may also be used to treat *Strongyloides*, but is less effective and has a worse side effect profile than ivermectin.[385,403,404] A reduction in immunosuppression is necessary, and it is particularly important that steroids be tapered rapidly.[387] Broad-spectrum antibiotics may be indicated if bacteremia, meningitis, or pneumonitis are suspected.[367] Malabsorption of drugs can be a barrier to effective treatment—for those patients with ileus, alternative methods of medication delivery may be required, such as via nasogastric tube, intravenously, or by enema or subcutaneous administration. In a case of disseminated infection in a patient with severe malabsorption and paralytic ileus, veterinary IV ivermectin (3 doses of 200 μg/kg, 48 hours apart and a follow-up dose 1 week later) was effective.[405] The patient recovered but relapsed a month later, at which point an additional 2-week course of daily oral ivermectin was administered, after which all further stool samples were negative. Treatment is recommended to continue for at least 2 weeks after the parasite is no longer detectable in stool or sputum.[390] In patients with hyperinfection syndrome, ivermectin is the drug of choice, and longer treatment courses may be required.

Other Fungal and Parasitic Infections

Trypanosoma cruzi

Chagas disease, caused by the parasite *T. cruzi*, is endemic to Central and South America. Asymptomatic parasitemia is more common than symptomatic disease in potential donors.[355] Antibodies against *T. cruzi* indicate a former infection; however, an issue for donor screening is the high rate of false positives yielded by current serological assays. Acute parasitemia may be detected by PCR or the Strout test, but these are generally not sufficiently sensitive for screening of organs and donors because parasitemia is intermittent.[5]

US guidelines recommend targeted *T. cruzi* screening for potential donors born in Mexico, Central America, and South America, with positive test results to be confirmed by secondary testing.[393] Because *T. cruzi* has a predilection for muscle, heart, and neurological cells, the utilization of hearts from donors infected with *T. cruzi* is not recommended; however, transplantation of kidneys and livers from infected donors may be considered with the informed consent of the recipient(s).[60] UK guidelines are more restrictive, and state that the following individuals are contraindicated from donating organs (unless they have been shown to not have antibody in their blood by a validated test for *T. cruzi* performed within the past 6 months)[29]:

- those born in South America or Central America (including Southern Mexico);
- those whose mothers were born in these countries;
- those who may have received a blood transfusion in these countries;
- those who have lived and/or worked in rural subsistence farming communities in these countries for a continuous period of 4 weeks or more.

Prophylactic treatment (benznidazole) in D+/R− combinations has had some success.[406] All recipients of organs from Chagas disease-positive donors should be closely monitored for evidence of disease transmission, with testing by PCR or microscopy of blood.[407,408] Treatment (benznidazole, nifurtimox) should be initiated promptly upon recognition of parasitemia. Adjustments to immunosuppression may also be warranted, and certain immunosuppressive therapies (eg, thymoglobine or mycophenolate) may need to be substituted in recipients of organs from Chagas disease-positive donors.[409]

In Australia and New Zealand, *T. cruzi* serology is unlikely to be available in a timely fashion. In the case of donors born in Central or South America, hearts should not be used (unless a negative antibody test is available) but other organs may be considered with informed consent.

Leishmaniasis

Leishmaniasis is a protozoan parasite that is spread by the bite of a sandfly, with dogs being its major animal reservoir. There are about 20 different species of *Leishmania*, affecting an estimated 12 million people worldwide.[367] *Leishmania* infection is clinically classified as (1) cutaneous leishmaniasis, predominantly occurring in Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran, Pakistan, Peru, Saudi Arabia, and the Syrian Arab Republic; (2) mucocutaneous leishmaniasis, 90% of which is found in the Plurinational State of Bolivia, Brazil, and Peru; and (3) visceral leishmaniasis, 90% of which is found in Brazil, Ethiopia, India, Somalia, South Sudan, and Sudan.[410] No autochthonous cases of leishmaniasis have been reported in Australia; however, imported cases are reported relatively regularly, affecting refugee populations and persons who have lived in or travelled to endemic regions. A study of patient biopsies and bone marrow specimens sent to St Vincent's Hospital Sydney from July 2008 to March 2014 found that cutaneous leishmaniasis was the most common manifestation in this population (94%), and approximately 47% of affected patients in this study had a history of travel to or residence in

Afghanistan.[411] Imported cases of leishmaniasis are becoming increasingly common in nonendemic locations including Australia, North America, and Northern Europe as a consequence of increased international travel and international migration.[412,413]

In the general population, visceral leishmaniasis is usually subclinical and establishes lifelong latency, with only approximately 10% to 20% of affected persons developing clinically overt disease.[414] Clinical visceral leishmaniasis is more common in immunocompromised persons: data from HIV-infected persons show the rate of clinically overt disease to be increased at least 100 times in this population.[414] Leishmaniasis is rarely reported in transplant recipients, but when it does occur, it is most commonly the result of reactivation of preexisting asymptomatic leishmaniasis in the recipient.[414] Cutaneous or mucocutaneous leishmaniasis are rarely reported in organ transplant recipients.[355,367] The majority of leishmaniasis cases reported in transplant recipients have occurred in countries of the Mediterranean basin (especially Spain, France, and Italy), where there are a large number of migrants from endemic countries and highly active transplant programs.[414]

Donor-transmitted *Leishmania* has been reported twice.[367,414] In 1 case, a Macedonian kidney recipient who had purchased the organ from an Indian vendor developed visceral leishmaniasis and died.[415] In a Swiss case from 1990, visceral leishmaniasis was detected in a liver transplant recipient 1 year posttransplant after the patient developed fever, pancytopenia, and persistent splenomegaly.[416] She was treated with pentavalent antimony for 42 days, though although symptoms improved, bone marrow cultures remained positive for *Leishmania* and significant side effects developed. Treatment with antimony was stopped and replaced by ciprofloxacin, then by amphotericin B, with therapy continued for another 40 days, after which the patient remained well.[416]

Acute visceral leishmaniasis is characterized by fever, hepatosplenomegaly, bone marrow suppression and hepatic dysfunction. Presentation in organ transplant recipients is similar to that of immunocompetent persons: fever with hepatosplenomegaly, wasting, hypoalbumineuria, and pancytopenia. Disseminated leishmaniasis involves infection of the spleen, liver and bone marrow and, without prompt treatment, results in multiorgan failure and death.[367] An issue for the diagnosis of leishmaniasis in the context of transplantation is that symptoms may be misdiagnosed or the disease may be concealed by the presence of opportunitistic infections with similar symptoms, leading to delayed treatment. Without antileishmanial treatment, visceral leishmaniasis is a fatal disease, with death caused by intercurrent infections or bleeding.[414]

Direct examination of amatigotes on bone marrow and spleen aspiration is the gold standard for diagnosis of visceral leishmaniasis.[414] Antibody detection and NAT have a higher sensitivity for detection of visceral leishmaniasis in its early stages, and should be used as an adjunct to diagnosis.[363] The recombinant kinesin antigen (rK39) has a sensitivity of 94% for visceral leishmaniasis in solid organ transplant recipients, whereas *Leishmania* PCR has an estimated sensitivity of 91%.[414]

Liposomal amphotericin B is a well-tolerated and effective treatment for visceral leishmaniasis, with cure rates of up to 95% in immunocompetent persons, and 84% in transplant recipients.[414,417] Antimony compounds are also used. Miltefosine has also been shown to be highly effective,

but is not currently approved for use in transplant recipients.[367] As relapse is relatively common, secondary prophylaxis with intermittent amphotericin or miltefosine may be warranted.[355,367]

Given the rarity of donor-derived infection, and the poor performance, limited availability and lengthy turnaround time of noninvasive assays, *Leishmania* testing is not recommended in the evaluation of potential organ donors.[354]

Candidiasis

Candidiasis in Kidney Transplantation

Donor-derived candidiasis occurs in approximately 1 in every 1000 kidney transplants, typically as a result of contamination of the preservation fluid before or at the time of organ procurement.[418] Rupture of an abdominal viscus is often the likely source of the contamination.[419] Transmission from donors with candidemia have also been reported.[31]

In kidney recipients, donor-derived candidiasis may present as candidemia, infected urinoma, perineal hematoma, abscess, or a fungus ball. Vascular complications, for example, mycotic aneurysm, anastomotic rupture, may also occur. Fluconazole is the preferred drug for treatment or prevention of donor-derived candidiasis.[418] In the absence of clinical infection, empiric antifungal therapy can be discontinued after 2 weeks. For patients with clinical or microbiological evidence of infection, therapy should be extended for 4 to 6 weeks, depending on the results of imaging, cultures and clinical data. If vascular complications are present, a minimum of 6 weeks of antifungal treatment is recommended.[418]

Where *Candida* is visualized on stains or grown in preservation fluid, or in cases of documented intestinal perforation in the donor, prophylactic antifungal treatment should be commenced in the recipient. United States guidelines state that donor candiduria is not a contraindication to kidney donation provided the recipient received appropriate antifungal therapy. Utilization of kidneys from donors with untreated candidemia, however, is not recommended.[418]

Candidiasis in Abdominal Organ Transplantation

Contamination of the preservation fluid with Candida occurs relatively frequently in liver transplantation (~4% of preservation fluids), and antifungal prophylaxis is commonly administered to liver transplant recipients considered at risk of invasive fungal infections.[418] When Candida is grown in preservation fluid cultures or when there is intestinal contamination during organ recovery, liver transplant recipients should receive empiric antifungal therapy for 2 weeks.

Studies of the microbiology of donor duodenal contents in pancreas transplants have also indicated frequent contamination with Candida, although there are limited data on donor-derived fungal infections in pancreas transplantation. Treatment as for kidney transplant recipients is recommended.[418]

Candidiasis in Thoracic Organ Transplantation

Candida species frequently colonize the oropharynx and commonly appear in respiratory tract cultures. Antifungal prophylaxis for approximately 3 months is commonly administered in lung transplantation[420]; however, if prophylaxis is not given and donor bronchopulmonary secretions yield *Candida*, then empiric therapy should be considered and continued until the integrity of the bronchial anastomosis is confirmed.

Cryptococcosis

Cryptococcosis occurs in 0.3% to 5% of transplant recipients,[421] primarily as a result of reactivated infection, although rare cases of de novo donor-derived cryptococcosis infection have also been described.[422-424] Donors with cryptococcosis at any site have the potential to transmit infection, and the possibility of cryptococcosis should be considered in donors with undiagnosed neurological illness or meningoencephalitis.[418] There has been at least 1 case of disseminated cryptococcosis transmitted by a donor with unrecognized meningoencephalitis.[422]

Risk factors for cryptococcosis in the donor include the administration of corticosteroids, iatrogenic immunosuppressants, sarcoidosis, end-stage liver or kidney disease, and rheumatologic disorders.[418] Donors with meningoencephalitis and donors with unexplained pulmonary lesions of fever of unknown cause should be tested for serum cryptococcal antigen. For donors with meningoencephalitis, evaluation for cryptococcosis should additionally include CSF cryptococcal antigen testing, cultures, neuroimaging, and histopathologic examination of any abnormal tissue.[418] As serum antigen has been demonstrated to have a lower diagnostic yield for isolated pulmonary cryptococcosis, in cases with focal disease, histopathological evaluation of biopsy material should be performed.

United States guidelines recommend that organs from donors with untreated cryptococcal disease be avoided, except in lifesaving circumstances. In cases where the donor is receiving antifungal treatment for cryptococcal disease, it is recommended that organ utilization be considered on a case-by-case basis, preferably after documentation of mycological eradication.[418] If transmission of cryptococcosis does occur, mild-to-moderate extraneural infections may be treated with fluconazole. Treatment for moderate to severe, disseminated and CNS Cryptococcus consists of induction with a lipid formulation of amphotericin B and flucytosine, followed by consolidation and maintenance therapy with fluconazole for a duration of at least 6 to 12 months.[418]

Aspergillus

Donor-derived invasive aspergillosis has been described in several case reports and is associated with a high rate of graft loss and mortality. Two case series describe the transmission of *Aspergillus fumigatus* by solid organ donors who subsequently became multiorgan donors themselves.[425,426] The first case series involved a heavily immunosuppressed liver transplant recipient who died 15 days posttransplant from intracerebral hemorrhage and then donated their kidneys and heart.[426] Three weeks after transplantation, the 2 kidney recipients developed a fever, and both experienced a decrease in kidney function that was treated with high-dose methylprednisolone. Urine cultures were positive for *A. fumigatus*. The first kidney recipient was treated with itraconazole 200 mg/d, but 1 week later was admitted to hospital with a grand mal seizure, and repeat blood and urine cultures were positive for CMV and *A. fumigatus*. Intravenous amphotericin B was commenced (0.7 mg/kg per day) and immunosuppression reduced. Fever persisted and the patient developed progressive respiratory distress. Transplant nephrectomy was performed 3 weeks later, and amphotericin B treatment continued for another 4 weeks. At month 25 posttransplant, the patient was alive and well on hemodialysis. The second

kidney recipient was commenced on IV amphotericin B (0.7 mg/kg per day) when *A. fumigatus* was detected, but fever persisted and urine cultures remained positive for *A. fumigatus*, and transplant nephrectomy was performed 2 months posttransplant. Amphotericin B treatment was continued to a cumulative dose of 2 g. At month 25 posttransplant, the patient was also alive and well on hemodialysis. The heart transplant recipient had an uneventful postoperative course, and a thorough investigation prompted by the clinical course of the kidney recipients showed no sign of Aspergillosis. However, 5 months posttranspalntation, the patient was admitted to hospital with blurred vision and a tender nodule on his right palm. A pars plana vitrectomy of the right eye was performed, and a fungal culture of vitreous humor grew *A. fumigatus*. A transesophageal echocardiogram showed a large vegetation on the aortic valve, and an urgent thoracotomy was performed. The patient was treated with amphotericin B (intraocular, then systemic, then liposomal), followed by oral itraconazole, and was well 18 months after the aortic valve replacement.[426]

The second case, reported by Mueller et al in 2009, involved a recipient of a heart transplant who died of cerebellar hemorrhage 5 days posttransplantation and subsequently donated their kidneys, liver, lungs and islet cells.[425] On donor autopsy, invasive aspergillosis of the brain was found, which may have been related to repeated infections of the donor's ventricular assist device experienced before her heart transplant, although repeated tests for fungi were consistently negative. The first kidney recipient was admitted to hospital on day 40 posttransplant with weakness, symptoms of UTI, and diarrhea. Ultrasound revealed renal congestion, and a cystoscopy showed white floating masses. A direct smear of a urine sample showed fungal hyphae, and liposomal amphotericin B was commenced. A CT scan of the abdomen showed multiple abscesses in the graft, and a transplant nephrectomy was performed on day 46. Antifungal treatment was switched to voriconazole, and the patient was well at the end of follow-up (duration not specified). The recipients of the second kidney recipient and the liver were examined for aspergillosis on day 48 posttransplant, in response to the clinical course of the other kidney recipient. Urine cultures from the second kidney recipient yielded *A. fumigatus* and voriconazole was commenced. The patient was treated for 10 months and did not show any signs of aspergillosis. The liver recipient received voriconazole for 5 months and showed no signs of aspergillosis. The lung recipient died on the operating day due to primary nonfunction of the graft, unrelated to infection.[425]

Invasive aspergillosis has also been described on multiple occasions in association with commercial kidney transplantation, with rates of graft loss or death reaching nearly 80%.[427]

Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies are a group of rare, transmissible, and lethal neurodegenerative disorders that can occur sporadically, due to genetic causes, or due to exposure to the transmissible agent (prion). Creutzfeldt-Jakob disease (CJD) is the most common human TSE, and can occur in both sporadic CJD (sCJD) and acquired SJD (vCJD) forms. In the hospital setting, sCJD has been transmitted through

medical or surgical procedures involving neurosurgical instruments, brain electrodes, tissue (human cornea and dura mater grafts) and tissue extracts (human pituitary hormones).[29] Although there have been no known transmissions of vCJD via surgery or tissue or organ donation to date, there have been cases of vCJD transmission via transfusion of red blood cells and plasma.[29]

Creutzfeldt-Jakob disease is invariably fatal and duration of illness is typically short. Of definite and probable cases in Australia, median duration of illness was 3.7 months for sporadic cases (range, 0.9–60 months), 6.3 months for acquired cases (range, 2–25 months), and 6 months for genetic cases (range, 1.3–192 months).[428] Of sporadic, acquired, and genetic cases respectively, 72%, 56%, and 51% were deceased 6 months after the onset of symptoms.[428]

Prospective CJD surveillance in Australia has been performed since 1993. Persons with suspected CJD are notified to the Australian National Creutzfeldt-Jakob Disease Registry, typically as a result of referral for diagnostic CSF 14-3-3 protein detection, or alternatively via personal communications from clinicians, hospitals, families, or CJD-related groups, and through health record searches.[428] Once notified, referrals are assessed and if the suspicion of prion disease is supported, then the case is added to the register. Sixty-six persons with suspected human prion disease were added to the CJD surveillance register in 2015, and the average crude rate of prion disease-related post mortems in Australia is 1.4 per million per year.[428] The current annual rate of CJD deaths in the general Australian population is 1.15 per million population.[313] vCJD has not been reported in Australia to date. The most common risk factor for CJD in Australia is having received a human pituitary hormone product before 1986.[313] Many of those affected would have received a "Medical in Confidence" letter from the Chief Medical Officer regarding this risk.

There is currently no minimally invasive test to detect TSE before the onset of symptoms nor is the prevalence of asymptomatic TSE known. Definitive diagnosis can only be made, if at all, by neuropathological examination of brain tissue after biopsy or autopsy. In symptomatic patients, investigations that may assist in the differential diagnosis of TSE include electroencephalograph, identification of protein 14-3-3 in CSF, magnetic resonance imaging, or direct amplification of misfolded prion protein in the CSF using Real-Time-Quaking Induced Conversion.[313] In the context of deceased organ donation, minimizing the risk of donor-derived TSE transmission relies on screening the patient's history for symptoms consistent with TSE, exposure to human blood, dura mater grafts, pituitary-derived hormones, contact with contaminated surgical instruments and/or prior notification from the department of health as being at increased risk of TSE due to exposure to 1 or more risk factors.

The risk of transmitting TSE associated with a given donor can be defined as high, low, or background risk. The Australian Government Department of Health defines these risk categories as follows:

- High-risk: people who represent a definite risk of CJD transmission (see Table 35). These patients typically report neurological symptoms and display neurological signs of disease.
- Low-risk: people who represent a potential risk of CJD transmission (see Table 36). These patients may report neurological

symptoms or be showing neurological signs or may have an identified risk factor.
- Background risk: the general population who represent no identified increased risk of CJD transmission.[313]

Australian Infection Control Guidelines for Creutzfeldt-Jakob recommend that the following people at risk of TSE should be excluded from the routine donation of organs and tissues (including blood and plasma):

- people classified as high-risk;
- people classified at low-risk (tissues are excluded from donation but organs may be donated if the informed consent of the recipient is obtained);
- people who die in psychiatric establishments, with the exception of those in whom CJD has been specifically excluded;
- people who die of dementia;
- people who die with any obscure undiagnosed neurological disorder.[313]

UK guidelines state that organ and tissue donation is contraindicated for individuals with confirmed or suspected TSE, with a neurological disease of unknown etiology, or anyone who is blood relatives with persons with familial CJD. Exception is made if a donor has 2 or more blood relatives who have developed TSE but has been informed by a genetic counselor that they are not at risk. Previous exposure to human dura mater grafts, human pituitary-derived growth hormone and/or gonadotrophin are considered by the UK guidelines to be relative contraindications to organ transplantation, to be considered on a case-by-case basis. Where donation and transplantation would be lifesaving, donor exposure to TSE risk factors is taken into account but does not necessarily preclude donation.

European guidelines consider that risk of TSE exists where (1) CJD or vCJD has been observed frequently within the family, (2) treatment has occurred with pituitary gland hormones or growth hormone of human origin, and (3) dura mater has been used during an operative procedure.[5] It is recommended that the informed consent of the recipient be obtained where such risk factors exist.

EMERGING PATHOGENS AND OTHER PATHOGENS OF SPECIAL INTEREST

Zika

Epidemiology and Transmission Risk

Zika is a flavivirus transmitted mainly by mosquitos in the genus Aedes. It was first isolated from rhesus monkeys in 1947, with the first human cases confirmed by neutralizing antibodies in sera detected in Uganda (1948), Tanzania (1952), India (1952), Malaysia (1953), Borneo (1953), Philippines (1953), Egypt (1954), Vietnam (1954) then Mozambique (1957), followed by numerous other countries in equatorial Africa.[429] Until 2007, only sporadic cases of Zika virus infection in humans were reported, although it is likely that this low level of reporting is at least partly due to the clinical similarities between Zika virus infection, dengue, and chikungunya resulting in misattribution of the pathogen.

The first large outbreak of Zika virus–associated disease was reported from the Micronesian island of Yap in 2007,

TABLE 35.

Definition of high-risk category for CJD transmission[313]

Classification of CJD	Clinical signs and risk factors
1. Sporadic TSE	Clinical signs:
1.1 Definite: Neuropathologically/immunocytochemically confirmed	I Rapidly progressive dementia
1.2 Probable:	II Myoclonus
1.2.1 Clinical sign I plus at least 2/4 of signs in groups II and III	Visual or cerebellar problems
1.2.2 Possible I plus positive 14-3-3 CSF assay	Pyramidal or extrapyramidal features
1.2.3. Possible I plus 2/4 of II and duration <2 years	Akinetic mutism
	III Typical EEG
2. Accidentally transmitted (iatrogenic) TSE	Recognized healthcare acquired risk factors:
2.1 Definite: Definite TSE with a recognized healthcare acquired risk factor	Treatment with human cadaver-derived pituitary growth hormone, human cadaver-derived pituitary gonadotrophin or human dura mater graft.
2.2 Probable:	
2.2.1 Progressive predominant cerebellar syndrome in human pituitary hormone recipients	Corneal graft in which the corneal donor has been classified as definitely or probably having a human prion disease.
2.2.2 Probable TSE with recognized healthcare-associated risk factor	Exposure to surgical instruments that have come into contact with higher-infectivity tissues previously used in a case of definite or probably human prion disease.
	The relevance of any exposure to disease causation must take into account the timing of exposure in relation to disease onset.
	(This list is provisional, as previously unrecognized mechanisms of human prion diseases may occur.)
3. Genetic prion diseases/TSE	Prion protein gene (PRNP) mutations
3.1 Definite	PRNP mutations associated with GSS neuropathological phenotype: P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T, 192bpi
1.1.1 Definite TSE and definite or probable TSE in first-degree relative	
1.1.2 Definite TSE with a pathogenic PRNP mutation	PRNP mutations associated with CJD neuropathological phenotype: D178N-129V, V180I, V180I + M232R, T183A, T188A, E196K, E200K, V203I, R208H, V210I, E211Q, M232R, 96 bpi, 120 bpi, 144 bpi, 168 bpi, 48 bp deletion
3.2 Probable	
1.2.1 Progressive neuropsychiatric disorder and definite or probable	PRNP mutations associated with FFI neuropathological phenotype: D178N-129M
TSE in first-degree relative	PRNP mutation associated with vascular PRP amyloid: Y145S
1.2.2 Progressive neuropsychiatric disorder and pathogeneic PRNP mutation.	PRNP mutations associated with proven but unclassified prion disease: H187R, 216 bpi.

CJD, Creutzfeldt-Jakob disease; TSE, transmissible spongiform encephalopathies.

during which an estimated 73% of the population was infected. In Africa and Asia, Zika virus continues to be reported relatively rarely and is associated with mild symptoms; by contrast, a lack of population immunity is thought to have contributed to widespread outbreaks over the past decade in the Pacific Islands (including French Polynesia, the Cook Islands and New Caledonia) and the Americas.

It was during the outbreak in French Polynesia in 2013 to 2014, causing disease in approximately 11% of the population,

that the first link was made between Guillain Barré syndrome and Zika virus infection.[430] Microcephaly cases were also retrospectively linked to this outbreak. The World Health Organization received first reports of locally transmitted infections in Brazil in May 2015.[429] On February 1, 2016, the Director General of the World Health Organization declared the epidemic of Zika virus infection in Brazil, and its association with clusters of microcephaly and other neurological disorders, a Public Health Emergency of International

TABLE 36.

Definition of low-risk category for CJD transmission[313]

People with a progressive neurological illness of less than 1 year's duration, with or without dementia for whom a determination to assign a high-risk status or background risk status cannot be made following competent professional review.

People with a progressive neurological illness of less than 1 year's duration, with or without dementia awaiting the outcome of a professional review to assign a high-risk status or background risk status.

Patients undergoing a diagnostic brain biopsy for progressive brain disease or patients undergoing neurosurgical investigations (including brain biopsy) or therapeutic procedures for a progressive disorder that includes dementia if <1 year duration and where professional review is unable to assign a high-risk status or a background risk status.

All genetically related members of any family in which there is a strong family history (2 or more first- or second-degree relatives) of dementia or neurological illness, and in which affected individuals have not been competently and completely assessed, specifically for CJD.

Recipients of cadaver-derived human pituitary hormones (growth hormone and gonadotrophins) before 1986.

Recipients of dura mater homografts or transdural neurosurgery before 1990, or neurosurgical patients for whom the use of dura mater homografts cannot be excluded by reference to patient records.

Individuals who have been contacted by a Health Department as part of a look-back procedure from exposure to surgical instruments that had previously been used on high or medium infectivity tissues from patients later found to have contracted CJD are likely to have a very low, but unquantifiable risk for CJD that is thought to be above background risk. Until further information on the likely risk of these individuals is available, they are conservatively placed in a low risk category.

CJD, Creutzfeldt-Jakob disease.

Concern.[429] As of July 25, 2017, 48 countries and territories have had confirmed cases of local vector-borne transmission of Zika virus, and another 5 countries have reported cases of sexually transmitted Zika virus.[430,431]

The growing evidence of the severity of the potential complications of Zika virus and the WHO declaration of a Public Health Emergency in relation to the current Zika epidemic in Brazil and Central America prompted concerns regarding the implications for blood, tissue, and organ donation. However, at the time of the 2016 outbreak, there were few data on the natural history of Zika virus infection—the incubation period, time to serological conversion, time to symptom onset, and time to viral clearance were unknown. It is now understood that Zika virus infections are symptomatic in only approximately 20% of cases, that it is shed in blood, saliva, urine, and semen, and that it is sexually transmissible. A recent retrospective analysis that included all case reports of Zika virus infection since 1956 that captured temporal data estimated the median incubation period of Zika virus–associated disease was 5.9 days (95% credible interval, 4.4–7.6) with a dispersion of 1.5 days (95% credible interval, 1.2–1.9). Thus, 95% of all symptomatic cases would be expected to develop symptoms within 11.2 days of infection (95% credible interval, 7.6–18.0).[432] The estimated mean time to seroconversion was 9.1 days after infection (95% credible interval, 7.0–11.6): 5% of cases would have detectable antibodies within 4.4 days (95% credible interval, 1.3–7.0) and 95% would have detectable antibodies within 13.7 days of infection (95% credible interval, 10.6–21.7). The mean time to viral clearance was estimated to be 9.9 days (95% credible interval, 6.9–21.4) after infection: 5% would have no detectable virus within 2.4 days (95% credible interval, 0.009–5.9), 95% within 18.9 days (95% credible interval, 13.6–79.4), and 99% within 23.4 days (95% credible interval, 14.3–154.3). Thus, a 300-day window from donation to the last date of travel in an endemic country would correspond to twice the upper 95% credible interval for viral clearance from 99% of infected individuals.[432] A relevant caveat to these findings is that the data are from people presumed to have been infected via mosquito bite, whereas the timing of incubation, seroconversion, and viral clearance may be different for cases with an alternative transmission route.[432]

Australia and New Zealand do not have local transmission of Zika virus. The mosquito that carries Zika virus, *Aedes aegypti*, is present only in some parts of Central and North Queensland. Health authorities in Queensland have programs to manage mosquitos in their state and have specific risk mitigation strategies in place in relation to Zika virus, thus Zika virus should be considered in potential donors with a history of recent travel to Zika-affected countries. The number of confirmed/probable cases of Zika virus diagnosed in Australia peaked in 2016 at 102 cases; in 2017, the total number of notified cases dropped to 9.[256] The majority of cases were acquired in Tonga, Fiji, Samoa, Mexico, or Brazil. The number of confirmed/probable cases of Zika virus diagnosed in New Zealand in 2016 was 100, with the majority of cases having been acquired in either Tonga, Samoa, or Fiji.[433]

An up-to-date list of countries with new Zika outbreaks or ongoing transmission can be found at the World Health Organization website (http://www.who.int/emergencies/zika-virus/classification-tables/en/—last accessed 20 March 2018). The World Health Organization defines 4 categories of Zika virus transmission. Category 1 defines countries with new introduction or reintroduction with ongoing transmission; category 2 defines countries with evidence of virus circulation before 2015 or countries with ongoing transmission that is no longer in the new or reintroduction phase, but where there is no evidence of interruption; category 3 defines countries with interrupted transmission and the potential for future transmission; category 4 defines countries with an established competent vector but no known documented past or current transmission. The CDC maintains a regularly updated map of countries and territories with risk of Zika virus infection (https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika).

Clinical symptoms of Zika virus infection are usually mild and include fever, rash, joint pain, conjunctivitis, muscle pain and retroocular headache. Few data are available on the clinical course of Zika virus infection in immunocompromised patients; the first reported case series of Zika virus infection in transplant recipients were published in 2017 from a hospital in Brazil.[434] Between January 2015 and April 2016, 187 kidney and 58 liver transplants were performed at Hospital de Base in São José do Rio Preto, northwest of São Paulo State, of which 40 recipients were suspected and screened for dengue virus. Four of these dengue-suspected screened recipients (2 liver recipients and 2 kidney recipients) were confirmed by RT-PCR to have Zika virus infection. The patients presented with fever, myalgia, adynamia, anemia, and thrombocytopenia, but none of the patients exhibited conjunctivitis, exanthema, or neurological symptoms. The mean time to onset of symptoms and hospital admission for these 4 patients was 7.25 days (range, 5–10).[434] All patients presented with complications, in particular bacterial superinfection, and all required hospitalization until symptoms had resolved. One of the liver transplant recipients required retransplantation due to hepatic artery thrombosis and biliary stenosis 91 days after Zika virus detection. All 4 patients had evidence of acute liver or kidney damage, and both kidney recipients needed to have their immunosuppression regimen altered.[434] More data are needed to establish whether Zika virus increases rejection rates, either via direct biological mechanisms, or indirectly due to the need to reduce immunosuppression.[435]

Direct-acting agents for the treatment of Zika virus infection are not yet available, nor has a vaccine yet been developed, and current treatment is supportive, including rest, fluids, and use of analgesics and antipyretics. Australian Department of Health recommendations are that aspirin and other nonsteroidal anti-inflammatory drugs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage. http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-zikavirus.

Little is currently known about the risk of Zika transmission through solid organ transplantation. Although it is known that Zika virus can be transmitted by blood exposure, there are few data on which specific organs can be infected with Zika or how long Zika virus might persist in these organs. In 1 fatal case of Zika virus infection in an adult with lupus erythematosus, rheumatoid arthritis, chronic use of corticosteroids and alcoholism, Zika virus RNA was detected in brain, liver, spleen, kidney, lung, and heart tissue.[436] However, it is unclear how infectious the virus would be infectious if these organs were to be transplanted.

Donor Screening and Risk Minimization

Using serology to diagnose Zika virus infection is complicated by the fact that Zika virus cross-reacts with antibodies

generated in response to other flaviviruses, such as dengue, yellow fever, WNV, and chikungunya, which cocirculate with Zika and have the same vectors.[437,438] Existing antibody-based assays are, therefore, labor-intensive and generally confined to research laboratories/specialist public health facilities.[437] Detection of Zika virus RNA is a more specific way of diagnosing Zika virus infection, and commercial Zika virus NAT systems were given investigational new drug approval by the US FDA in 2016.[439-441] However, false-negative NAT results are common due to the short duration of viremia and low viral loads soon after symptom onset—a study from Brazil found that only 45% of patients with suspected Zika infection returned a positive result on RT-PCR.[442] For this reason, the development of accurate commercial antibody tests for the diagnosis of Zika virus has been a priority.[437] In a recent publication, a multinational research team reported on the successful validation of the Zika NS1 blockade-of-binding (BOB) ELISA, demonstrating sensitivity of 91.8% and specificity of 88.9% at longer than 10 days postsymptom onset.[443]

According to the guidelines of the CDNA, a case of Zika virus infection is considered confirmed only where there is laboratory definitive evidence of infection.[444] Laboratory definitive evidence may include:

- detection of Zika virus by NAT or virus isolation, OR
- IgG seroconversion or a significant increase in antibody level or a fourfold or greater rise in titer of Zika vrus specific IgG, and recent infection by dengue or other epidemiologically possible flaviviruses has been excluded, OR
- detection of Zika virus-specific IgM in CSF, in the absence of IgM to other possible infecting flaviviruses.

Zika virus NAT may be performed on blood or urine (or amniotic fluid or CSF): it is unclear whether there is any difference in viral loads between blood and urine, although there is some evidence that Zika virus RNA appears to be detectable for longer in urine.[432,445,446]

A probable case, as defined by the CDNA, is one where there is both laboratory suggestive evidence and epidemiological evidence. Laboratory suggestive evidence includes detection of Zika virus–specific IgM in the absence of IgM to other epidemiologically possible flaviviruses or flavivirus vaccination within the 3 weeks before testing (if exposure was >4 weeks before the specimen was taken, then Zika virus-specific IgG must also be positive; if Zika-specific IgG was initially negative and subsequent testing longer than 4 weeks after exposure fails to demonstrate seroconversion, the case should be rejected). Epidemiological evidence includes travel to or residence in a Zika-receptive country or area in Australia, or sexual exposure to a confirmed or probable case within the previous 2 weeks (where symptoms are present) or 2 months (where symptoms are absent).

A clinical case is defined by the CDNA as a patient who develops an acute illness within 2 weeks of exposure, with 2 or more of the following symptoms:

- fever,
- headache,
- myalgia,
- arthralgia,

- rash,
- nonpurulent conjunctivitis.

International guidelines do not recommend routine screening of potential organ donors for Zika virus, but instead generally recommend targeted Zika screening for[447]:

- people with a recent medical diagnosis of Zika virus disease,
- residents of affected areas,
- travellers returning from affected areas,
- sexual contacts of men who have been diagnosed with Zika virus infection or who have travelled to or lived in a Zika-affected area during the 3 months before the sexual contact.

Summaries of published international recommendations regarding Zika virus and organ transplantation are given in Table 37 and Table 38.

West Nile Virus
Epidemiology

West Nile virus is an arbovirus that is maintained in nature in a transmission cycle between birds and mosquitos and is transmitted to humans and other mammals via bites from infected mosquitoes of the genus Culex. First identified in Uganda in 1937, WNV is commonly found in Africa, parts of Europe, the Middle East, North America and West Asia. The largest historical outbreaks have occurred in Greece, Israel, Romania, Russia and the United States, with the location of outbreak sites corresponding with major bird migratory routes.[449] WNV was imported into the United States in 1999 from the Middle East, causing an outbreak that spread throughout the continental United States, establishing WNV from Canada to Venezuela over a period of 10 years.[449]

Risk of infection transmission increases during times of year with the highest probability of mosquito bites. In temperate climates, therefore, WNV is seasonal as mosquitoes need air temperatures above 15°C to fly.[450] To date, there have been no documented cases of human-to-human WNV transmission via casual contact; however, infections have occurred through organ transplantation, blood transfusions and breast milk.[449] WNV infection is asymptomatic or associated with only mild flu-like symptoms in most cases (>99%); however, in some cases, WNV causes severe neuroinvasive disease, including meningitis, encephalitis and acute flaccid paralysis.[449] Immunocompromised persons have a much higher risk (~50%) of developing severe disease, and a much higher risk of death as a result.[450] Compared to a mortality rate of 4% among symptomatic WNV cases in the general population, the mortality rate among transplant recipients with symptomatic WNV is approximately 25%.[451]

Kunjin virus is a variant of WNV that is endemic to tropical northern Australia, and tends to result in less severe disease compared to WNV variants endemic to other parts of the world. Most people with the Kunjin lineage of WNV have mild or no symptoms; when symptoms do occur, they may include fever, malaise, headache, muscle aches, swollen lymph nodes, fatigue, rash, and swollen and aching joints.[452] In rare cases, infection may progress to encephalitis. There was an average of 1.6 notifications of WNV or Kunjin virus infection per year in Australia for the past decade (see Figure 15). Some of these cases were acquired internationally in endemic

TABLE 37.

International guidelines on Zika virus and organ donation

Guideline	Date last updated	Recommendation
Scanditransplant[a]	February 15, 2016	For donors with recent travel history to Latin America or other affected areas who do not have any symptom of viral infection, the risk of Zika infection is low. The low-risk of Zika should be balanced against the harms of declining the organs.
		Patients with Zika virus infection are viremic for a short period (approximately 14 days) but the virus can be found in other tissues after the viremia has cleared. There is no possibility to screen for the Zika virus infection in deceased donors since PCR diagnosis can take several days and IgM antibodies against Zika virus have strong cross-reactivity, which may generate false-positive results in serological tests.
		It is probable that infection can be transmitted by organ transplantation but the impact of immunosuppression on the natural history of Zika virus infection is not known.
OPTN[b]	February 8, 2016	OPOs should focus on recent travel history and epidemiologic risk factors, as well as recent donor symptoms. Although infected potential donors may possibly transmit Zika virus to recipients, DTAC, AST and ASTS do not believe concern for Zika virus infections should summarily exclude donors from transplantation; rather, the risk of donor-derived infection should be balanced with the benefits of transplantation in each potential recipient. In the case of potential living donors with a history of travel to Zika-endemic areas, donation should be deferred where possible. Routine donor laboratory screening is not currently recommended (for either living or deceased donors). Recommended screening protocols for donors (living or deceased) with a recent history of travel to an affected area and clinically compatible illness are as follows:
		– Specimens collected <4 days after symptom onset should be subjected to molecular testing (RT-PCR) for Zika, dengue, and chikungunya
		– Specimens collected 4–7 days after symptom onset should be subjected to molecular testing and serologic testing for virus-specific IgM antibodies, with a convalescent-phase sample also sent later
		– Specimens collected >7 d after symptom onset should be subjected to serologic testing for virus-specific IgM antibodies.
		Because of the cocirculation of Zika, dengue and chikungunya viruses, it is recommended that testing for all 3 viruses should be performed where appropriate.

[a] Guidelines for prevention of transmission of infectious diseases from organ donors to recipients. Scanditransplant, April 2016.
[b] Guidance for organ donation and transplantation professionals regarding the Zika virus. OPTN/UNOS, February 2016; Guidance on Zika virus. OPTN/UNOS, July 2016.
PCR, polymerase chain reaction; OPTN, Organ Procurement and Transplantation Network; OPO, organ procurement organization; DTAC, Disease Transmission Advisory Committee; AST, aspartate aminotransferase; RT-PCR, reverse transcriptase PCR.

countries (the 3 cases reported in 2013/2014 were acquired in Papua New Guinea, Timor-Leste, and Djibouti, and the 2007 case was acquired in Israel); however, the cases reported between 2008 and 2013 were all locally acquired.[257,453-457] In 2017, Western Australia experienced an outbreak of Kunjin in the Kimberly region involving multiple clinical cases, although it is likely that for every notified case in this outbreak there were also many more subclinical, potentially viremic, cases (personal communication V Sheppeard).

Suitable vectors for WNV do not exist in New Zealand, and to date, there have been no notified cases of WNV in New Zealand, including cases acquired abroad.

TABLE 38.

Generalized recommendations for prevention of donor-derived Zika virus transmission in solid organ transplantation, by nature of donor exposure

Donor exposure	Recommendation
Deceased donors	
Asymptomatic donor with travel to area of Zika transmission in the preceding 4 weeks	May be considered for organ donation after discussion about risks and benefits and informed consent
Asymptomatic donor with history of unprotected sexual activity with men who had been to area of Zika transmission in the preceding 4 weeks	May be considered for organ donation after discussion about risks and benefits and informed consent
Potential donor with symptoms suggestive of Zika virus infection and with travel to area of Zika transmission in the preceding 6 months	Do not use donor organs unless symptoms can be attributed to a condition other than Zika virus and this other condition does not preclude donation
Donor with symptoms suggestive of Zika virus infection and with history of unprotected sexual activity with men who had been to area of Zika transmission in the preceding 6 months	Do not use donor organs unless symptoms can be attributed to a condition other than Zika virus and this other condition does not preclude donation
Living donors	
Asymptomatic living donors with history of travel to area of Zika transmission	Defer donation for 4 weeks after return. If no symptoms develop in 4 weeks, may donate after discussion about risks and benefits and informed consent
Asymptomatic living donors with history of unprotected sexual activity with men who had been to area of Zika transmission in the preceding 4 weeks	Defer donation for 4 weeks after last unprotected sexual encounter. If no symptoms develop, may donate after discussion of risks and benefits and informed consent.
Living donors with Zika virus infection	Defer donation for 6 months after onset of symptoms. If recipient's clinical condition does not allow the delay in transplantation, obtain Zika virus PCR 4 weeks after resolution of symptoms and consider donation only if PCR is negative and after discussion of risks and benefits of potential donor-derived infection and informed consent.

Adapted from Silveira and Campos.[448]
PCR, polymerase chain reaction.
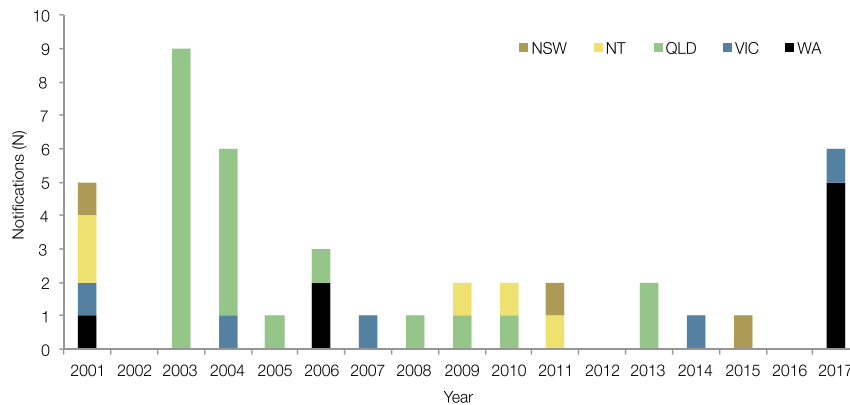
FIGURE 15. Number of notifications of West Nile/Kunjin virus infection received from Australian State and Territory health authorities from 2001 to 2017.[36] NSW, New South Wales; NT, Northern Territory; QLD, Queensland; VIC, Victoria; WA, Western Australia.

Multiple cases of WNV transmission from organ donors to recipients have been reported in the published literature, with a high rate of adverse outcomes (see Table 39). Of 23 recipients of solid organs from 8 WNV-infected donors, 20 (87%) developed WNV infection, of whom 14 (70%) developed encephalitis. The most common presenting symptoms among recipients with donor-derived WNV were fever, myalgias, arthralgias, fatigue or diarrhea.[458] With the exception of 1 case (Morelli et al), the potential for WNV infection in the donor was not suspected, and diagnosis was only made retrospectively after clinical symptoms developed in the recipient (s). To date, there have been no cases of the Kunjin lineage of WNV being transmitted by organ transplantation.

Donor Screening and Risk Minimization

The incubation period for WNV is approximately 3 to 15 days, and infected individuals are viremic for up to a week. The majority of viremic persons (~80%) are asymptomatic. Laboratory studies for WNV diagnosis include analysis of serum and CSF by:

- IgG antibody seroconversion (or significant increase in antibody titers) in 2 serial specimens collected at 1 week intervals by ELISA,
- IgM antibody capture ELISA,
- neutralization assays,
- viral detection by reverse transcriptase polymerase chain reaction (RT-PCR) assay,
- virus isolation by cell culture.

IgM can usually be detected within ~8 days after initial exposure in CSF and serum samples taken from WNV-infected patients who present with clinical symptoms.[449] Serum WNV IgG is produced ~3 to 4 days after IgM, and the presence of serum IgG confers lifelong protection against reinfection.[467]

Serological screening in the context of deceased donation is complicated by the fact that transmissible WNV may be present in potential donors who test negative on both serology and NAT at the time of donation. Because viremia is transient, WNV-NAT may be negative even during the acute phase of infection.[451] Retrospective screening of stored donor serum in cases of donor-derived WNV transmission found that only 50% of donor serum tested positive for WNV by RT-PCR, and only 38% of donor serum tested positive for WNV IgM.[458] Given the complexities of virus

dynamics and the antibody response, testing of paired serum and CSF WNV IgM and IgG in conjunction with RT-PCR would improve WNV detection in potential donors.[468] Conversely, false-positive results are possible and positive serology may result from cross-reacting antibodies from other prior flavivirus infections in the donor.[5] Urine testing may prove to be more useful than blood testing, because the kidney is a site of WNV replication and WNV is shed for longer in the urine and at a higher viral load. Currently, however, there are no studies confirming the clinical utility of urine screening for WNV.[5]

Routine WNV screening is neither practical nor cost-effective outside of endemic areas.[450] Targeted screening restricted to potential donors who display symptoms of WNV is also problematic, as most infected persons will be asymptomatic. In most published cases of donor-derived West Nile transmission, the donors did not show any signs or symptoms of WNV infection in the period leading up to donation that might have prompted screening.[458] Given these considerations, European guidelines recommend routine screening for WNV only when locally increased rates of WNV are detected, and for potential donors coming from regions with ongoing outbreaks.[5] Organs from such donors may be used before test results are available; however, prophylactic monitoring of recipients of organs from donor with confirmed WNV is recommended. Where a donor is known to be viremic for WNV, European guidelines state that a transplant infectious disease expert should be consulted before such organs are used.

This approach has been successful in detecting WNV in a timely manner—for example in the Italian case of donor-derived WNV transmission reported by Morelli et al.[462] As the donation occurred in an endemic area during a WNV outbreak, routine WNV screening of the donor by NAT was performed on the day after organ transplantation occurred. The positive result in the donor was followed by WNV detection in the recipient by NAT on day 3 posttransplant, at which point, immunosuppression was reduced and prophylaxis with fresh frozen plasma infusion of WNV IgG was commenced. After 23 days of prophylaxis, the patient developed a WNV IgM antibody response that reached 1:1600, at which point, the immunoprophylaxis was stopped. The patient was discharged from hospital on posttransplant day 45, without having developed clinical symptoms of WNV.[462]

In those OPOs in the United States that test for WNV, testing is generally performed during seasons when WNV is

TABLE 39.

Donor and recipient characteristics in cases of donor-derived WNV transmission (deceased donors)

Reference	Organ	Donor Serum results			Recipient Serum results			Recipient CSF results			Clinical course	Treatment	Immunosuppression strategy	Outcome
		PCR	IgM	IgG	PCR	IgM	IgG	PCR	IgM	IgG				
Winston et al, 2014[458]	Kidney	–	+	+	+	+	–	+		–	Fever, myalgias, diarrhea (day +10), lethargy, encephalopathy, tachypnea, hypotension (day +13), left side weakness followed by coma (day +15), care withdrawn (day +23)	Polyvalent IVIG (500 mg/kg per day), subcutaneous interferon alfa-2b (3 mill units per day)	Reduced	Dead
	Kidney	–	+	+	+	+	–	+	+	–	Fever (day +17), headaches, disorientation (day +19), fever resolved and mental status returned to normal after treatment (day +28), discharged (day +30)	Polyvalent IVIG (500 mg/kg per day), subcutaneous interferon alfa-2b (3 mill units per day), infusions with plasma containing WNV IgG	Discontinued until fever resolved	Alive
	Lungs	–	+	+	–	–	–	+	+	+	Dyspnea, hypoxemia (day +13), encephalopathy, right upper-extremity weakness, respiratory distress (day +20), complete flaccid paralysis and multiple seizures, death (day +38)	Polyvalent IVIG (500 mg/kg per day), subcutaneous interferon alfa-2b (6 mill units, then 3 mill units per day for 3 d, then 1 mill units per day for 3 d)	Reduced	Dead
	Liver	–	+	+	–	–	+	+	+	–	No clinical symptoms	Oral ribavirin (600 mg every 12 hours), polyvalent IVIG (500 mg/kg daily for 4 days then every other day)	No change	Alive
Rabe et al, 2013[459]	Kidney	+	–	+	+	+	+	+	–	+	Confusion (day +8), deterioration of mental status (day +13), coma, death		Reduced, then discontinued	Died
	Kidney	+	–	+	+	+	+	+	+	+	Headache, backache (day +16), no other symptoms			Alive
Inojosa et al, 2012[460]	Kidney	–	+	+	+	+	+	+	+	+	Fever, myalgias, fatigue (day +11), tremulousness, confusion, dysarthria, mental deterioration, mechanical ventilation, coma	Fresh frozen plasma infusion containing WNV IgG (15 mL/kg per day)		Coma
Rhee et al, 2011[461]	Liver	+	–			+		+	+	+	Fever (day +15), confusion, dysarthria, tremulousness, lower extremity paresis (day +3), improved mental status and motor strength (day +5)	IV immune globulin (0.4 g/kg)	Discontinued	Alive
Morelli et al, 2010[462]	liver	+			+						No clinical symptoms	Fresh frozen plasma infusion containing WNV IgG	Reduced	Alive

Reference	Organ	Donor Serum results			Recipient Serum results			Recipient CSF results			Clinical course	Treatment	Immunosuppression strategy	Outcome
		PCR	IgM	IgG	PCR	IgM	IgG	PCR	IgM	IgG				
CDC, 2009[463]	Heart	–	(+)[a]	–						+	Tonic-clonic seizures requiring intubation (day +8), fever, mental deterioration			Alive
CDC, 2005[464]	Kidney	–	+	+	+	–	+				No clinical symptoms	Prophylaxis with IV immune globulin		Alive
	Kidney	–	+	+	–	–	–				No clinical symptoms	Prophylaxis with IV immune globulin		Alive
	Liver	–	+	+	+	+	+	+	+	–	Fever, altered mental status (day +13), respiratory distress (day +18), coma, acute flaccid paralysis	High doses of IV immune globulin with high antibody titers against WNV		Coma

TABLE 39. (Continued)

Reference	Organ	Donor Serum results			Recipient Serum results			CSF results			Clinical course	Treatment	Immunosuppression strategy	Outcome
		PCR	IgM	IgG	PCR	IgM	IgG	PCR	IgM	IgG				
	Lung	–	+	+		+	+	–	+	+	Fever, dyspnea (day +16), altered mental status, seizures, acute flaccid paralysis, coma	High doses of IV immune globulin with high antibody titers against WNV		Coma
Costa et al, 2011[465]	Kidney	–	+	+	+	+	+	+	+	+	Fever, encephalitis	High titer West Nile IVIG		
	Kidney	–	+	+	+	+	+	+	+	+	Fever, encephalitis	None		
Iwamoto et al, 2003[466]	Kidney	+	–			+		+		+	Fever, rash, upper respiratory tract symptoms, backache, diarrhea (day +12), decline in mental status, became unresponsive requiring mechanical ventilation (day +16), condition improved			Alive
	Kidney	+[b]	–			–		–		–	Fever, headache, myalgia, arthralgia, diarrhea (day +17), mental deterioration, became unresponsive requiring mechanical ventilation (day +20), brain stem herniation (day +26)			Dead
	Heart	+	–		+	+			+	+	Fever (day +9), confusion, diarrhea, incontinence, leg weakness (day +10), dysarthria, tremors (day +13), requiring mechanical ventilation (day+18), symptoms improved			Alive
	Liver	+	–			+					Fever (day +6), diarrhea, generalized weakness, back pain (day +12), mild cognitive impairment, fever resolved (day +14)			Alive

[a] Donor was negative for WNV RNA and WNV IgG and IgM antibodies. The donor had received 10 blood products before brain death; one of the donor's serum subsequently tested positive of WNV IgM.

[b] Quantitative PCR performed on brain tissue obtained at autopsy.

PCR, polymerase chain reaction; CDC, Centers for Disease Control; CSF, cerebrospinal fluid.

predicted to be active in the donor service area.[469] Modeling indicates that universal screening for WNV in the United States would be associated with a net loss of life due to missed opportunities for organ donation, therefore, as in Europe, recommendations at the current time are to screen donors using NAT when there are WNV cases in the region, and to avoid donors with unexplained encephalitis at all times.[393,470] The use of WNV serology or urine testing for donor screening is not recommended in the United States at this time.[393] UK guidelines recommend donor screening for WNV using NAT only in the presence of symptoms in the potential donor compatible with NAT infection, or travel history to an area with an ongoing outbreak.[450]

There is no effective therapy for WNV and treatment is largely supportive. Case reports of WNV in transplant recipients have described clinical improvement with IVIG +/− interferon-alpha 2b (see Table 39). There is some evidence that early versus late administration of IVIG may improve the outcome.[467] Temporary reduction of immunosuppression to restore any natural immunity to WNV is also recommended, although evidence to support this is minimal and the strategy is unlikely to be effective in nonendemic areas where natural immunity is unlikely.[450,467]

In the Australian context, WNV is an uncommon pathogen. Routine screening is not required and testing would only need to be considered in a donor with a compatible clinical illness with history of travel to an endemic area.

RECIPIENT CONSENT

It is a legal requirement in Australia and New Zealand to inform potential organ recipients of all risks associated with acceptance or nonacceptance of a particular organ. At the time of an organ offer, decisions about whether to accept the organ may be made too quickly for the potential recipient to adequately consider the risks and benefits. For this reason, the possibility of accepting an organ that carries a risk of infectious disease transmission should be discussed with the recipient at the time of waitlisting, and then periodically thereafter. It is the responsibility of the transplant team to ensure that the potential transplant recipient understands the following before an organ offer being made[44,471]:

- no pathology test that is performed on a donor is entirely capable of reducing risk of transmission to nil, although all efforts are taken to reduce risk of BBV transmission, effectively resulting in extremely low risk;
- there is a small chance that screening of the donor has not identified a serious infectious disease;
- tests are not performed for all known infectious diseases;
- false-positive and false-negative test results are possible;
- it is not possible to know everything about an individual donor, and donor histories reflect only the knowledge of the person providing the history;
- there are rare instances where transplantation results in the transmission of infections that have not been described before;
- all transplantation carries risks, but often not performing the transplant carries a higher risk of death than the risk of morbidity and mortality attributable to a donor-derived infection.

Discussions with the potential recipient should acknowledge that different patients would have different views of the risks of infectious disease transmission, depending on their current health status and risk of death without a timely transplant. Each patient will weight the risks differently according to their personal circumstances and preferences. Potentially, patient views about infectious disease risks will also evolve as they spend longer on this waiting list or their medical status changes—hence it is necessary to periodically revisit the discussion of consent.

At the time of organ offer, the transplant team should discuss the risks and benefits with the potential recipient, presenting case-specific information. Information should include:

- the infection(s) that may be transmitted and the likely risk of transmission;
- the potential severity of infection;
- the ease of treating the infection should transmission occur;
- whether all testing of the donor has been completed;
- the risk of significant morbidity or mortality without transplantation at this time; and
- the benefit of accepting this organ at this time.

Transplant physicians are responsible for ensuring that recipients give their valid consent to accept a particular organ immediately before transplantation. The consent form completed at the time of transplant must expressly include recipient's acceptance of a potentially infectious organ. For consent to be valid, the person must (i) have the capacity to give consent and understand the implications of their consent to transplantation; (ii) give that consent freely, without pressure from hospital staff, medical practitioner, or family; (iii) consent specifically to receive the particular organ in question.[472] Sufficient information must be provided for there to be genuine understanding of the risks involved in proceeding or not proceeding with transplantation, and the more likely a specific risk, the more detail that should be provided about that risk.[472]

Informed Consent in the Context of the Transplantation of Organs at Known Risk of BBV

A major challenge for transplant systems is how to safely maximize the utilization of organs from donors at known risk of BBV while respecting individual patient preferences. Communicating to the potential recipient the actual risks of infectious disease transmission in the case of a donor with social risk factors for BBV can be complex, and the proper goal must be education rather than coercion.

Northwestern University has developed a mobile web application, Inform Me, to increase knowledge about increased risk donors among kidney transplant candidates.[473] The app can be accessed at https://informme.cbits.northwestern.edu/system/index.html (last accessed May 13, 2018). A trial of the app in 288 kidney transplant candidates demonstrated that it was successful in increasing knowledge about increased-risk donors compared with routine transplant education.[473] Although it was hypothesized that greater knowledge would be associated with greater willingness to accept increase-risk kidneys, this was not observed, which may be a function of the fact that Inform Me was designed a neutral decision aid, not intended to exert overt influence on treatment choice.[473]

The Victorian and Tasmanian Renal Transplant Advisory Committee has taken an "opt-in" approach to increased-risk donors, whereby an additional waiting list has been created for those kidney transplant candidates who specifically

consent to receiving an organ from a donor who is at increased risk of BBV infection. Kidney transplant candidates are provided with educational materials as part of the consent process; these materials explain which donors are considered increased viral risk donors, what the risks are of catching a bloodborne viral infection from an increased-risk donor, and what treatment is available in the event of disease transmission. The current Victorian and Tasmanian Renal Transplant Advisory Committee patient information and consent form for accepting a kidney from an increased viral risk donor is given in **Materials and Methods 2, SDC,** http://links.lww.com/TXD/A153. By choosing to be added to the additional waiting list for kidneys from increased viral risk donors, the patient's position in the standard waiting list is not affected. This, therefore, frames the offer of an increased viral risk donor as an additional opportunity for transplantation, rather than as an offer of a risky or inferior organ. The additional waiting list of preconsented individuals is also intended to encourage more frequent organ retrievals from increased viral risk donors.

An emerging issue with respect to recipient consent and the risk of BBV is the utilization of HCV-viremic donors. The availability of DAAs for HCV and the use of organs from HCV-viremic donors for HCV nonviremic recipients will require its own specific consent process. Using HCV-NAT–positive organs has the potential to reduce waiting times and improve survival for those recipients who would not be expected to receive another organ offer in a timely manner. However, because this practice is new, there are minimal data on which to base informed consent. The potential concerns related to transplanting HCV-viremic organs into nonviremic recipients include increased rates of infection, increased rates of rejection, HCV-related fibrosis in the allograft, or infection with a more difficult to treat genotype.[162] Questions that need to be addressed include: which patients should be encouraged to accept HCV-positive organs, what are the cost implications, and what are the residual risks of viral complications or unsuccessful DAA therapy, and what are the risks of transmission to a sexual partner?[474] Although the available data from clinical trials conducted so far suggest these risks are minimal, they are still unknown in the setting of intentional HCV transmission. As more clinical trial data become available, it will hopefully be possible to answer some of these questions and for consent processes in this context to be improved.[46]

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