T • S • A • N • Z

The Transplantation Society of Australia and New Zealand

Infectious Disease Transmission in Solid Organ Transplantation:

Donor Evaluation, Recipient Risk & Outcomes of Transmission.

S. L. White | May 2018

Produced in partnership with

Australian Government
Organ and Tissue Authority

donatelife

This literature review was written and prepared by Dr Sarah L. White, with funding from The Transplantation Society of Australia and New Zealand and the support of the Australian Government Organ and Tissue Authority. A number of experts in the field consulted on the contents of this document, and their contribution is acknowledged with thanks below.

Review steering committee

Name	Affiliation
Stephen Alexander	Westmead Hospital and University of Sydney and the Transplantation Society of Australia and New Zealand
Jeremy Chapman	Westmead Hospital and University of Sydney
Lindsay Grayson	Infectious Disease & Microbiology, Austin Health and University of Melbourne
Eva Mehakovic	Organ and Tissue Authority
Helen Opdam	Austin Hospital and Organ and Tissue Authority
Vidya Ramachandran	Serology & Virology Division, Prince of Wales Hospital
Bill Rawlinson	SEALS Microbiology, Serology & Virology Division, Prince of Wales Hospital
Debbie Verran	Royal Prince Alfred Hospital
Germaine Wong	Westmead Hospital and University of Sydney

Expert advisory group members

Name	Affiliation
Peter Boan	Departments of Infectious Diseases and Microbiology, Fiona Stanley Hospital and PathWest Laboratory Medicine
Scott Campbell	Princess Alexandra Hospital
Steven Chadban	Royal Prince Alfred Hospital and University of Sydney
Toby Coats	Royal Adelaide Hospital and the University of Adelaide
Michael Fink	Austin Health and The University of Melbourne
Allan Glanville	St. Vincent's Hospital Darlinghurst
Anthony Griffin	Princess Alexandra Hospital
Ashley Irish	Royal Perth Hospital
Michael Ison	Transplant Infectious Diseases Service, Northwestern University, United States
John Kaldor	Kirby Institute, University of New South Wales
Peter Macdonald	St Vincent's Hospital Darlinghurst
Paul Manley	Auckland District Health Board
Alicia Mitchell	Woolcock Institute of Medical Research, University of Technology Sydney and St Vincent's Hospital Darlinghurst
Carl Pederson	Consumer representative
Vicky Sheppeard	Communicable Diseases Network Australia, The Department of Health
Karen Waller	University of Sydney
Angela Webster	Westmead Hospital and University of Sydney
Kate Wyburn	Royal Prince Alfred Hospital and University of Sydney
Greg Snell	The Alfred Hospital

Disclaimer

The information contained in this document is for general information only. It is designed to be educational, and is not intended to be – and is not – a complete or definitive statement on any area of medical practice or procedure. The Transplantation Society of Australia and New Zealand, its directors, and other officers make no express or implied warranties as to the suitability for a particular purpose or otherwise regarding the information included in this document. Rapid advances in medicine may cause information contained in this document to become outdated or subject to debate, and this should be taken into account when interpreting the information contained herein. Readers of this document who are not medical practitioners qualified in the field should seek further professional advice before any action is taken in relation to the matters described or referred to in the document.

Suggested citation: White, S.L. Infectious disease transmission in solid organ transplantation: donor evaluation, recipient risk and outcomes of transmission. The Transplantation Society of Australia and New Zealand; Sydney, 2018.

TABLE OF CONTENTS

List of Acronyms

ALT	Alanine aminotransferase
ANZOD	Australia and New Zealand Organ Donation Registry
ATL	Acute t-cell leukaemia/lymphoma
ATSI	Aboriginal and Torres Strait Islander
BAL	Bronchoalveolar lavage
BBV	Blood borne virus
CMV	Cytomegalovirus
CJD	Creutzfeldt-Jakob disease
vCJD	Variant Creutzfeldt-Jakob disease
sCJD	Sporadic Creutzfeldt-Jakob disease
CSF	Cerebrospinal fluid
DAA	Direct acting antivirals
DTAC	Disease Transmission Advisory Committee (OPTN)
EBV	Epstein Barr virus
EDQM	European Directorate for the Quality of Medicines and Health Care
EFRETOS	European Framework for the Evaluation of Organ Transplants
EIA	Enzyme immunoassays
ELISA	Enzyme-linked immunosorbent assay
FTA-ABS	Fluorescent treponemal antibody absorption test
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV-1/2	Human T-lymphotropic virus 1/2
ICU	Intensive care unit
IGRA	Interferon gamma release assay
IVDU	Intravenous drug user
KSHV	Kaposi sarcoma herpes virus
LCMV	Lymphocytic choriomeningitis virus
MDR-TB	Multidrug resistant tuberculosis
MRSA	Methicillin resistant *Staphylococcus aureus*
MSM	Men who have sex with men
NAT	Nucleic acid testing
NHSBT	United Kingdom National Health Service Blood and Transplant
NNDSS	National notifiable disease surveillance system
OPO	Organ Procurement Organisation
OPTN	Organ Procurement and Transplantation Network (United States)
PHS-IR	United States Public Health Service increased risk classification
PTLD	Post-transplant lympho-proliferative disorder
RPR	Rapid plasma reagin
SaBTO	United Kingdom Advisory Committee on the Safety of Blood, Tissues and Organs
SOHO V&S	European Union Substances of Human Origin Vigilance and Surveillance Project
STI	Sexually transmitted infection
TP-PA	Treponema pallidum passive particle agglutination assay
TSE	Transmissible spongiform encephalopathies
TSP/HAM	Tropical spastic paraparesis HTLV-1 associated myelopathy
UNOS	United States United Network for Organ Sharing
UTI	Urinary tract infection
VRE	Vancomycin-resistant *Enterococci*
WNV	West Nile Virus

1. INTRODUCTION

1.1. Background and scope of the review

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 regards to the risk trade off between accepting an organ with an increased risk of disease transmission versus remaining on the waiting list.

This literature review summarises 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 blood borne 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 post-transplant in the event of possible infectious disease transmission;
vii. Vigilance and surveillance systems in organ donation and transplantation.

The potential to transmit blood-borne viruses (BBV) – human immunodeficiency virus (HIV), hepatitis C virus (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, *Treponema pallidum, Mycobacterium tuberculosis*, multi-drug 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 and Zika virus.

The review excludes:

i. Detailed discussion of the biological mechanisms of disease transmission;
ii. Cell and tissue donation;
iii. Transmission of non-infectious 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. Vascularised composite allotransplantation (VCA): given that the intended outcomes of VCA is quality of life (not survival), much stricter donor eligibility criteria apply with regards 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, while 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.

1.2. 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 infected with a given pathogen (for example cytomegalovirus or Epstein Barr virus). It is expected that this pathogen will be transmitted to the recipient(s) of their organs, for whom risk mitigation strategies will be employed (e.g. 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].

Table 1.1 Definitions of imputability for donor origin of disease transmission – United States* [1, 4].

Term	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 pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation[a]
Probable	Strong evidence suggesting but not proving disease transmission. Both of the following two 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 pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation
Possible	Used for all situations where data suggest a possible transmission but are insufficient to fulfil 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, non-donor origin of disease
Intervention without documented transmission	All or some of the recipients received an intervention (i.e. 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 (i.e. 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] 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 (i.e. molecular fingerprinting of bacteria). If this was not possible, a lower grade classification would be used.
* Sources are directly quoted, which is why malignancy is mentioned in this context despite not being a focus of the current review.

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 1.1 and Table 1.2). Transmission events reported in this review refer to proven/definite and probable/likely cases unless otherwise specified.

Standardised 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 prior to 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].

Table 1.2 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 favour 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 favour of attribution to alternative causes.
Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes – i.e. there is evidence clearly in favour of attributing the adverse reaction to other causes than the process or transplanted organ
Not assessable	Insufficient data for imputability assessment.

1.3. Donor risk stratification

Donor-related infectious disease transmission risk can be conceptually divided into two stages: the pre-transplant phase and the post-transplant phase. In the pre-transplant 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 pre-transplant 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 post-transplant 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 post-transplant phase, risk mitigation practices consist of:

i. Prophylaxis in the recipient (including antimicrobials, immunoglobulin and/or vaccination);
ii. Additional screening of donor samples (e.g. finalizing blood and urine cultures and drug sensitivity testing if these were not completed prior to transplant);
iii. Post-transplant monitoring of recipients;
iv. 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 five levels of risk, originally developed for donor evaluation by the Italian National Centre for Transplantation, was used until recently (see Table 1.3); Europe has now also transitioned to a system of dichotomous categorisation of donor risk [8]. The approach currently used in Australia similarly defines potential donors as either increased-risk or non-increased-risk.

Table 1.3: 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 non-treatable 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, e.g. in cases of patients with fulminant hepatitis, liver primary non-function, 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 one or more assessment elements are missing (e.g. 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, since null risk does not exist, infectious or neoplastic pathologies can still be transmitted even if guidelines and good clinical practice are followed.

The categorisation 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 (e.g. nucleic acid testing), 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 ‘labelling 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 criteria for high risk of HIV, HBV and HCV (labelled 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 post-transplant 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 labelled 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 needs 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 or IVR donor). IVR donors are defined as (i) having known increased risk behaviour AND (ii) risk behaviour 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 section 7.

Table 1.4 Clinical characteristics and outcomes of unexpected infectious disease transmission events in Australia (published and unpublished reports) involving deceased donors.

Author [ref]	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 year old male	Severe respiratory distress and fever	Day 14	No	No
			Lung	17 year old female	No (vaccinated and received oseltamivir prophylaxis)	No	No	No
Pilmore et al. [15]	2009	HHV-6	Kidney	47 year old male, second transplant	Severe diarrhoea, liver dysfunction, pancytopenia, acute abdomen	No	No	Day 31
			Kidney	33 year old male, combined heart/kidney transplant	Severe musculoskeletal pain, liver dysfunction, pancytopenia, thrombocytopenia	No	No	No
Jensen et al. [16]	2016	*M. tuberculosis**	Lung	31 year old woman	Cough	No	No	No
Palacios et al. [17]	2008	Arenavirus	Kidney	63 year old woman	Fever, sepsis, encephalopathy, acute tubular necrosis, chest infiltrates	Yes	No	Day 36
			Liver	64 year old woman	Fever, confusion, encephalopathy with myoclonus, chest infiltrates	No	No	Day 30
			Kidney	44 year old woman	Fever, intra-abdominal hematomas and effusion, encephalopathy	Yes	No	Day 29
Personal communication (K Wyburn)	2008/ 2009	HCV	Kidney**	28 year 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***	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 post-transplant, 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***	Male 60s	Asymptomatic	No	No	No
			Lungs***	Female 60s	Asymptomatic	No	No	No
Rogers et al. [19]	2008	*T. gondii*	Kidney	60 year old male	Kidney dysfunction, liver dysfunction, tachypnoea, hypoxia, hypotension, cardiogenic shock	No	No	Day 30
			Kidney	59 year old female	Fever, hypotension, thrombocytopenia, liver dysfunction, multi-organ failure, cardiogenic shock	No	No	Day 32
(Personal communication A Webster & D Verran)	2015	Disseminated candidiasis	Kidney	-	-	-	Yes	Day 98

*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.
** HCV was transmitted to the recipient of one kidney, however the second potential recipient avoided transmission as results of retrospective NAT were available prior to the transplant surgery.
***The kidney-pancreas recipient of the original donation died nine days post-transplant and his lungs and the previously transplanted kidney were retrieved and transplanted into two new recipients.

1.4. History of infectious disease transmission events in Australia and New Zealand

As of November 2017, the surveillance of adverse events following 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 Section 1.6). The historical absence of an integrated biovigilance and surveillance system means that a central database of infectious disease transmission events occurring in Australia New Zealand does not currently exist. Table 1.4 was compiled based on expert consultation, and summarises occurrences of serious adverse events involving infectious disease transmission from organ donors to recipients from 2008 onwards (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 eight deaths (mortality rate of 44%). No two cases involved the same pathogen. Assuming that the list of cases in Table 1.4 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 at 2016 (18 transmission events versus approximately 10,000 solid organs transplanted from deceased donors in Australia) – a rate that is similar to the reported rate of donor-derived infectious disease transmission in the United States of 0.16% [3].

1.5. 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 (personal communication P. Clayton). The corresponding proportion in the UK was 0.3%, whereas in the United States it was 9.3% (see Figure 1). While 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 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 six out 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 versus 625) [21].

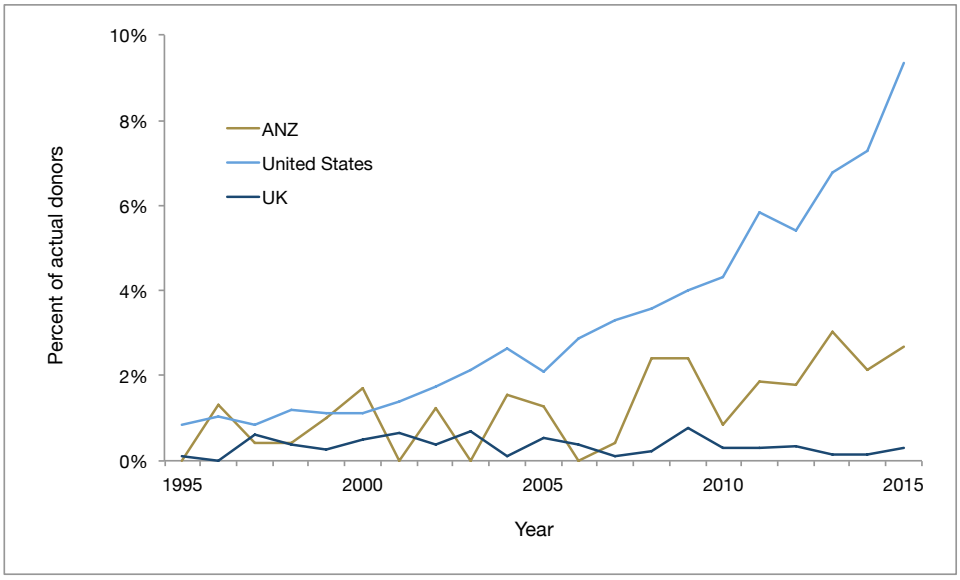


Figure 1: 20-year trends in the percentage of donors with drug overdose (intended or unintended) as a cause of death in Australia and New Zealand compared with the United Kingdom and United States (Data sources: ANZOD, OPTN, NHSBT).

Compared to a drug-related mortality rate in the United States population aged 15-64 in 2014 of 233.8 per million population, the drug-related mortality rate in Australia in 2013 was 116.2 per million population aged 15-64; in New Zealand it was 26.7 per million population aged 15-64 [22]. In the United Kingdom, the drug-related mortality rate was 66.7 per million population aged 15-64 in 2014 [22]. In allthreecountries, opioids were the number one drug causing death [22]. Notably, the rate of deaths due to opioids (including prescription opioids) in Australians aged 15-54 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 deaths 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 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.

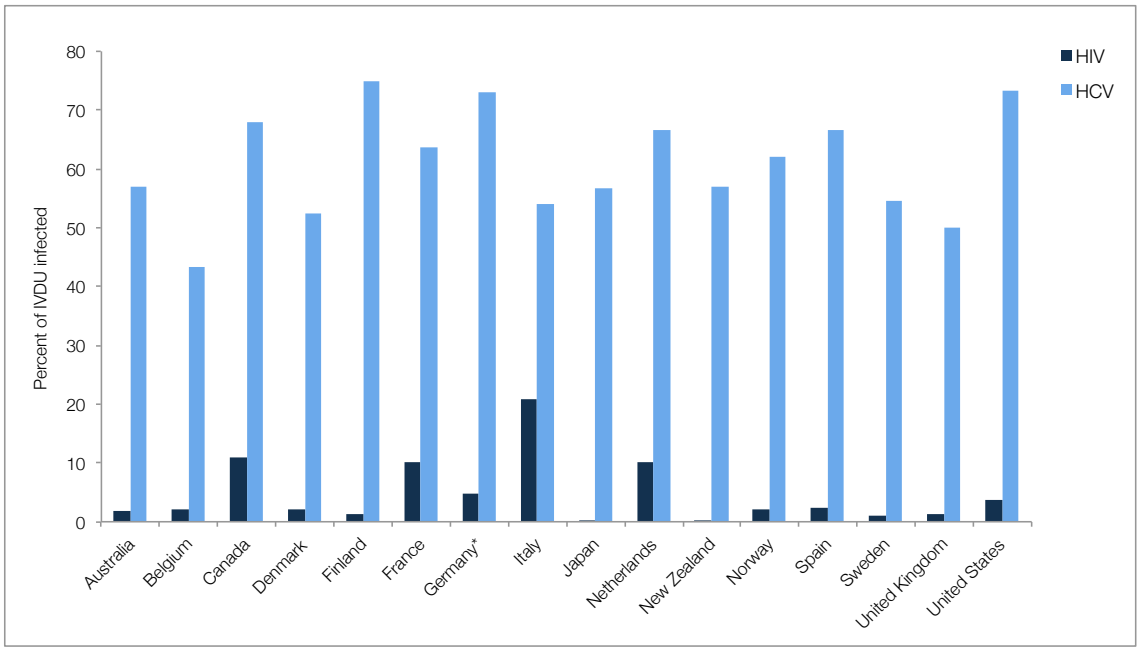


Figure 2: Estimated prevalence of HIV and HCV among people who inject drugs in selected high-income countries. HCV prevalence estimates represent mid-range estimates (source of HCV data: United Nations Office on Drugs and Crime http://unodc.org; source of HIV data: UNAIDS aidsinfo.unaids.org). *HCV estimate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

1.6. Vigilance and surveillance

While cases of donor-derived disease transmission are rare, the immediate reporting and investigation of any post-transplant 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 centre/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 two pertinent items to the World Health Organisation'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 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 non-transplantation will be better understood.

Internationally, however, centralized systems for surveillance of donor-derived infectious disease transmission events are still largely non-existent or in developmental stages. Well-established biovigilance systems currently exist only in France, Italy and the United States. Australia has been working towards 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 inter-jurisdictional 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].

1.6.1. 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 SOHO V&S (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 EFRETOS (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 centres 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 centres and tissue establishments being alerted;
- Ideally, transplant centres should have a designated vigilance coordinator;
- Central coordination and oversight should be in place for centre 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 centres;
- Computerised systems for data collection and management should be established;
- Data collection should be integrated with existing organ donation and transplant registries.

United Kingdom

SaBTO guidelines recommend the routine screening of recipients at one year post-transplant for presence of pathogens potentially transmitted from the donor [29]. NAT is preferred, to account for the effect of immunosuppression on serological test accuracy, and ideally samples from the recipient taken pre-transplantation would be available to differentiate between pre-existing and newly acquired disease. 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 post-exposure 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 (GIG), 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 GIG 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 amongst 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 NHSBT CARE Committee, which has oversight across NHSBT [30].

United States

The National Organ Transplantation Act of 1984 (NOTA) 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/UNOS, where cases are then reviewed by the Disease Transmission Advisory Committee (DTAC). DTAC 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 post-transplant discovery of disease in donors or recipients are given in Table 1.5 [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. DTAC then engages in an email-based confidential medical peer review process. 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].

Based on DTAC reports for 2013, the most frequently reported potential transmission events involved HCV, tuberculosis, HIV, Chagas, HBV, toxoplasmosis and West Nile Virus, 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].

Table 1.5: OPTN Transplant Program requirements for communicating post-transplant discovery of disease or malignancy (OPTN Policies; Policy 15: Identification of Transmissible Diseases) [32].

15.5.A Transplant Program Requirements for Post-Transplant 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 Post-Transplant 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 Post-Reporting 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 staff 2. 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 3. Contribute to a follow-up review of the event in partnership with OPTN patient safety staff 4. Provide additional related information or specimens if requested.

Overall, the estimated rate of proven/probable unexpected disease transmission events in the United States is low: from 1 July 2015 to 30 June 2016 there were 19 proven/probable infectious disease transmission events out of ~15,500 donors (9,500 deceased donors), affecting 73 recipients [33]. Death in association with a proven/probable infectious disease transmission event occurred in three recipients in this 12-month period [33]. These numbers are likely, however, to be affected by under-recognition and under-reporting 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 MRSA, VRE or multi-drug 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 Centre (CNT) and the EU-funded SOHO V&S (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 under-reporting, or delays in reporting. Where organs are distributed across multiple transplant centres, 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.

1.7. 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 United Kingdom Department of Health 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 (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 Organisation [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 Appendix 8.2. Given the absence of biovigilence systems in most jurisdictions and a general under-reporting 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 centralised recording of donor disease status for all utilised 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 centre's experience). Given these limitations, reported transmission events are summarised 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.

2. DECEASED DONOR EVALUATION FOR INFECTIOUS DISEASE RISK

2.1. Donor medical history and behavioural 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 intravenous drug use (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 (see Section 0). 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 behavioural risk factors, decisions about whether to utilize 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.

2.2. 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, immunisation and/or monitoring. It is necessary to test for both active and latent infections in donors and recipients prior to 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 cytomegalovirus (CMV), Epstein-Barr Virus (EBV), human immunodeficiency virus (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 12-18 hours, whereas blood donor screening can take place 24-48 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 turn-around time under ~12 hours. Another key consideration for screening protocols is the serological window for blood borne viruses (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).

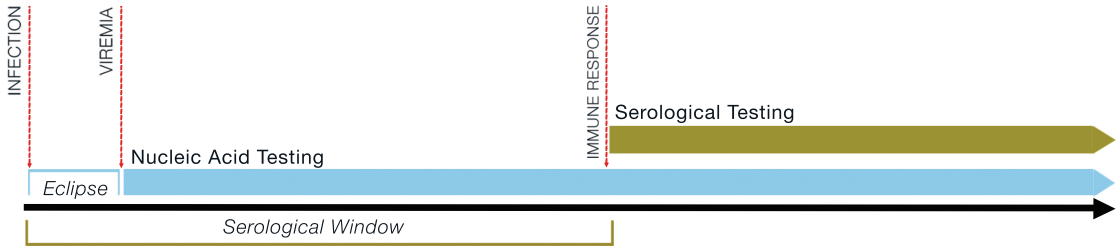


Figure 3: Generalised diagram of eclipse and window periods

Figure 4 shows the serological and nucleic acid testing (NAT) windows for HIV, HCV and HBV. The eclipse period refers to the pre-ramp phase and the portion of the ramp-up/exponential phase where the viral titre in peripheral blood has not yet reached levels that are detectable by NAT. Once the viral titre reaches detectable levels (5-6 days post-infection 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 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.

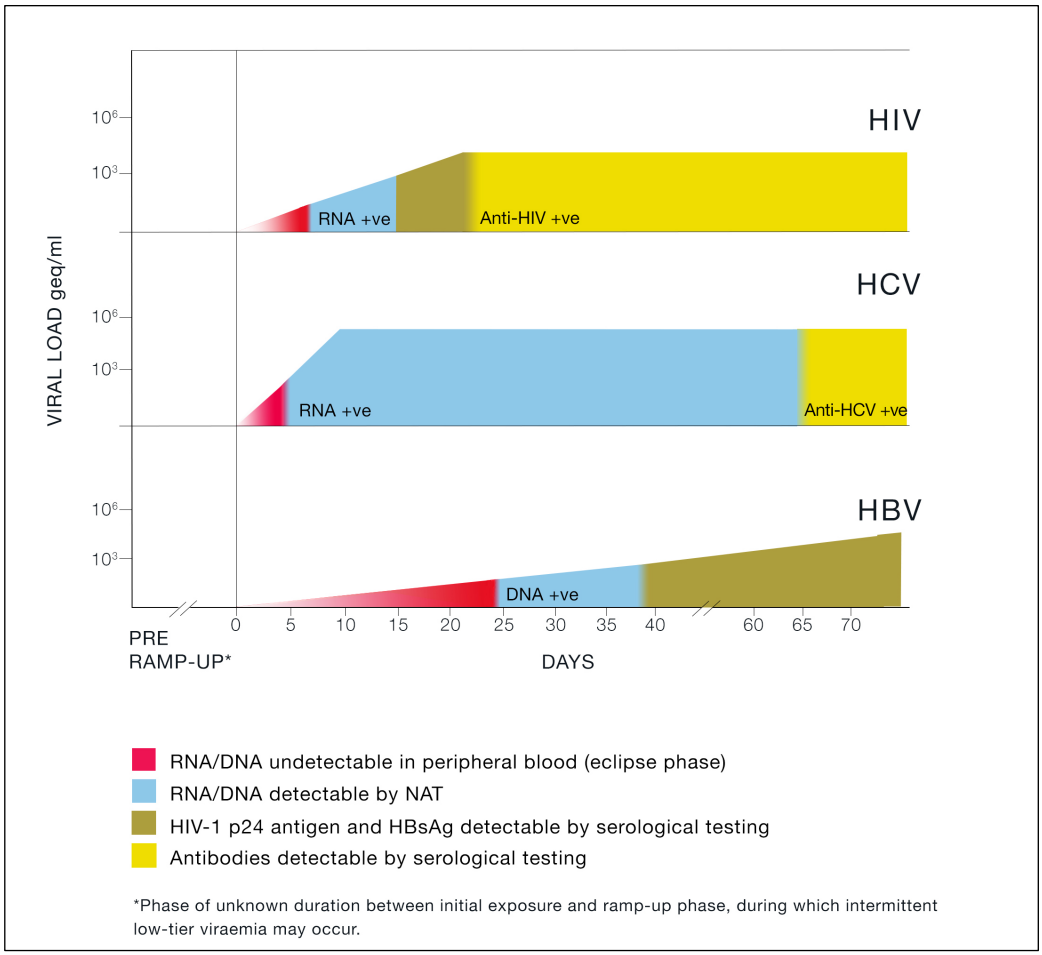


Figure 4: Serological and NAT window for HIV, HCV and HBV (source: SEALS)

Table 2.1: Length of window period for selected blood borne viruses under different testing methods [44].

Pathogen	Standard serology	Enhanced serology (fourth generation or combined antibody-antigen tests)	Nucleic acid testing*
HIV	17-22 days	~7-16 days	5-6 days
HCV	~70 days	~40-50 days	3-5 days
HBV	35-44 days	Not applicable	20-22 days

*Based on Gen Probe TMA for HIV and HCV, and Roche Cobas MPX for HBV

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 4-6 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 2.2). UK guidelines recommend NAT testing for HIV whenever this is feasible (i.e. where turnaround times and logistics permit), and require all donors to be screened using the combined anti-HIV antigen/antibody test at a minimum. EDQM 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 U.S. Public Health Services Guidelines. In this circumstance the receiving transplant hospital must obtain documented informed consent from the potential recipient (or their authorised agent) before transplantation can take place [45].

Both OPTN and SaBTO guidelines require HCV-NAT among mandatory tests for all donors, whereas EDQM only recommend NAT for donors at increased risk of HCV infection and donors with an anti-HCV reactive result, to determine whether clearance of viraemia exists. Historically, a positive HCV-NAT would have been a contraindication to transplantation. However, with the advent of direct-acting antiviral agents 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 section 3.1.2.

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 treponemal test (TP-EIA) is performed, with a positive result confirmed by a non-treponemal 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 (TPPA) 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, TPPA 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.

Table 2.2: International protocols for Infectious disease testing - mandatory testing requirements for potential deceased donors of solid organs in the United States, UK and Europe.

OPTN[a,b]	SaBTO[d]	EDQM[g]
• 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[c], 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 haemodialysis in the past 12 months.	• NAT test for HIV or anti-HIV Ag/Ab combination test[e] • NAT test for HCV or anti-HCV[e] • NAT test for HBV or HBsAg and anti-HBc[e,f] • 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 prior to 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]Organ Procurement and Transplantation Network (OPTN) Policies: Policy 2.9 (effective date 10 November 2016)
[b]All tests must be FDA licenced, approved or cleared for screening organ donors.
[c]As defined under the U.S. Public Health Services (PHS) Guideline [52].
[d]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.
[e]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 prior to 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 prior to organ donation, combined antigen and antibody assays (rather than testing alone) are required for HIV, and should be considered for HCV.
[f]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.
[g]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.

The TSANZ Clinical Guidelines for Organ Donation and Transplantation from Deceased Donors (April 2016) broadly outline the standard routine investigations and recommended investigations for deceased donors in Australia and New Zealand Table 2.3. Organ Donation New Zealand has their own jurisdiction-specific donor screening policy (Table 2.3), as do each of the Australian States and Territories (see Table 2.4). Jurisdiction-specific policies are generally similar to/informed by the TSANZ guidelines, though with some variations as outlined in Tables 2.3 and 2.4. 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 non-increased 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 regards 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 (e.g. 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 post-transplant 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].

Table 2.3: Policies for infectious disease screening in potential organ donors: Australia and New Zealand (see also Table 2.4)

TSANZ [59]	New Zealand[a]
Mandatory • Anti-HIV-1/2 • HBsAg and anti-HBc and anti-HBs • Anti-HCV Recommended • HIV-NAT* • HCV-NAT* • HBV-NAT* • Anti-HTLV 1/2** • Anti-CMV*** • Anti-EBV*** • Anti-*T.pallidum**** *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 Public Health Service [52] **Strongly recommended for potential donors from population groups with a high prevalence of infection ***Recommended but not mandatory	Standard-risk donors *Prospective tests* • Anti-HIV-1/2 OR anti-HIV Ag/Ab combination test • HBsAg and anti-HBc and anti-HBs • Anti-HCV • Anti-CMV • Anti-HTLV 1/2 • Anti-*T.pallidum* (EIA) Retrospective tests • Anti-EBV (IgG and IgM) • Toxo IgG and IgM* • Anti-HSV 1 (IgG) and Anti-HSV 2 (IgG)* • Anti-VZV (IgG)* Increased-risk donors All prospective and retrospective tests as listed above, with the addition of HIV, HCV, and HBV NAT** *Performed for heart donors and lung donors only **All donors who donate heart valves or skin will also have retrospective NAT completed.

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

Table 2.4: 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 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 pre-transfusion 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 haemodiluted then a pre-dilution blood sample MUST be sourced for the accurate testing for presence of viruses. If a suitable pre-dilution 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] Personal communication N Palk, DonateLife South Australia

[d] DonateLife Tasmania Clinical Practice Guideline.

[e] DonateLife Victoria Clinical Practice Guideline.

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

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 considered to be at increased-risk). Where donor information about behavioural risk factors is incomplete, the donor should be treated in the same way as an increased-risk donor [52].

Another issue for donor screening is haemodilution: where the donor requires multiple blood transfusions or significant infusions of intravenous fluids prior to donation, haemodilution 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 non-haemodiluted blood samples for the purpose of serological screening of deceased donors wherever possible [45]. If only a haemodiluted sample is available, that donor is treated as though they are an increased-risk donor according to the U.S. Public Health Service Guideline (i.e. 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.

2.3. 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 2.5.

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 post-transplant interventions [7]. United States recommendations are that kidneys and livers from potential donors testing positive for *T.cruzi* be utilized 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 utilized [60].

Table 2.5: Additional tests which might be considered for donors who have lived in areas with endemic disease [5].

Test	Central & South America	North Africa	Sub-Saharan Africa	Indian sub-continent	Southeast Asia
HTLV-1/2 serology	Always	Always	Always	Always	Always
NAT for *Plasmodium spp.*	Central America & Amazon	No	Always	Always	Always
Stool examination*	Always	Always	Always	Always	Always
Urine examination**	No	Egypt	Always	No	No
Strongyloides stercoralis serology	Always	Always	Always	Always	Always
Schistosoma spp. serology	Caribbean, Venezuela and Brazil	Always	Always	No	Always
Trypanosoma cruzi serology for screening; NAT or Strout test for exclusion of parasitaemia	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

**Entamoeba histolytica*, *Clonorchis* spp., *Opisthorcis* spp., *Schistosoma* spp., *Strongyloides* spp.
***S. haematobium*

Table 2.6: Current (November 2017) international recommendations for donor suitability and organ allocation based on the results of infectious disease screening

Test result	TSANZ [59]	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.*	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 post-transplant.	Excluded from organ donation for HCV-negative recipients, may be accepted for recipients who are anti-HCV positive or HCV-NAT positive.**	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.**	May be utilized 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; non-liver 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 titre <100IU/L: Non-liver organs accepted. Detection of anti-HBcAb without detection of anti-HBsAg is considered a relative contraindication to liver donation. Anti-HBsAb titre >100IU/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 life-long monitoring.	Livers usually not accepted but can be used in emergency situations and for HBsAg-positive/vaccinated recipients. Non-liver 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 prior to 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.****	Donor anti-HTLV-I/II-positive to recipient-negative transplants are not permitted.	Excluded from organ donation.****
Anti-toxoplasma 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.

* "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 non-specific in confirmatory testing and HIV-1 RNA is undetectable."
** "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."
*** "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."
**** "HTLV-1/2 testing is only performed if donor is from a geographical area with a higher prevalence of HTLV-1/2 infections."

2.4. Donor suitability and recommendations for organ allocation

Table 2.6 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 section 2.2. 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 direct acting antivirals able to effectively treat infection in the event of disease transmission (see Section 3.1.4). 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.

3. VIRAL INFECTIONS IN THE DECEASED DONOR

3.1. HIV, hepatitis C and hepatitis B

3.1.1. 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 intravenous drug users (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].

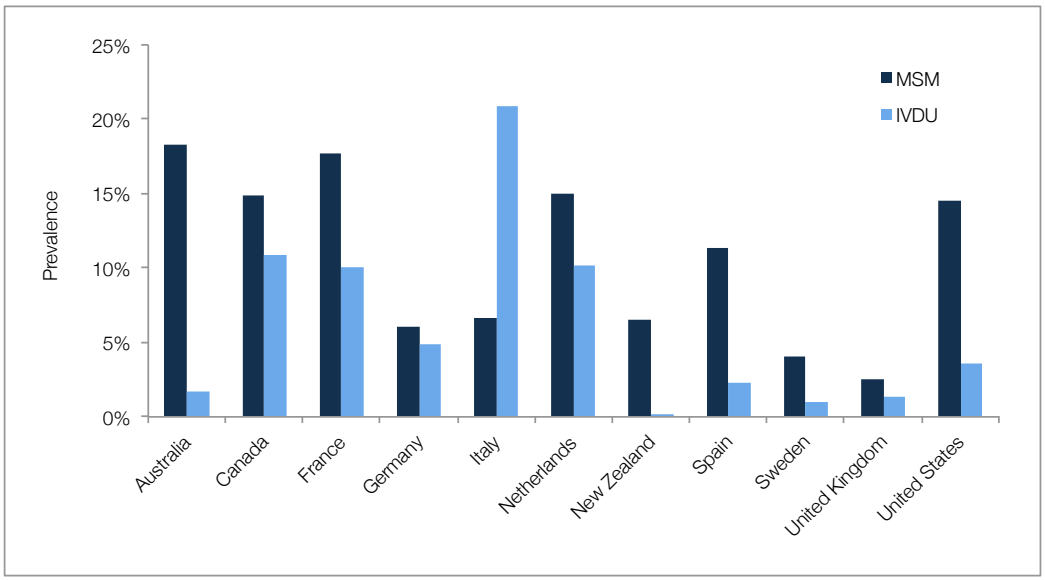


Figure 5: Estimated prevalence of HIV among increased-risk groups in selected high-income countries in 2016 (data source: www.aidsinfo.unaids.org, accessed February 2018).

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

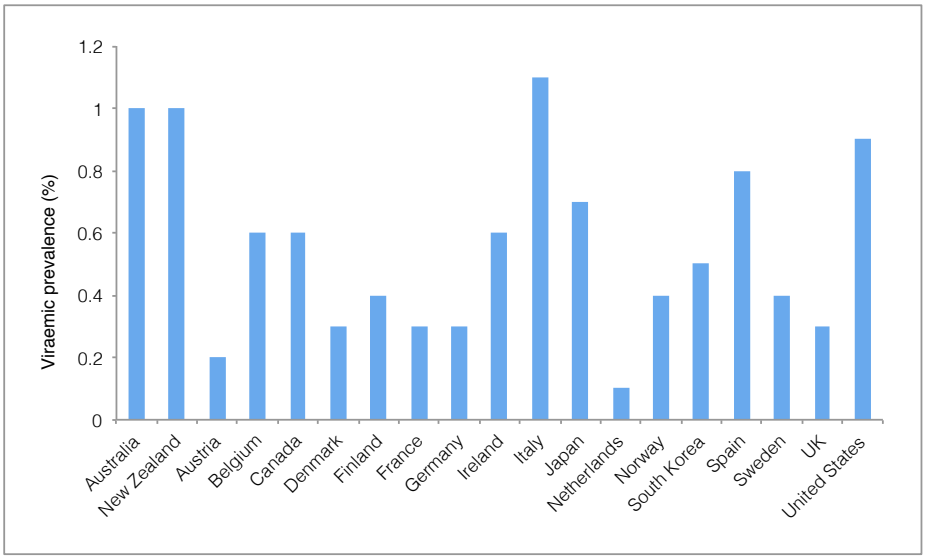


Figure 6: Viraemic prevalence of HCV in selected high-income countries, estimated for the year 2015 [65].

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 categorising 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 minimise 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:

- Men who have sex with men (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
- STI in the past 12 months
- Cosmetic body piercing/tattooing
- Cocaine snorting
- Physician concern (based on medical history or physical examination).

The United States Public Health Service (PHS) published *Guidelines for Preventing Transmission of Human Immunodeficiency Virus through Transplantation of Human Tissue and Organs* in 1994, with an update subsequently published in 2013, and implemented in 2014 [52]. These evidence-based guidelines outline behavioural 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 3.1).

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, gonorrhoea, 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 3.1, 19.5% of potential donors were labelled as increased-risk in 2014 [13]. Thirdly, labelling organs as “increased-risk” has an impact on organ utilisation as patients and physicians tend to be risk averse when in 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 stigmatised social behaviours (IVDU) and stigmatised diseases (HIV and HCV) [13]. The criteria above therefore describe a large proportion of the population, yet the risk factors stipulated will be routinely under-reported by next of kin; further, despite systematic misclassification, patients and physicians will place undue emphasis on an “increased-risk” label when making acceptance decisions.

Table 3.1: 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 [52]

Pathogen	Behavioural characteristics	Non-behavioural characteristics
HIV	• MSM • IVDU • Non-injection 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 • Non-injection 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 non-professional	• Hemodialysis • Receipt of blood transfusion • Signs and symptoms (e.g. jaundice, elevated ALT) • STI • Marital status
HBV	• MSM • IVDU • Multiple sex partners	• Hemodialysis • STI • Marital status

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 26,444 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 (e.g. 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 20-29 year age group (17.1 per 100 000), followed by the 30-39 year age group (16.1 per 100 000). Of the total number of new HIV diagnoses in 2016, 5% were in Aboriginal and Torres Strait Islander people. HIV prevalence among Aboriginal and Torres Strait Islander 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 anti-retroviral 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 ten years. Of those on antiviral therapy, 93% had a supressed viral load, corresponding to 72% of all people living with HIV in Australia having a suppressed viral load [37]. In addition, large, state-funded pre-exposure 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 six-year average, while among Australian-born MSM the number of new diagnoses was 19% less in 2017 compared to the previous six-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 six-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 men who have sex with men. In contrast to HIV trends, HCV notifications in Australia fell consistently between 2005 to 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 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 direct-acting antiviral treatments. The majority (67%) of HCV notifications in 2016 occurred in males, with the highest notification rate in the 25-29 year age group (84.6 per 100 000), followed by the 40+ age group (56.4 per 100 000) [37]. Nine percent of HCV notifications occurred among Aboriginal and Torres Strait Islander people.

Interferon-free direct-acting antiviral (DAA) regimens became available on the Pharmaceutical Benefits Scheme in Australia from March 2016. Of an estimated 227,306 people living with HCV in Australia at the start of 2016, 32,550 received treatment and 30,434 (93%) were cured, reducing the number living with chronic HCV at the end of 2016 to 199,412 (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 had a 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%.

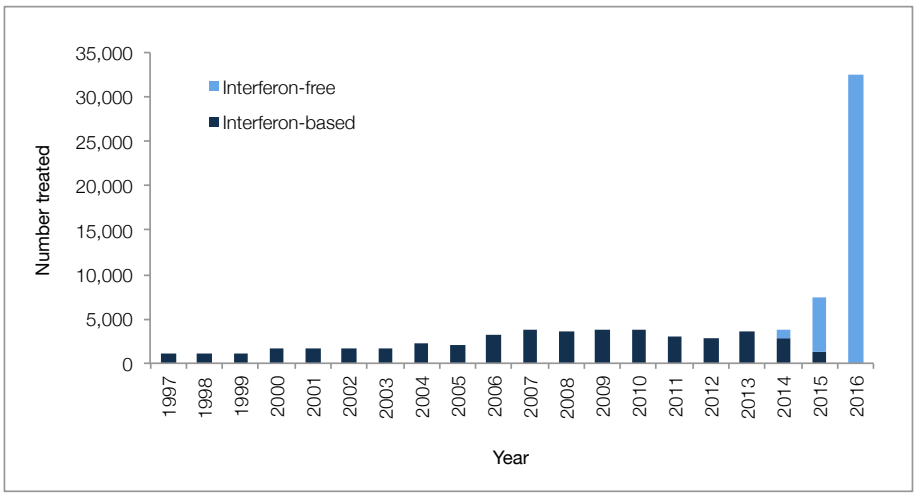
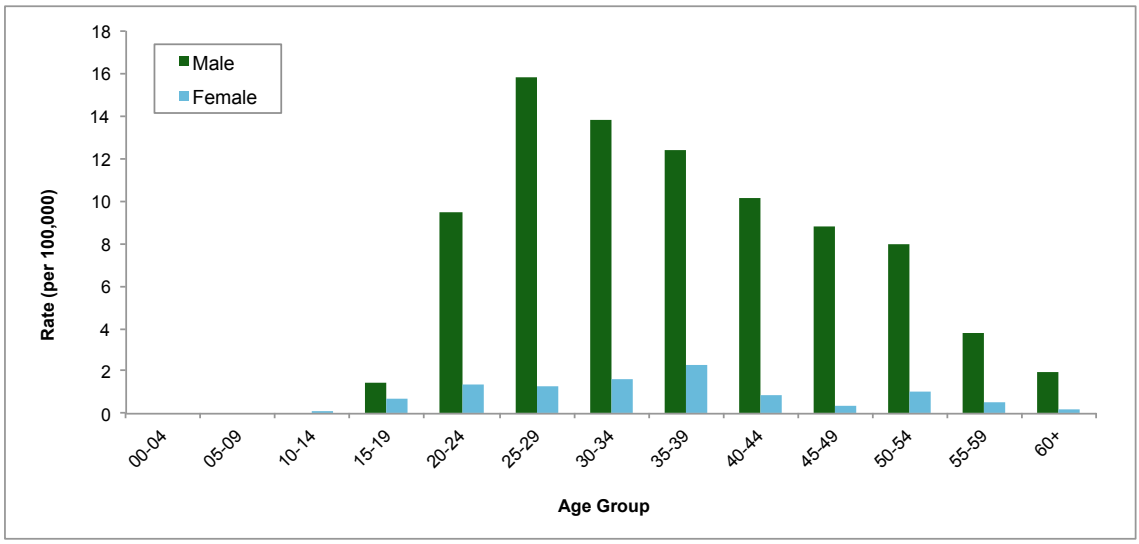


Figure 7: The estimated number of people living with hepatitis C who received treatment, 1997-2016 [37].

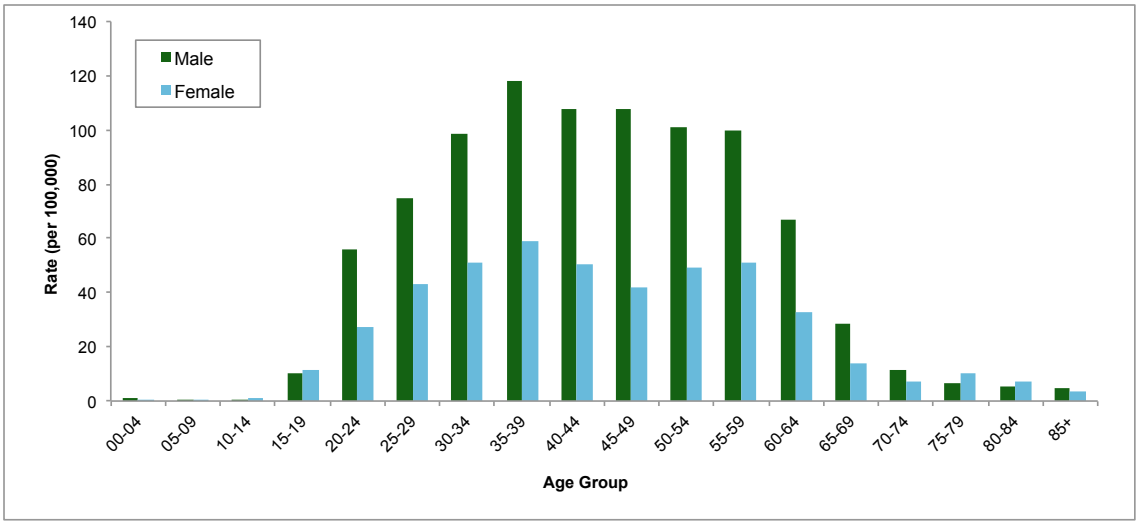
HBV notifications have been declining over the past decade in younger age groups due to the impact of vaccination programs. The greatest decline in newly acquired HBV cases has been in the 20-24 year age group (females in particular). Chronic HBV cases in Australia are concentrated among four key populations: migrants from high prevalence countries (especially Northeast and Southeast Asia), people who inject drugs, Aboriginal and Torres Strait Islander peoples, and men who have sex with men. Of the estimated 233,034 people living in Australia with chronic HBV infection at the end of 2016, 38% were born in the Asia-Pacific, 9.3% were Aboriginal and Torres Strait Islander peoples, 6% were IVDUs and 4% were men who have sex with men [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 25-30. The highest residual risk of HCV transmission would be for male donors aged 35-40.

A



B



C

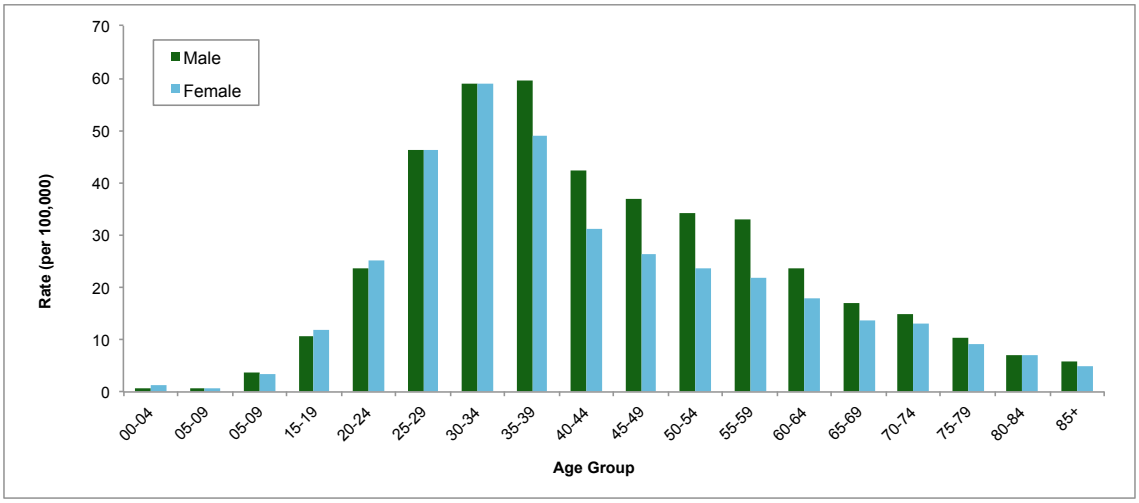


Figure 8: Graphs of (A) HIV (B) HCV and (C) HBV notification rates by age and sex (Data sources: The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia - Annual Surveillance Report 2016, and The Kirby Institute, UNSW Australia, Sydney; 2015 Australian HIV Public Access Dataset http://kirby.unsw.edu.au/surveillance/Australian-HIV-Public-Access-Dataset - NB this dataset excludes Queensland diagnoses)

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 six 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 2011-2016 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 2011-2016 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 versus 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 ten-times that of those who are HIV-negative (HCV prevalence of 9.4% versus 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 amongst 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 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 50-57% [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 out of 1,235 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 versus 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% versus 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 Aboriginal and Torres Strait Islander population in 2016 than in the Australian-born, non-Indigenous population (6.4 versus 2.9 per 100,000) [37]. Whereas HIV notification rates in the Australian-born, non-Indigenous population have declined since 2014, in the Aboriginal and Torres Strait Islander population there has been a steady increase in the annual HIV notification rate over the past five 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 Aboriginal and Torres Strait Islander 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 Aboriginal and Torres Strait Islander people has been

increasing, and in 2016 was nearly 4-times greater than for the non-Indigenous population (172.7 versus 45.2 notifications per 100,000) [37].

The estimated prevalence of HBV in Aboriginal and Torres Strait Islander 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, one person was infected through IVDU, and five 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 subsidised 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].

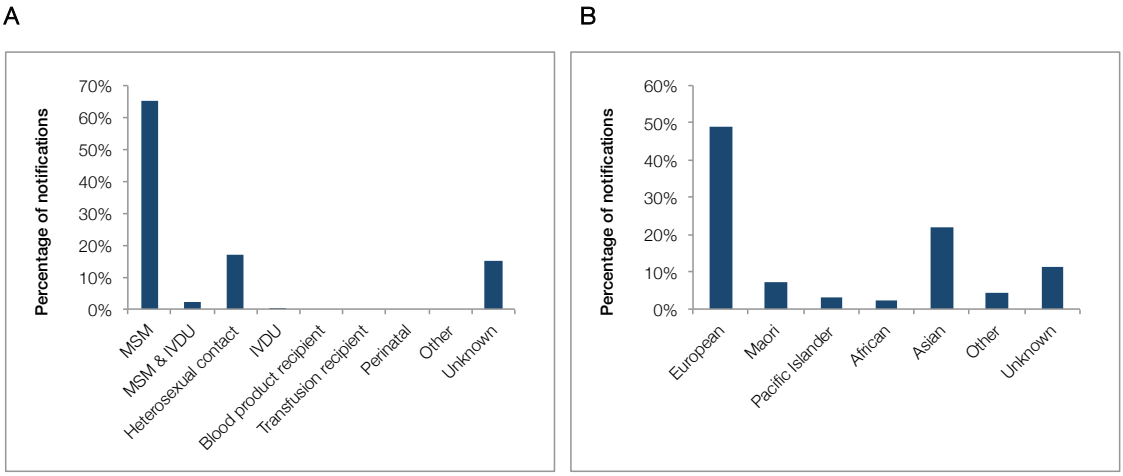


Figure 9: Distribution of HIV notifications in New Zealand in 2016 by (A) exposure category, and (B) ethnicity [62].

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 0.4-0.8 cases per 100,000 population for the past decade (versus 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 two 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 amongst 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 2010-2015 had a reported history of BBV and/or social risk factors for BBV [74]. The proportion of all donor referrals with a documented history of increased-risk behaviour 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 one 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 2010-2015 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 behaviour, 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 3.2 shows the proportions of potential organ donors tested at the SEALS laboratory (NSW) 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 under-referral of potential donors at increased risk of BBV, or routine referral of potential donors at low risk of BBV for NAT, despite current guidelines.

Table 3.2: 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 viraemia (HIV-RNA, HCV-RNA, HBV-DNA) and evidence of infection (Anti-HIV, Anti-HCV, Anti-HBc). (Source: Personal communication S Ray and W Rawlinson).

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

3.1.2. 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 modelling 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 utilisation 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 3.1.3). 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, 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 three weeks to up to six months (average window period of 17-22 days), however p24 antigen can be detected ~7-16 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; i.e. 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:

$$\text{Risk of window period infection} = 1 - e^{-(\text{incidence rate x window duration})}$$

The risks of window period infection calculated by Waller et al. are reported in Table 3.3. 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.

Table 3.3: Residual risk per 10,000 of an HIV infection occurring during the window period, by ELISA and NAT, calculated for the Australian population (personal communication, Karen Waller)

Risk category	# patients	#HIV sero-converted	Person Years	Pooled incidence per 100 PYS (95% CI)	Residual risk (95% CI), ELISA	Residual risk (95% CI), ELISA + NAT
MSM	10414	175	15280.5	1.05 (0.59-1.63)	6.3 (3.6-9.8)	2.0 (1.1-3.1)
IVDU	76596	717	-	0.33 (0.30-0.35)	2.0 (1.8-2.1)	0.6 (0.6-0.7)
Incarcerated	196784	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)

HCV

The serological window for HCV antibody detection is long: at least 40-70 days. NAT reduces the HCV detection window to ~4-6 days and is highly sensitive, allowing for HCV RNA detection at levels as low as 2.0-9.4 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 3.4). 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 two 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 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 post-transplant 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 Section 3.1.4). 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 post-transplant.

Table 3.4: Interpretation of results of HCV screening in organ donors and implications for utilization [5].

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

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 3.5). Anti-HBc of IgM class indicates a current or recent infection with HBV, while 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 titre, 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 titre >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 titres 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].

Non-liver 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 2.6). Non-liver 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 titre [59]. 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 35-44 days; NAT reduces this window to 20-22 days [44]. NAT is still useful, however, as it will detect viral replication in potential donors who are anti-HBc positive but HbsAg negative – i.e. 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 characterised 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 anti-viral 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 >10 IU/L has been demonstrated to be protective for recipients of anti-HBc-positive kidneys, however in liver recipients a threshold of HBsAb>100 IU/L is often applied [97]. In one study the risk of anti-HBc seroconversion post-liver transplant was 4% when pre-transplant HBsAb titres in the recipient were >100 IU/L, and 10% when pre-transplant titres were <100 IU/L [98].

Table 3.5: Interpretation of results of HBV screening in organ donors and implications for utilization [5]

HBV test	Conclusion	Implications for liver utilisation	Implication for utilisation of non-liver 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 viraemia but low-level viraemia 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*	Transmission is unlikely: allow transplantation of organs in vaccinated or infected recipients. Organs may also be used in other recipients with/without prophylaxis* and with monitoring for at least 12 months.

*HBV prophylaxis= anti-viral treatment (and HBIG) as well as life-long monitoring (serology and NAT) required In recipients with appropriate own immunological protection against HBV after vaccination, discontinuation of anti-viral treatment can be considered on a case-by-case basis

3.1.3. Transmission Risk

HIV

Table 3.6 summarises published reports of unexpected HIV transmission from deceased donors to recipients. Reports were identified as per the search strategy described in Appendix 9.2. Given that transmission events are not systematically reported in peer-reviewed journals, it is unlikely that Table 3.6 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 anti-retroviral therapy in 1996. Reviews of HIV infection in solid organ transplantation from the early 1990s reported five-year mortality rates among recipients who seroconverted post-transplantation of 30-50% [99, 100]. From three cases of HIV transmission reported in the past decade affecting eight recipients, there was only one 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 (2010) and Bellandi et al (2010), HIV transmission from an Italian donor to three recipients (2 kidney recipients and one liver recipient) occurred due to a “chain of errors during the donation process” [58, 101]. The donor in this case was a woman in her forties who died of a brain

haemorrhage 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 [102]. Routine blood tests showed that the donor was infected with HIV, however the lab 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 lab machine into the lab information system, as 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 lab 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, firstly, that biovigilance systems with clear lines of communication are essential for rapid notification of recipients potentially affected. Secondly, there is always the potential for human error, and systems therefore need to be computerised as far as possible, and designed with the potential for 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 "non-reactive" by the transplant coordinator [103]. Precautionary measures proposed by the regional health authorities subsequent to the Italian HIV transmission event included [102]:

- Cross-checking of laboratory reports and transcription of test results confirmed by double signature
- Computerised 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 (2011), a 39 year-old male donor transmitted HIV and HCV to four recipients (2 kidney recipients, one heart recipient, and one liver recipient) [54]. 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 prior to 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 post-transplant. The recipient of the right kidney experienced graft rejection that resulted in transplant nephrectomy 19 months post-transplant. The recipient of the liver, despite aggressive treatment, died 12 months after transplantation (less than two months after the detection of HIV and HCV). The recipient of the heart stopped adhering to treatment nine months after being diagnosed with HIV and HCV, and died three 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 behaviours. 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 post-transplant 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 to the cases reported by Borchi et al and Bellandi et al.). Data from DTAC clearly demonstrate improved outcomes with early recognition and expedited communication [104]. If NAT is not performed prior to donation, it should be performed retrospectively for increased-risk donors, and recipients should be routinely screened with HIV-NAT seven 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. Thirdly, 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 centre [105].

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.

Table 3.6: Reports of unexpected donor to recipient transmission of HIV and clinical outcomes (deceased donors only). Excludes reports with no evidence of donor origin of infection

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 [106]	1984	Presumed illicit drug use	27	27	No	No
	Poli, 1989 [106]	1984	Presumed illicit drug use	40	40	No	No
	Poli, 1989 [106]	1984	Illicit drug use	13	19	No	No
	Poli, 1989 [106]	1983	Illicit drug use	11	21	No	No
	Poli, 1989 [106]	1983	Illicit drug use	16	33	Yes	No
	Poli, 1989 [106]	1982	Illicit drug use	2	59	Yes	No
	Briner, 1989 [107]	1984	IVDU	<1	59	Yes	No
	Erice, 1990 [99]	1984	Transfusion[a]	33	67	No	No
	Simonds, 1992 [108]	1985	None known	17	32	Yes	No
	Simonds, 1992 [108]	1985	None known	7	14	Yes	Yes
	Schwarz, 1987 [109]	1986	IVDU, alcoholism	2	15	No	Yes
	Schwarz, 1987 [109]	1986	Homelessness, alcoholism	1.5	33	No	No
	CDC, 1987 [110]	1986	None known	2	7	No	No
	Bowen, 1988 [111]	1988	MSM	<1[b]	15	No	No
	Borchi, 2010 [101]	2007	None known	<1	35	No	No
	Bellandi, 2010 [58]	2007	None known	<1	35	No	Not reported
	Ison, 2011 [54]	2007	MSM	10[c]	14	No	Yes
	Ison, 2011 [54]	2007	MSM	10[c]	24	No	Yes
	Mukhopadhya, 2012 [112]	.	.	9	9	No	Not reported
Liver	CDC, 1987 [110]	1986	None known	3	7	No	No
	Samuel, 1988 [113]	1986	Not reported	<1	1.5	Yes	No
	Simonds, 1992 [108]	1985	None known	<1[d]	<1	Yes	No
	Bellandi, 2010 [58]	2007	None known	<1	35	No	Not reported
	Ison, 2011 [54]	2007	MSM	11[c]	12	Yes	No
Heart	Erice, 1990 [99]	1984	Transfusion[a]	25	72	No	No
	Simonds, 1992 [108]	1985	None known	8	9	Yes	No
	Ison, 2011 [54]	2007	MSM	11[c]	35	Yes[e]	No
Pancreas	Erice, 1990 [99]	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.

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 utilised for HCV-negative recipients in life-saving 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 to December 1999 reported a three-year actual survival rate of 40% for recipients who were at risk of imminent death prior to 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, four out of 17 recipients who survived more than 60 days post-transplant seroconverted to HCV positive; of this four, only one began to show elevated liver function tests at one year post-transplant. The donors in the analysis were restricted to those testing positive for HCV on 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 post-transplant and six out of nine patients surviving beyond three months post-transplant developed evidence of hepatitis, including severe liver injury in two patients [118].

Table 3.7 summarises 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. and Nampoory et al. 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 female with no known risk factors [119] and an 11-year-old boy [120]; both were seronegative for HCV. In the case reported by Nampoory et al, HCV was detected in both kidney recipients four and eight 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, none of the recipients had died or lost their graft within the 14 month follow-up time frame [119].

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 two kidneys both had positive results on HCV-NAT when tested six months after transplantation; the liver recipient was HCV-positive prior to 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. reported three 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 prior to donation, NAT for HCV, HBV and HIV were all negative, and the heart, liver and both kidneys transplanted into four recipients after consent was obtained to receive organs from an increased-risk donor. The liver and right kidney recipients had known HCV infection prior to transplantation: nine days post-transplant 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 post-transplant, and treatment with pegylated interferon (27 weeks post diagnosis) and ribavirin (16.5 weeks post diagnosis) 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 of >69 million IU/mL approximately eight months post-transplant. After the patient developed cirrhosis due to non-alcoholic steatohepatitis approximately two years post-transplant, 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 two kidneys were transplanted into two HCV-negative recipients after providing informed consent. HCV RNA was detected in the recipient of the right kidney one month post-transplant, however the left kidney recipient had undetectable HCV RNA at one, two and three months post-transplant. The right kidney recipient developed a low level of elevated liver enzymes at four months post-transplant, and died 19 months post-transplant 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 six recipients. HCV RNA was detected in the recipient of the left lung on routine screening 66 days post-transplant, and in the kidney/pancreas recipient 73 days post-transplant. The right lung recipient developed primary graft dysfunction and died shortly after transplantation: retrospective testing detected HCV RNA in a sample taken 20 days post-transplant. HCV RNA was not detected in the right kidney and heart recipients at seven and six months post-transplant respectively.

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

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 following an opiate overdose. HCV serology was negative, however routine recipient follow-up at day 40 post-transplant 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 two 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 post-transplant, 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, two 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 [124]. 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 [125].

Table 3.7: Reports of unexpected donor-derived transmission of hepatitis C virus and clinical outcomes. Restricted to reports proving information on clinical outcomes; deceased donor transplants only.

Transplanted organ	Ref	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, 1995 [119]	1995	None known	Serology	<1	10	No	No
	Krajden, 1995 [119]	1995	None known	Serology	8	12	No	No
	Nampoory, 1999 [120]	1996	None known	Serology	8	36	No	No
	Nampoory, 1999 [120]	1996	None known	Serology	4	Not reported	Yes	No
	Ison, 2011 [54]	2007	MSM	Serology	10[a]	14	No	Yes
	Ison, 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, 2015 [122]	2011	IVDU (COD drug overdose)	Serology, NAT	<1	24	No[b]	No
	Suryaprassad, 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, 2011 [54]	2007	MSM	Serology	11[a]	12	Yes	No
Heart	Krajden, 1995 [119]	1995	None known	Serology	<1	18	No	Not reported
	Ison, 2011 [54]	2007	MSM	Serology	11[a]	35	Yes	No
	Suryaprassad, 2015 [122]	2011	IVDU (COD drug overdose)	Serology, NAT	1	Not reported	No	No
Lung	Krajden, 1995 [119]	1995	None known	Serology	3	14	No	Not reported
	Tugwell, 2005 [126]	2000	Alcoholism	Serology	Not reported	14	Yes	Not reported
	Tugwell, 2005 [126]	2000	Alcoholism	Serology	Not reported	Not reported[e]	Yes	Not reported
	Suryaprassad, 2015 [122]	2013	IVDU	Serology, NAT	2	7	No	No
	Suryaprassad, 2015 [122]	2013	IVDU	Serology, NAT	2	3	Yes[f]	Yes
Pancreas	Suryaprassad, 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 non-alcoholic steatohepatitis two years post-transplant 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 four months post-transplant and died at post-transplant 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 following HCV detection in the left lung recipient, stored serum samples obtained pre and post-transplantation were tested and showed HCV RNA was undetectable on pretransplant samples but weakly detectable in a sample taken on day 20 post-transplant.

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 anti-viral 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 1995-1998 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 two consecutive samples post-transplantation) 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 0-2.4% [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 – while 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 post-transplant, 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 post-transplant [93, 130, 134-136]. There have been at least two 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 three 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 of >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 Hepatitis B immune globulin and/or entecavir or tenofovir is highly effective in preventing *de novo* HBV infection post-transplantation.

Table 3.8 summarises reports of donor-derived HBV transmission according to donor serological status. Only three reports of HBV transmission by kidney transplantation were identified that also provided information on patient outcomes. Wolf et al reported three cases of HBV transmission from HBsAg positive kidney donors to recipients occurring at the University of California San Francisco between 1975 and 1977 [143]. 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 post-transplant [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 post-transplant, 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 haemorrhage. The patient was found to be HBsAg positive 10 weeks post-transplant, and retrospective testing of post-transplant blood samples showed serum was first HBsAg positive on day six post-transplant [144]. In the case reported by Magiorkinis et al (2012), a kidney from an HBsAg-positive donor was transplanted into a vaccinated recipient under the cover of prophylaxis (intravenous hyperimmune gammaglobulin). The recipient developed acute HBV hepatitis four months post-transplant and died one month later from encephalopathy, Child-Pugh Class C, and renal hepatic syndrome type 1 despite treatment with Entecavir. Genotype 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 [55].

The majority of case reports of donor-derived HBV transmission occurred via liver transplantation. Several of the cases summarised in Table 3.8 involve HBsAg-negative donors who were found to be anti-HBc-positive

on retrospective testing post-transplantation. Gow & Mutimer (2001) retrospectively searched the database of the liver transplant unit at the Queen Elizabeth Hospital, Birmingham, for cases of *de novo* HBV post-transplantation from 1982 to 2000, when screening for HbsAg was standard but routine screening for anti-HBc had not yet been implemented in the UK [145]. They found four 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 the time the infectious risk was not appreciated (see Table 3.8).

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 recognised by anti-HBV, resulting in a loss of immunoreactivity [146]. “Vaccine escape mutants” may evade detection via standard serological testing, and cause infection in immunised recipients and recipients receiving immunoprophylaxis with polyclonal anti-HBs (HBIG) [146]. Moraleda et al (2006) 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 pre-liver transplant period (anti-HBs titre >10 IU), was found to have active HBV infection seven months post-transplant [147]. 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 (2013) 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.

Table 3.8: Reports of donor-derived transmission of hepatitis B virus in recipients seronegative for HBV prior to transplantation. Restricted to reports proving information on clinical outcomes; deceased donor transplants only.

Transplanted organ	Ref	Year of transplant	Results of donor serological testing available prior to donation				Donor HBV-NAT (serum)	Recipient serological status (pre-transplant)			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, 1979 [143]	.	Positive	.	.	Positive	.	Negative	.	.	.	21	No	Yes
	Wolf, 1979 [143]	.	Positive	.	.	Positive	.	Negative	.	.	.	23	Yes	No
	Wolf, 1979 [143]	.	Positive	.	.	Negative	.	Negative	.	Negative	.	6	No	No
	Lutwick, 1983 [144]	1980	.	.	.	.	.	Negative	.	Negative	2	18	No	Yes
	Magiorkinis, 2012 [55]	2007	Positive	.	.	Negative	.	Negative	Negative	11.6 IU/L	2	17	Yes	No
Liver	Douglas, 1997[148]	.	Negative	Positive	Positive	.	Positive (serum)	Negative	Negative	Negative	<6	124	No	No
	Douglas, 1997 [148]	.	Negative	Positive	Positive	.	Negative	Negative	Negative	Negative	<6	116	No	No
	Douglas, 1997 [148]	.	Negative	Positive	Positive	.	Positive (liver)	Negative	Negative	Negative	>24	63	No	No
	Gow, 2001 [145]	1990	Negative	.	.	.	.	Negative	Negative	.	36	96	Yes[a]	No
	Gow, 2001 [145]	1993	Negative	[b]	.[b]	.	.	Negative	Negative	.	9	24	Yes[c]	Yes
	Gow, 2001 [145]	1994	Negative	Positive	.	.	.	Negative	Negative	.	48	72	No	No
	Gow, 2001 [145]	1999	Negative	[b]	.	.	.	Negative	Negative	.	14	14	No	No
	Castells,1999 [149]	.	Negative	Positive	13 IU/L	.	Negative	.	Negative	181 IU/L	24	36	No	No
	Castells,1999 [149]	.	Negative	Positive	88 IU/L	.	Positive	.	Negative	5 IU/L	48	48	No	No
	Cahlin, 2001 [150]	.	Negative	[b]	.	.	.	Negative	Negative	Negative	2	19	Yes	Yes
	Cahlin, 2001 [150]	.	Negative	[b]	.	.	.	Negative	Negative	Negative	10	19	No	No
	Moraleda, 2006 [147]	2006	Negative	Positive	Positive	.	.	Negative	Negative	Negative	7[d]	40	No	No
	Molina Rueda, 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 three weeks after transplantation. They were transplanted two more times, and died due to primary non-function of the 3· transplant.

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

3.1.4. Recipient management

The case reports described in section 3.1.3 highlight the importance of close monitoring of recipients for *de novo* infection with BBV in the weeks and months following transplantation. Recipients who are on immunosuppression may not seroconvert despite being viraemic, 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, post-transplant monitoring for donor derived BBV infection should include NAT screening for HIV, HBV, HCV at two and four weeks, and screening by both NAT and serology at 12 and 48 weeks.

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 anti-retroviral 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 three HBsAg-positive donors were utilized [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 [59, 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 post-transplant in this case would involve (personal communication P Boan):

a) Hepatitis B immune globulin (HBIG) if recipient HBsAb<100 IU/L or unknown. One regimen described is 800 IU/L intramuscularly daily for seven days, then monthly for 12 months [154];
b) Potent antiviral therapy (e.g. entecavir and/or tenofovir) for 12 months for recipients of non-liver 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 following prophylaxis might be observed (personal communication P Boan):

a) If recipient has HBsAb >100 IU/L recorded in the last three months, no prophylaxis is required. If recipient has HBsAb <100 IU/L or if HBsAb titre is unknown, intramuscular HBIG 800 IU should be administered daily for one week for non-liver transplant recipients. For recipients of liver transplants, treatment should extend to 12 months of HBIG 800 IU monthly.
b) Non-liver transplant recipients should receive entecavir 0.5mg daily (adjusted if creatinine clearance <50 ml/min) for one 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 summarised in Table 3.9.

For all recipients of organs from donors testing positive for HBsAg and/or HBsAb, ongoing post-transplant surveillance for the appearance of HBV infection is essential. Patients receiving prophylaxis should be screened for HBV DNA at least every three months post-transplant through to 12 months post-antiviral cessation. Patients not receiving prophylaxis should be tested monthly through to 12 months post-transplantation. 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].

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

Table 3.9: Suggested hepatitis B virus prophylaxis for liver and non-liver 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
Non-liver 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.

The introduction of DAAs for HCV has entirely changed the landscape of recipient management in relation to the risk of HCV infection. Prior to 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 60-75% 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 analogue 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 of >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 90-98%, 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 60-75% in recipients with severe hepatic impairment [166, 167]. Only minor side effects – e.g. 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 – THINKER – 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. Recipients were given intravenous glucocorticoids and rabbit anti-thymocyte globulin, followed by oral tacrolimus, mycophenolate mofetil, and prednisone. HCV viral load was measured three days post-transplant, 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 three post-transplant and elbasvir-grazoprevir was initiated, with a total treatment course of 12 weeks. All ten recipients were cured of HCV (defined as a sustained virologic response 12 weeks after the end of DAA treatment). At six 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 pre-emptively treated with elbasvir-grazoprevir, with a single dose given pre-transplant, and then daily doses for 12 weeks post-transplant [169]. If HCV genotype 2 or 3 was detected then sofosbuvir was added to the treatment regimen. HCV RNA was quantified on post-operative day one and then weekly for the first month, then every four weeks until 12 weeks post-transplantation. Preliminary results for eight HCV-negative recipient/HCV-positive donor pairs were presented at the 2017 American Society of Transplantation meeting: HCV RNA was detected in four recipients on post-transplant day one 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-viraemic donor to a non-viraemic 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, six 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 male who had died from an intravenous heroin overdose: the donors HCV genotype was not known at the time of transplantation, but three days following transplantation the recipient's HCV genotype was reported as 1A. Treatment with ledipasvir/sofosbuvir was commenced on post-transplant day 25, and HCV RNA was undetectable by week eight post-transplant. Two years post-liver transplant, the patient remained HCV-RNA negative, with excellent graft function [170].

One of the areas where more evidence is currently required is with regards 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 eGFR <30 mL/min/1.73m^2 [171]. The HCV protease inhibitor asunaprevir and the Ns5A inhibitor daclatasvir are mainly eliminated through the liver, and combination therapy with daclatasivir and asunaprevir has been demonstrated to be highly effective and safe in genotype 1 HCV-infected patients with eGFR <45 mL/min/1.73m^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 stage 4 and 5, including haemodialysis 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 1-3 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 (e.g. 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 (e.g. 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 post-transplant. 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.

3.2. HTLV-1

3.2.1. 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, intravenous drug use, sexual intercourse or blood transfusion. While infection is usually asymptomatic in most individuals, approximately 2-5% of infected individuals will subsequently develop acute T-cell leukaemia/lymphoma (ATL) around 20-30 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 supresses 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 *Staphylococcus 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), parts of the Middle East and Australo-Melanesia [182]. It is hypothesised 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 amongst 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 <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 1.2-3%, 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 gender, previous STI, and residence in the south or west of Central Australia [183]. Each of the major recognised complications of HTLV-1 – ATL, HAM/TSP, infective dermatitis, strongyloidiasis, HTLV-1-associated pulmonary disease, crusted scabies – have been described in 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 two case series of 10 and 16 recipients followed for an average of 13 and eight years respectively [186, 187]. In

contrast, a third case series Japan observed three cases of ATL at six, nine and 25 months after living donor liver transplantation from eight HTLV-1 infected recipients [188]. There has also been one report of an HTLV-positive recipient developing HAM/TSP following a living donor kidney transplant, and one report in which three recipients from a single deceased donor rapidly developed HAM/TSP post-transplant [189, 190].

3.2.2. 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 non-endemic 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 sub-populations or endemic areas [191, 195]. OPTN has removed the requirement for pre-transplant 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 innogenetics 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 utilisation [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 Aboriginal and Torres Strait Islander people living in the Northern Territory, Queensland, Kimberley and northern South Australia.

3.2.3. Transmission

Between 1994 and 2001, the United States United Network for Organ Sharing reported 12 HTLV-positive deceased donors, from whom 5 organs were transplanted. As of 2003, four out of five recipients were alive and without malignancy, and a heart transplant recipient of an HTLV-positive organ had died one month post-transplant 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 two kidney recipients) presented two years post-transplant 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 hypothesise 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 1,298 organ donors. Not a single seropositive donor was identified. Simultaneously, HTLV screening was conducted in a sample of 1,079 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 amongst native Spaniards with a high suspicion of HTLV-1 infection [195].

3.2.4. 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 post-transplant, and should receive ongoing clinical monitoring for the appearance of unexplained neurological disease and/or T-cell leukaemia/lymphoma [194]. Counselling 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 characterised. 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 (e.g. 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 human leukocyte antigen (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 hypothesised 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: while there have been several cases of ATL and TSP/HAM in HTLV-1 positive organ recipients following 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].

3.3. Herpes Viruses (excluding Epstein-Barr virus and *Cytomegalovirus*)

3.3.1. Epidemiology

Herpes simplex virus

Data on the epidemiology of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in Australia come from the baseline AusDiab survey, a population-representative survey of adults aged 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 65-74 year age group at 85%, compared to a seroprevalence of 67% in the 25-34 year age group. Seroprevalence of HSV-2 peaked in the 35-44 year age group at 16%, compared to the lowest seroprevalence of 8% in the 65-74 year age group.

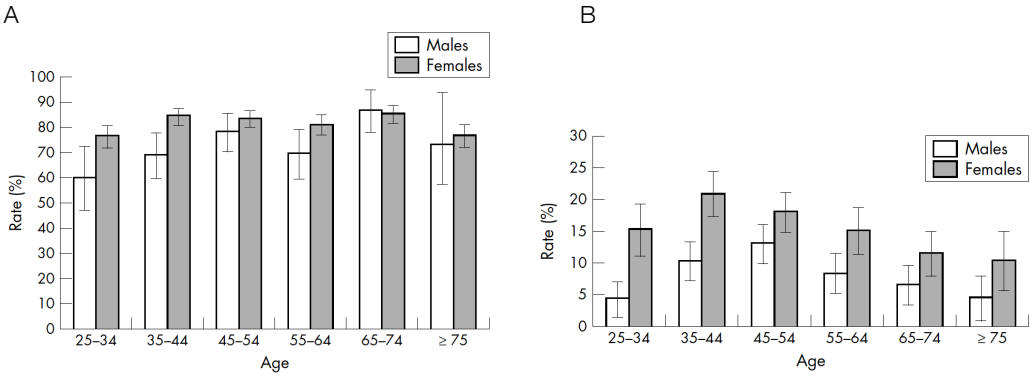


Figure 10: Seroprevalence of (A) HSV-1 and (B) HSV-2 in the Australian adult population, by age and sex [204].

Seroprevalence of both HSV-1 and HSV-2 were higher in women than in men (80% versus 71% and 16% versus 8% respectively). Seroprevalence of HSV-2 was higher in capital cities (14%) and metropolitan areas (13%) compared to rural and remote areas (9%). Estimated seroprevalence of both HSV-1 and HSV-2 were higher in Aboriginal and Torres Straight Islander people than non-Indigenous Australians (100% versus 75% and 18% versus 12% respectively). Although not analysed as part of the AusDiab survey, international studies have reported HSV-2 seroprevalence among men who have sex with men of 24-87% [205, 206].

Kaposi sarcoma herpes virus (KSHV) or human herpes virus-8 (HHV-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 wide geographic variation. Seroprevalence is estimated to be <10% in North America and northern Europe, and between 20% to 80% in the Mediterranean and parts of Africa [207]. Modes of KSHV transmission vary in different parts of the world: in non-endemic 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].

3.3.2. 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 section 3.3.3), as well as the potential for reactivation in latently infected recipients. Active infection in the potential donor should also not be disregarded. Some transplant centres perform retrospective additional donor tests for latent HSV in cases of sero-negative recipients (usually in the case of paediatric recipients) in order to decide on specific anti-viral 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 viraemia in the donor without effective anti-viral treatment [5].

Kaposi sarcoma herpes virus (KSHV) or human herpes virus-8 (HHV-8)

KSHV 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 anti-lytic anti-latent antibodies in areas of high KSHV prevalence (e.g. Mediterranean region) [5]. As KSHV serology is generally unavailable prior to deceased donor organ transplantation, screening for KSHV antibodies may be performed retrospectively in the days immediately following 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].

3.3.3. Transmission

Herpes simplex virus

A case of donor-derived HSV-2 infection affecting six solid organ recipients occurred in Victoria in 2014 [18, 215]. Lungs, kidneys, pancreas and liver were retrieved from the original donor and transplanted into four recipients. The recipient of the kidney-pancreas had an acute myocardial infarction and cardiac arrest two days post-transplant and subsequently deteriorated, with brain death declared on day nine. Serological testing on day nine 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 past 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 prior to 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 viraemia and clinical symptoms. Evidence of hepatitis was observed on day 13 post-transplant, and HSV-2 viraemia was detected. Valaciclovir treatment was increased to 1g 8-hourly, but on day 19 a disseminated rash developed suspected to be cutaneous HSV. The patient was admitted and intravenous acyclovir 600mg was administered eight hourly, and eventually the hepatitis and rash resolved and the patient remained symptom free at 12 months post-transplant.

None of the other recipients in this case became symptomatic. The recipient of the lungs from the original donor had received CMV prophylaxis with intravenous ganciclovir and CMV hyper-immune globulin due to CMV-status mismatch, and there was no evidence of viraemia or HSV disease up to 12 months post-transplant. The recipient of the second kidney from the original donor also received anti-CMV prophylaxis (valganciclovir 450 mg 12-hourly) and did not develop viraemia 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 1g daily on day one post-transplant. HSV-2 viraemia was noted on day five and treatment switched to intravenous acyclovir 400mg; viraemia resolved and the patient was asymptomatic at 12 months post-transplant.

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 intravenous ganciclovir 5mg/kg on day one post-transplant. HSV-2 viraemia was detected on day two post-transplant, and the patient switched to valaciclovir 1g every eight hours. Viraemia resolved and the patient was asymptomatic at 12 months post-transplant.

These two 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 pre-existing immunity and on the prophylaxis regimen used. Symptomatic HSV disease only occurred in the recipients who were serologically negative and did not receive prophylactic anti-viral therapy.

Kaposi sarcoma herpes virus (KSHV) or human herpes virus-8 (HHV-8)

Studies of the seroprevalence of HHV-8 in organ donors and recipients pre- and post-transplantation 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 non-malignant illnesses following donor-derived transmission of HHV-8 have 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 tumours in the recipient [210].

Table 3.10 summarises published cases of donor-derived KSHV transmission and their outcomes.

Table 3.10: Case reports of donor-derived KSHV in solid organ transplant recipients (deceased donors).

Transplanted organ	Ref	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, 2000 [218]	1998	5	12	Fever, enlarged spleen, anaemia, thrombocytopenia, acute kidney failure	No	Acyclovir, ganciclovir	Yes
	Luppi, 2002 [219]	1998	4	24	.	KS, haemophagocytosis	Reduction of immunosuppression, foscamet, microsomal daunorubicin	No
	Chiereghin, 2017 [216]	.	1.5	2	Severe lung infection	No	.	Yes
	Chiereghin, 2017 [216]	.	6	.	None (HHV -8 detected on routine screening)	No	.	No
	Park, 2017 [220]	.	5	6	maculopapular skin rash, fever, pancytopoenia	KS	Change in immunosuppression then reduction immunosuppression, then discontinuation, acyclovir, foscarnet, cytotoxic therapy (etoposide and dexamethasone)	Yes*
Liver	Marcelin, 2004 [221]	2000	5	5	Rash, polyadenopathy, fever, anemia, thrombopoenia	KS, solid form of primary effusion lymphoma (lung, spleen, stomach)	.	Yes
	Pietrosi, 2011 [214]	2007	2	3	Fever, cough, bilateral pleural effusion, multiorgan failure	No	Cidofovir, probenecid	Yes
	Pietrosi, 2011 [214]	2007	6	2	Ascites, increase in liver function tests, kidney failure, liver failure	No	Cidofovir	Yes
	Pietrosi, 2011 [214]	2008	6	15	Fever, weakness, severe sinus tachycardia and maculopapular skin rash	KS	Cidofovir, liposomal-doxorubicin	No
	Pietrosi, 2011 [214]	2010	<1	4	None (HHV -8 detected on routine screening)	No	Cidofovir	No
	Chiereghin, 2017 [216]	.	1.5	10	Dyspnea, malaise, pancytopenia, pleural effusion, kidney failure, liver failure, multiorgan failure.	No	Reduction of immunosuppression, cidofovir	Yes

*Death was due to septic shock due to a multi-drug resistant bacterial infection with lobar pneumonia

3.4. *Cytomegalovirus* and Epstein Barr Virus

The majority of adult populations worldwide are latently infected with *Cytomegalovirus* (CMV) and/or Epstein Barr virus (EBV), which affect somewhere between 20-100% and 50-90% 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 9-10 year-olds, 80% of 16-19 year-olds, and in 92% of young adults [223]. More recent data are available on CMV prevalence: in 2002, 3,593 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 1-2 year age group, increasing to 50% in the 15-19 year age group, and reaching 79% in the 55-59 year age group, with little difference in seroprevalence between males and females [225].

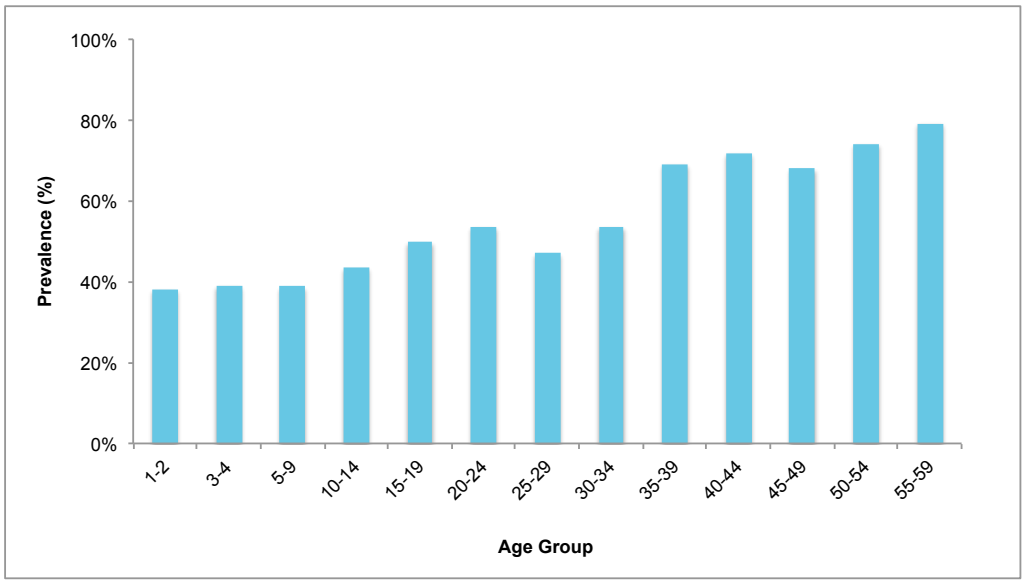


Figure 11: Estimated CMV seroprevalence in the Australian population by age group (source: Seale et al. [225])

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 post-transplantation. 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 pre-emptive treatment.

EBV transmission to naïve recipients increases the risk of post-transplant lympho-proliferative disorders (PTLD). 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 post-transplantation, 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 six times higher for D+/R- deceased-donor transplants compared to R+ transplants [226]. For chemo-prophylactic 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 post-transplant 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, naïve recipient, UK guidelines advise close monitoring of EBV DNA levels post-transplantation in patients at risk [29].

European guidelines recommend specific anti-viral prophylaxis for CMV-naïve recipients and virological monitoring and pre-emptive 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 PTLD 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 in order to use a life-sustaining organ. For D+R- CMV transplants, antiviral prophylaxis according to international guidelines will be utilised, with CMV hyperimmune globulin also considered in some thoracic transplant units. For EBV D+R- transplants, EBV viral load in blood is recommended (e.g. monthly for six months then three monthly to 12 months post-transplant; most EBV related PTL presents within one year post-transplantation) with investigation (e.g. PET scan) and consideration of intervention (e.g. reduction in immunosuppression, rituximab) with a significant rise in viral load (e.g. >10^{3} IU/mL).

3.5. Yearly epidemic influenza

3.5.1. Epidemiology

Influenza affects 5-10% of the Australian population each year and is estimated to cause over 3000 deaths, and more than 13,500 hospitalisations among Australians aged over 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 1-2% 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 one week [230].

In general, non-lung 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 non-lung 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 post-transplant 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 six post-transplant and following a five-day course of oral oseltamivir 2 x 75mg daily the patient cleared the virus and was doing well three 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 non-lung 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 utilisation 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?
- Is the potential donor considered to still be infective?
- Has the potential donor received an anti-viral agent and, if so, has the duration 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 (e.g. within the previous two weeks) should likely be deferred for lung and small bowel transplantation, however may be considered if the donor has received appropriate antiviral therapy with input from the organ procurement organisation'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 5-10 day course of influenza therapy for the recipient if the donor did not complete a course of treatment [Kumar D, Morris MI, Kotton CN, Fishcer SA, Michaels MG, Allen U, Blumberg EA, Green M, Humar A, Ison MG. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. Am J Tranplant 2010; 10(1): 18-25].

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 utilised 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.

3.6. Other viral pathogens

3.6.1. 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 anti-hepatitis 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. HDV 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). HDV coinfection/superinfection complicates the management of HBV and results in a poorer prognosis – compared with mono-infection with HBV, persons with HDV are three times more likely to develop cirrhosis, typically at a younger age, and a high proportion will subsequently require liver transplantation [233]. Coinfection may result in more severe hepatitis compared to superinfection; of those with superinfection, approximately 90% will develop chronic HDV, which will then lead to cirrhosis within 5-10 years in 70% of patients [234]. Coinfection usually appears first as IgM anti-HDV and then converts to IgG anti-HDV, while HDV RNA levels remain low [233]. 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 [233].

Internationally, the burden of HDV is highly variable and does not follow patterns of HBV prevalence [235]. 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 [233, 236]. Elsewhere, the average proportion of chronic HBV patients who are also infected with HDV is 5%, although wide local/regional variation exists [233]. For a detailed map of global HDV prevalence among HBV carriers, see reference [237]. Transmission can be blood borne, sexual, percutaneous, permucosal or perinatal. Prevalence of HDV is generally highest in the 20-40 year-old age group, and the majority of transmission is thought to be sexual or related to IVDU [233].

In the two decades since it's 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) [238]. As a result, awareness of HDV and rates of testing fell, contributing to the perception that HDV was being eradicated [238]. 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 [233]. A German study, for example, showed that 75% of HDV-positive patients were originally form Turkey or Eastern Europe [239].

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 [240]. The median age at diagnosis was 34, 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 3.11). There was one 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 to 16 notifications per year. Forty-one per cent of HDV notifications occurred within one year of HBV notification (median lag time between HBV and HDV notification of two 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, while HDV-Ag is only briefly detectable in serum. In the Victorian study for example, only six people tested positive for HDV-Ag. NAT is therefore the most reliable method for detection of HDV [233]. Nevertheless, measures to prevent transmission of HBV to the recipient will also prevent HDV.

Table 3.11: Notifications for HDV in Victoria 2000-2009 [240]

Country of birth	Number of 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)*	13	-	-	-
Not Stated	31	35.6%	29.0%	1.69 (0.27-3.43)
Total	87	-	34.5%	2.02 (0.21-4.83)

*Countries of birth with one 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'.

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 (e.g. 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 [241]. 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 [241, 242]. 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 [241]. 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 U.S. Food and Drug Administration. For a thorough review of these new therapeutic agents, see reference [241].

Hepatitis E virus (HEV) is overall the world's most common cause of acute viral hepatitis. First identified in Kashmir in 1978, HEV has two 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 [243]. 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 3.12. 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 [243]. Those affected in high-income countries are generally older (>50 years), with risk factors including cirrhosis, liver transplantation, and HIV [243]. While in the viraemic phase, HEV can also be transmitted by blood transfusion, and several cases of transfusion-transmitted HEV have been reported [244-246].

There are four 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 [247]. 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 [247].

Table 3.12 Global distribution of hepatitis E virus [243]

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		Oman		
Sri Lanka	East Africa	Bahrain		
	Kenya	Iran		
Southeast Asia	Uganda	Kuwait		
Burma	Burundi	United Arab Emirates		
Cambodia				
Indonesia	West Africa	Southeast Asia		
Thailand	Ivory Coast	Singapore		
Vietnam	Liberia			
Laos	Nigeria	South America		
	Mali	Brazil		
Central Asia		Argentina		
Kazakhstan	North America	Ecuador		
Tajikistan	Mexico	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.

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 [248]. Anti-HEV IgM titres peak at 6-8 weeks post-infection but then rapidly wane; anti-HEV IgG antibody titres 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 two weeks post-infection, but HEV RNA testing is recommended for persons who are immunosuppressed [243].

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, following HEV infection. HEV is amenable to treatment with ribavirin monotherapy – for a summary of the effect of different antivirals and immunosuppressants on HEV-3 replication, see Table 3.13.

Table 3.13: Effects of antiviral and immunosuppressant therapy on HEV replication in the context of chronic HEV infection in solid organ transplant patients [243].

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

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 [249, 250]. 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 four 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 further information was provided about the donors (travel history was not given). At 37 days post-transplant, 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 post-transplant 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-post-transplant, the patient presented with oedema 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 prior to death detected anti-HEV IgM and IgG antibodies. Stored donor samples were then screened and, while 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 [249].

In the case from Singapore, the recipient was a 48-year-old male with chronic HBV and multifocal hepatocellular carcinoma that was outside of the eligibility criteria for liver transplantation in Singapore [250]. The donor procured a commercial deceased donor liver graft in 2009 (country not reported), and was deeply jaundiced on returning to Singapore three 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 was 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 one month after transplantation showed moderate acute cellular rejection, which responded well to pulse methylprednisolone, yet his liver function continued to deteriorate and six months post-transplant he was admitted to hospital with jaundice, ascites, peripheral oedema, 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 [250]. 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 [251]. 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 [252]. 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 [253]. 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 [254]. The recommendations of the British Transplantation Society with regards to donor screening and management of HEV in solid organ transplant recipients are summarised in Table 3.14.

Table 3.14: Statements of recommendations regarding HEV and solid organ transplantation, British Transplantation Society. Adapted from [254].

Testing of solid organ donors for HEV
• All solid organ donors are screened for HEV in line with the UK Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) recommendations. • The detection of HEV viraemia in a donor is not an absolute contraindication to the use of an organ from that donor, but will inform clinical management decisions post-transplant.
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 haemoglobin monitoring should be conducted during ribavirin treatment, as anaemia 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 minimise 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 towards 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.

In summary, HAV and HEV pose a threat to transplantation in their acute phase, although outbreaks occur rarely in 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 post-transplant (see Table 3.13). 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 (e.g. acute hepatitis) and epidemiological risk for HEV infection.

3.6.2. Arboviruses

Arboviruses refer to any viruses transmitted by arthropod vectors (e.g. mosquitoes, ticks, sandflies). Arboviruses endemic to Australia include the flaviviruses Murray Valley encephalitis virus, the Kunjin lineage of West Nile virus, 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 [255]. 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 [256]. Symptoms of Barmah Forest virus similarly include arthralgia, rash, fatigue and flu-like symptoms, although again many people infected will be asymptomatic [255]. 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 12. 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 over-diagnosis particularly in the off-season [255].

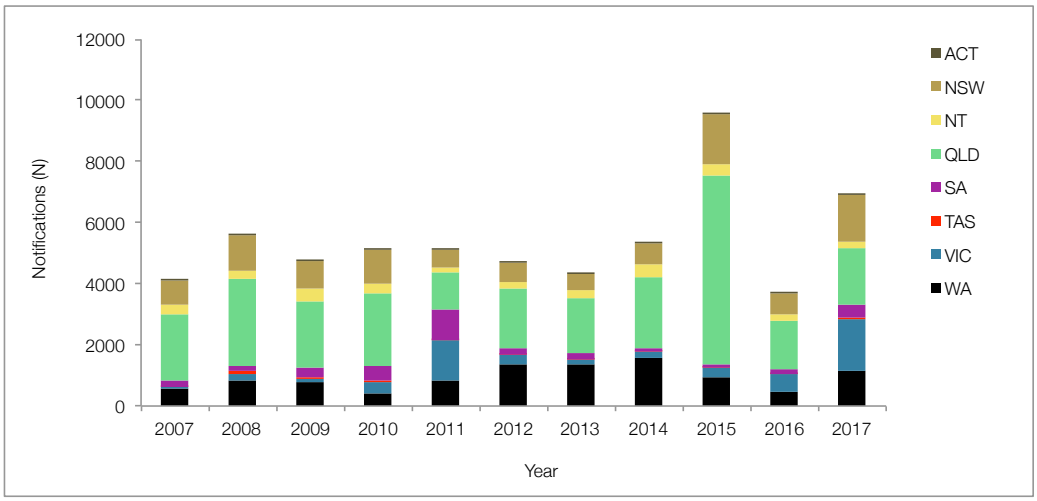


Figure 12: Ross River virus notifications (number) received from State and Territory health authorities, 2007 to 2017 [36].

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 one report in the literature of a case of Ross River virus transmission via blood transfusion occurring in Western Australia in 2014 [257]. The blood donor developed fatigue and arthralgia two 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 prior to 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 [257]. 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 West Nile virus and Murray Valley encephalitis virus are infrequent and mostly sporadic, with approximately 10 cases in recognised outbreak years, generally affecting residents of and visitors to the Kimberley region of Western Australia or the Northern Territory [36, 258]. However, despite the low notification rate, it is recognised that for every clinical case of there may be hundreds of asymptomatic infections, as the vast majority of Kunjin virus and Murray Valley encephalitis virus infections are asymptomatic [257]. 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 [258]. When Murray Valley encephalitis virus does cause clinical disease, symptoms are generally more than severe than for Kunjin virus: an estimated one in 1000 infections with Murray Valley encephalitis virus results in clinical encephalitis [259]. Encephalitis is less common in cases of Kunjin virus infection [258]. 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, non-endemic arboviruses of public health importance to Australia include dengue virus, chikungunya virus, and Zika virus. Non-endemic arboviruses are of concern primarily in the case of donors whose recent travel history includes south and south-east 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 3.15).

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 one 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 three 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 three 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 four 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].

Table 3.15: Notifications of non-endemic arboviral diseases in Australia in 2017, by country of acquisition [260]

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

The flaviviruses Zika virus and West Nile virus are discussed separately as pathogens of special interest in sections 6.1 and 6.2 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 6.1. 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 six months prior to donation [261]. Five days post-transplant 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 post-transplant the recipient developed upper gastrointestinal bleeding, gross haematuria and tachycardia. Three days later he complained of left flank pain and abdominal distension, and a large retroperitoneal haematoma at the bed of the transplanted kidney was revealed on computed tomography. Emergency surgery to evacuate the haematoma was successful and repeat NAT was negative for dengue. The recipient then went on to have an uneventful recovery, with resolution of haematemesis and haematuria 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 2-7 days [261].

European guidelines recommend ruling out acute infection with arboviral diseases including dengue, chikungunya and West Nile virus 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.

3.6.3. 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 [262]. Next-generation sequencing techniques have permitted a new appreciation of the diversity of resident viral species within individuals, a large proportion of which remain uncharacterised [262]. Metagenomic studies of samples from cystic fibrosis patients and lung transplant recipients have found that up to 88% of lung virome sequences were unknown [263, 264]. 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, as 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 [265].

To date, there has been a single study characterising the lung virome of lung transplant recipients [264]. 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 BAL from transplant recipients compared to healthy controls. Anelloviruses are ubiquitous in humans and have not yet been causally linked to human diseases [266], however Young et al also observed that high anellovirus loads correlated with dysbiotic bacterial communities in the allograft – i.e. the higher the anellovirus titre, the greater the divergence between the corresponding bacterial community and healthy controls [264]. The cause and clinical implications of this observation are not yet clear. Other viruses detected within the lung virome by this study included Epstein-Barr virus, human herpesvirus, human papillomavirus, and various bacteriophage genomes (e.g. 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. While next-generation sequencing may be of use for lung donor screening in the future, currently for practical purposes viral testing of the donor prior to implantation and BAL post-implantation will capture most viruses provided that samples are properly handled (personal communication A Glanville)

3.6.4. Meningoencephalitis of viral origin

Donors with undiagnosed meningoencephalitis are an uncommon but potentially lethal source of donor-derived infection [267]. Transmission of rabies, Lymphocytic choriomeningitis virus, West Nile Virus, *Mycobacterium tuberculosis*, *Cryptococcus*, *Coccidiodes immitis*, *Aspergillus* and *Balamuthia* have occurred when donors with meningitis or encephalitis of unknown cause have been used as organ donors [268]. For this reason, any meningitis or encephalitis without a proven cause is should be an absolute contraindication to transplantation [5, 7, 268], according to international guidelines [29] .

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 haemorrhage who had rabies [267, 269]. 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 Organ Procurement and Transplantation Network 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 West Nile Virus, followed by syphilis, histoplasmosis, toxoplasmosis and Chagas disease [267].

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, 268]. 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 [268]. Where the cause of the meningoencephalitis is confirmed as a virus that is amenable to treatment, for example herpes simplex virus encephalitis, the organs might be used if the donor is not viraemic and provided that the recipient is seropositive pre-transplant and/or is given appropriate prophylaxis [5, 29]. Meningitis of bacterial origin is discussed in section 4.4, and West Nile Virus is discussed as a special case in section 6.2.

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, four 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 computed tomography of the brain revealed a subarachnoid haemorrhage, which progressed to brain death four 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 four 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 [269].

A second report of unrecognized central nervous system infection involved two clusters of lymphocytic choriomeningitis virus (LCMV) in which seven out of eight recipients died [270]. LCMV 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 [271]. Transmission can occur vertically from mother to fetus, but other forms of human-to-human transmission do not normally occur. The two 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 aetiological agent causing the deaths of the recipients, LCMV could not be detected in either of the two 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 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 leucocytosis, with onset within three weeks of transplantation. The one patient who survived was a recipient of a kidney from the female donor. LCMV was identified as the aetiological agent on day 25 post-transplant and intravenous ribavirin was initiated for the kidney recipient on day 26 (loading dose of 30 mg per kilogram every six hours for four days then 8 mg per kilogram every eight hours); unfortunately by this time all of the other recipients of organs from the female donor had already died without confirmation of the aetiological agent and without receiving targeted treatment. After the patient's clinical condition had stabilised 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 post-transplant, the patient had stable graft function and was able to resume full immunosuppressive therapy [270].

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 male who died of cerebral haemorrhage 10 days after returning to Australia from a three-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 three recipients, all of whom developed febrile illness with varying degrees of encephalopathy and proceeding to death within four to six 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, serum, liver and kidney of one of the kidney recipients, and from the cerebrospinal fluid and serum of the liver recipient. High-throughput sequencing of amplified RNA samples and examination of Vero E6 cells inoculated with homogenised fresh-frozen kidney tissue revealed the presence of an arenavirus with an identical but previously uncharacterised genetic sequence in the recipients.

The case above highlights the challenges of identifying central nervous system infections particularly in donors dying from CVA and the potential for rare and uncharacterised infectious agents to be transmitted by organ transplantation. To aid decision-making in this context, the United States Organ Procurement and Transplantation Network 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 3.16.

Table 3.16: Questions for consideration when completing screening procedures for potential organ donors[268]

Question
What is the potential donor's age and cause of brain death? Were there any comorbidities that may support stroke/CVA diagnosis (i.e. diabetes, hypertension, prior CVA) versus 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. While 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 (e.g. 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 haemorrhage; 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 (i.e. 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 West Nile Virus activity would be at greater risk for West Nile Virus 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 (e.g. tuberculosis or extended outdoor exposure that may increase risk for vector borne illness – like West Nile Virus, Lyme Disease, rabies etc).

4. BACTERIAL INFECTIONS IN THE DECEASED DONOR

4.1. *Mycobacterium tuberculosis*

4.1.1. Epidemiology

The number of tuberculosis notifications in Australia in 2016 was 1217 (5.1 per 100,000 population, NNDSS 2016 dataset). 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 versus 0.7 notifications per 100,000 in 2013 respectively) [272]. NSW and Victoria account for more than 50% of all tuberculosis cases in Australia, while the Northern Territory has the highest jurisdiction-specific notification rate (17.1 per 100,000 in 2013). Tuberculosis incidence in Aboriginal and Torres Strait Islander peoples was 4.6 cases per 100,000 in 2013 [272].

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 [272]. Of those diagnosed within four 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 – ABS 34120DO001_201415) would account for the bimodal distribution of tuberculosis notifications seen in Figure 13.

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 [272].

Table 4.1 Notified tuberculosis cases in 2013 by country of birth and residency status [272].

Country of birth	Residency status			Total cases (n)	Estimated resident population[a]	Estimated rate per 100,000	WHO incidence rate, per 100,000[b]
	International students (n)	Permanent Residents (n)	Other (n)				
India	31	101	87	219	337,120	65	176
Vietnam	6	92	12	110	207,620	53	147
Philippines	8	80	20	108	193,030	56	265
China[c]	16	43	15	74	387,420	19	73
Nepal	21	20	16	57	27,810	205	163
Indonesia	14	21	21	56	73,060	77	185
Afghanistan	0	13	29	42	32,970	127	189
Myanmar	1	20	18	39	24,430	160	377
Papua New Guinea	3	16	16	35	30,650	114	348
Pakistan	5	6	19	30	34,150	88	231
Sri Lanka	0	19	6	25	99,740	25	66
Cambodia	1	18	3	22	32,510	68	411
Sudan	0	14	6	20	22,000	91	114
Thailand	3	10	5	18	52,990	34	119
Rep. Korea (South)	4	8	4	16	85,930	19	108
Somalia	0	11	5	16	6,590	243	286
Other overseas born	17	144	58	219	-	-	-
Total overseas-born	130	636	340	1,106	-	-	-
Australia-born	-	-	-	156	-	-	-
Total	-	-	-	1,263	-	-	-

[a]Population data sourced from the Australian Bureau of Statistics estimated resident population, June 30, 2011.
[b]Rates for countries of birth, taken from World Health Organization TB Burden Estimates in 2012.
[c]Excludes Taiwan and Special Administrative Regions.

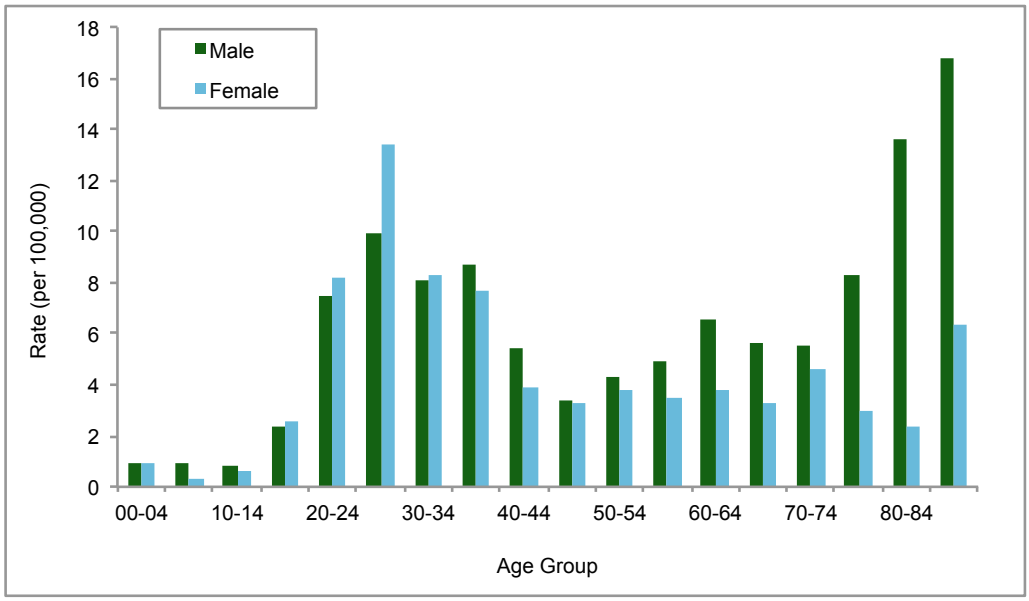


Figure 13: Notification rate of tuberculosis in Australia in 2016, by age group and sex (Data: NNDSS)

Australia has had very few cases of multi-drug 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) [272]. Zero cases of extensively drug-resistant tuberculosis were reported in 2013 – only two cases of XDR-TB have been reported since 1995 [272, 273]. Figure 14 shows trends in the proportion of tuberculosis cases that were multi-drug resistant since 1995. The spike in 2010 is accounted for by ten patients with MDR-TB from Papua New Guinea accessing health care services in the outer Torres Strait Protected Zone [273].

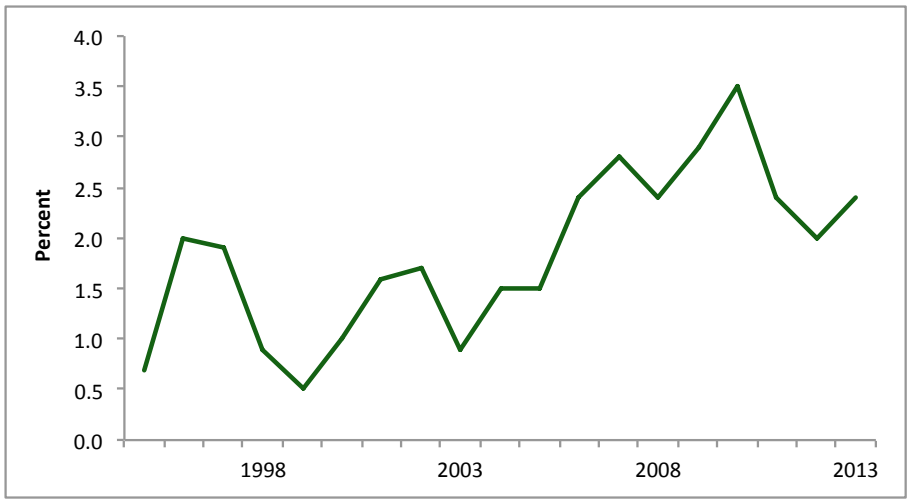


Figure 14: Percentage of tuberculosis cases with drug resistance testing indicating multi-drug resistance [272, 273]. (Toms C. CDI, 2015;39:E217 and Lumb R. CDI, 2014;38(4):E369)

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 [274]. Tuberculosis most commonly appears in the transplanted population due to reactivation of latent infection – an audit at Westmead Hospital Sydney estimated 30% of waitlisted patients had latent tuberculosis (personal communication: A Webster) – but it may also be acquired as a *de novo* infection post-transplant, 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 <5% of these cases [275]. 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, BMI<18.5, diabetes mellitus, and/or cigarette smoking [276].

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 of 14 versus 0 days) and more often required invasive procedures [277]. This study also found that rates of tuberculosis-related mortality were higher among transplant recipients than the general population (18% versus 6%), as were rates of toxicity associated with anti-tuberculosis treatment (38% versus 10%) [277]. 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 [276]. Pulmonary disease accounts for approximately 60% of cases in the Australian general population, with 40% being extrapulmonary [272]. By comparison, extrapulmonary disease accounts for closer to half of tuberculosis cases in the transplant population, and disseminated tuberculosis is substantially more common [277, 278]. 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.

4.1.2. Donor Screening and risk minimisation

In living donors it is possible to perform tuberculosis screening in accordance with recommended guidelines, however in potential deceased donors this is problematic as there are no proven methods for screening deceased donors for tuberculosis. Chest X-ray and direct microscopy of bronchoalveolar lavage for acid-fast bacilli have a low sensitivity, and cultures may take up to eight weeks to turn positive [276]. Tuberculin skin testing is also impractical in the context of deceased donation given a turn-around 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 [276].

Interferon-Gamma Release Assays (IGRAs) might theoretically be useful given their shorter turn-around 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 [276]. IGRAs 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, 276]. Further, false positive results will be common in low-risk populations, while 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 [276].

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

Table 4.2 Summary consensus recommendations of the Donor-Derived Infections Consensus Conference on *Mycobacterium tuberculosis* – recommendations relating to deceased donors [276]

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 my 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 prior to 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) prior to donation.
5. Molecular methods from mycobacterial culture and species identification are preferred to standard culture if available, due to the shorter turn-around time.
6. There is insufficient evidence to recommend 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 utilize 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 prior to 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.

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 [276]. A summary of the recommendations of this group is provided in Table 4.2.

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 six months of anti-tuberculosis treatment. However, organs can be considered for transplant if a recipient has received a six-month course of chemotherapy, unless the isolate is found to be resistant to appropriate antituberculosis drugs. If there is a past 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 six months may be considered, with prophylaxis and/or empiric treatment considered for the recipient in accordance with international guidelines [5].

4.1.3. Transmission

Numerous cases of unexpected tuberculosis transmission from donors to recipients have been reported in the literature (see Table 4.3). 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* [279-281]. For example, in a case of multi-drug 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 [279]. 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 [280, 282, 283].

Table 4.3 summarises the tuberculosis risk factors present in donors who subsequently transmitted *M. tuberculosis* to one 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 emphasise the importance of donor 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 five years prior to death, which had been treated with nine months of preventive isoniazid therapy despite the index case demonstrating *M. tuberculosis* resistance to isoniazid [16].

A retrospective Spanish study of deceased donors utilized 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 two cases (transmission rate of 18.2%) [274]. 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 out of 29 (52%) 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 [284, 285]. 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) [284]. The most common presenting symptoms among reported cases were fever and dyspnoea, 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) [284]. Of the identified cases of donor-derived tuberculosis in lung transplant recipients, three out of 15 (20%) were fatal. Another lung recipient died from causes unrelated to tuberculosis [284].

In recipients of non-lung 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 4.3). Of the reported cases of donor-derived tuberculosis in kidney transplant recipients, three out of 11 (27%) were fatal, with one additional death from unrelated causes.

Table 4.3: Case reports of unexpected donor-derived tuberculosis transmission in solid organ transplantation (deceased donors).

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
Kidney	Weile 2013 [286]	2011	Severely reduced health and hygiene status, alcoholism, pneumonia	<1 month	None	5	No	Yes[b]	Not reported
	Weile 2013 [286]	2011	As above	<1 month	None	17	No	No	No
	Edathodu 2010 [282]	2009	Immigrant from Indonesia with CNS infection of unknown cause	2	Fever	12	No	No	Not reported
	Edathodu 2010 [282]	2009	As above	<1	Fever	1	No	Yes (week 3)	Yes
	CDC 2008 [278]	2007	Alcoholism, homelessness, incarceration, pneumonia	1.5		2	No	Yes (week 9)	No
	CDC 2008 [278]	2007	As above	1.5		12	No	No	No
	Malone 2007 [283]	2003	Immigrant from the Philippines	29	Nausea, deteriorating renal function	48	No	No	No
	Mourad 1985 [287]	1982	None	4	Fever, asthenia, disorientation	26 (?)	No	No	No
	Mourad 1985 [287]	1982	As above	7	Fever, cough, headache	26 (?)	No	No	No
	Peters 1984 [288]	1981	Active disseminated TB that was confirmed three weeks after transplantation	1	Deteriorating renal function	5	No	Yes (week 22)	Yes
	Peters 1984 [288]	1981	As above	1	Not reported	12(?)	No	No	Yes
Liver	Edathodu 2010 [282]	2009	Immigrant from Indonesia with CNS infection of unknown cause	3	Fever	9	No	No	Not reported
	Coll 2013 [274]	Between 1998-2011	Parents from a highly endemic country	2	Not reported	17	No	No	Not reported
Heart	Weile 2013 [286]	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[b]	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[a]	Cough	9	Yes	No	No
	Kumar 2013 [285]	2012	Immigrant from Vietnam	3	Cough	Not reported	No	No	Not reported
	Coll 2013 [274]	Between 1998-2011	Immigrant from a highly endemic country	<1	Not reported	14	No	No	Not reported
	Mortensen 2014 [284]	2008	Recent immigrant from Mexico, incarceration	6	Fever, dyspnoea	10	No	Yes[b]	Yes
	Mortensen 2014 [284]	2008	Proximity to TB outbreak, incarceration	2	None (detected during scheduled BAL specimen collection)	3	No	No	No
	Mortensen 2014 [284]	2009	Recent prior residence in the Philippines	4	None (detected during scheduled BAL specimen collection)	7	No	No	Yes
	Boedefeld 2008 [289]	2008	Immigrant from Peru	3	Sepsis	3	No	Yes	Yes
	Winthrop 2004 [281]	2002	Recent arrival in the U.S. from Guatemala	<1	None (detected during scheduled BAL specimen collection)	31	No	No	No
	Wong 2008 [290]	2002	None	<12	Not reported	Not reported	No	No	Yes
	Lee 2003 [279]	1999	Recent arrival in Hong Kong from China	3[a]	Malaise	36	Yes	No	No
	Shitrit 2004 [291]	1999	Close family contact with TB	2.5[a]	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 [280]	1993	None	1.5	Fever	Not reported	No	No	No
	Carlsen 1990 [294]	1990	Not reported	5	Dyspnoea	6	No	Yes (week 31)	Yes
Pancreas	No reports								

[a] 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

[b] Death was from causes unrelated to *M. tuberculosis* infection

4.1.4. Recipient management and outcomes

Table 4.4 summarises the 2012 recommendations of the Donor-Derived Infections Consensus Conference on *Mycobacterium tuberculosis* with regards to clinical management of solid organ transplant recipients under different deceased donor scenarios. In summary, potential donors with a past history of tuberculosis may be considered on a case-by-case basis only if they have received active treatment for at least six 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 [276]. 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 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 (i.e. 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 post-transplant by more than half (RR 0.35, 95% CI 0.14-0.89) [295]. 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 three 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 judgement [276]. Notably, the tuberculin skin test and IGRAs have poor sensitivity in immunosuppressed persons following solid-organ transplantation, and in any case are not recommended tests in the diagnosis of active tuberculosis.

Table 4.4: Recommendations for clinical management of recipients under different scenarios of tuberculosis risk – deceased donors [276]

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 caviation 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 (i.e. pulmonary tuberculosis in a kidney donor)	Treated appropriately over two 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 two 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 (i.e. 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 non-standard 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 recognised pre-transplant		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 pre-transplant		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 interferon gamma release assay, biopsy of affected organ can be taken for pathologic examination and NAT during organ procurement. Decision regarding recipient treatment versus chemoprophylaxis will depend on final outcome of donor cultures.
Positive acid-fast bacilli stain, NAT or tuberculosis culture, only known post-transplant		High	Treat recipient for active tuberculosis, and report test results to the organ procurement organisation immediately; consult with an ID specialist
Findings consistent with tuberculosis but no cultures available, data only known post-transplant		High	Favour treating recipient for active tuberculosis. Pursue molecular testing where possible, consult with an infectious disease specialist

4.2. Multi-drug resistant bacteria

4.2.1. Epidemiology

In cases where bacterial infections are transferred from donor to recipient, these cases frequently involve resistant bacteria – in particular methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus (*VRE) and multi-drug-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 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 anti-microbial 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 [296]. There was wide variation between institutions in the proportion of *S. aureus* that was MRSA, from 7% to 56% [296]. 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 [296].

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* bacteraemia isolates in Australia that are antimicrobial resistant, reporting that 18.8% of *S. aureus* bacteraemia cases were MRSA – a high relatively high proportion compared to several European countries [297].

Enterococcus

Enterococci are among the leading causes of bacteraemia, and are intrinsically resistant to a broad range of antimicrobials. Moreover, their ability to acquire resistance through plasmid transfer and transposons have 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 [298].

AGAR commenced the Australian Enterococcal Sepsis Outcome Programme (AESOP) in 2011 for the surveillance of *Enterococcus faecalis* and *Enterococcus faecium* bacteraemia and to monitor evolving patterns of antimicrobial susceptibility. Of the enterococcal bacteraemia cases identified by AESOP in 2014, 54.9% of isolates were *E. faecalis* and 39.9% were *E. faecium.* Of the *E. faecalis* bacteraemia cases, 36.5% were hospital-acquired, however of the *E. faecium* cases, 71.8% were hospital-acquired [298]. 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 non-susceptible to multiple antimicrobials, including ampicillin (90%), erythromycin (95%), tetracycline (53%), ciprofloxacin (92%), nitrofurantoin (77%), and high-level gentamicin (62%), and 46.1% were non-susceptible to vancomycin [298]. 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 bacteraemia in Australia, the proportion of *E. faecium* that is resistant to vancomycin is high by international standards [298]. Vancomycin resistance is usually acquired through the acquisition of either the *vanA* or *vanB* operon. The first vancomycin resistant *E. faecium* (VRE) case detected in Australasia occurred in 1994 in a liver transplant patient at Austin Health in Melbourne [299].

Although this first case was a *vanA*-positive *E. faecium*, the majority of VRE subsequently detected between 1994 and 2011 was *vanB* [299, 300]. In late 2013, however, a shift from *vanB* to *vanA E. faecium* occurred across Australia [300]. 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 [301]. In certain centres dramatic shifts occurred, with *vanA* almost entirely replacing *vanB* between 2013 and 2014 [300]. 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 [301]. Of 1729 patients admitted over the study period, 5.3% were colonised 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* [301]. The emergence of *vanA* VRE in Australian hospitals will likely lead to a larger overall burden of VRE in Australia and New Zealand [301]. Recently, the rapid dissemination of novel clone of *vanB* VRE (ST796) was also reported, first recognised 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 [299].

Drug resistant Gram-negative bacilli

AGAR has been monitoring sepsis due to *Escherichia 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%) [302]. Moderate levels of resistance were found in *E. coli* isolates towards cefazolin (21%) and trimethoprim (29%). Multi-resistance is on the rise, particularly in *E. coli* and *E. cloacae* isolates, with multi-resistance 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 pneumonia 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 nine institutions across five Australian states and territories were found to have a carbapenemase gene. Thus, carbapenem resistance attributable to acquired carbapenemases currently remain uncommon in Australia, although five difference gene variants were detected in 2014 (IMP, KPC, VIM, NDM, and OXA-181-like) [302].

Compared to 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 [303, 304].

4.2.2. Transmission and recipient outcomes

With the rise of multi-drug resistant bacteria in hospital environments, an increasing number of potential donors are being exposed to multi-drug resistant bacteria in the ICU, which may then be transmitted to recipients by organ transplantation. Of particular concern are VRE, multi-resistant *Pseudomonas aeruginosa*, ESBL-producing enterobacteriaceae, carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumonia* and other carbapenem-resistant enterobacteriaceae [5]. Lanini et al 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%) [305]. 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 [306]. 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 [305].

Donor-related risk factors for infection or colonization by multi-drug resistant bacteria include prolonged hospital stay (7 days or longer), vasopressor use, and requirement for cardiopulmonary resuscitation or abdominal packing [307, 308]. However the absence of these risk factors does not preclude nosocomial infection/colonization with multi-drug resistant bacteria, as was demonstrated in a case of carbapenem-

resistant *Acinetobacter baumannii* transmission from a donor with a hospital stay of only two days [309]. In addition, donor country of origin/prior residence is also a potential risk factor: donors from countries with high rates of gut colonisation of multi-drug-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 post-transplant to be infected or colonized with carbapenem-resistant gram-negative bacteria, with proven transmission to the organ recipient in 13% (4 out of 30) of affected transplants [310]. 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 bacteraemic and the donor organ was culture-positive. The first two transmission cases involved a donor who died of cerebrovascular accident after four 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 *Klebsiella pneumonia*. Liver, lungs, and pancreas were donated to four recipients. The recipient of an extended right graft of the donor liver received pre-emptive treatment with meropenem alone for three days, starting on day four post-transplant. On day seven, samples from abdominal drainage fluid were sent for microbiological testing and cultures were positive for carbapenem-resistant *Klebsiella pneumoniae*. The patient was treated with colistin and tigecycline, and the infection was resolved by day 37 post-transplant. The lung recipient was commenced on meropenem alone on day two post-transplant; on day ten, cultures from bronchoalveolar lavage grew carbapenem-resistant *Klebsiella 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 *Klebsiella pneumonia* initially in the lung and later in the rectum [310].

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 *Klebsiella pneumonia* after organ retrieval and transplantation. The kidney recipient, who received a full, targeted antibiotic treatment regimen (gentamicin and meropenem for eight days), remained negative for carbapenem-resistant *Klebsiella pneumonia*; however the liver recipient, who received only three days of full antibiotic treatment (gentamicin and meropenem), developed leucocytosis, pleural effusion and an intra-abdominal collection on day 12 post-transplant [310]. On day 24, the liver recipient developed fever and infection of the abdominal wound; cultures from the wound swabs grew carbapenem-resistant *Klebsiella pneumonia*. 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 *Klebsiella pneumonia*. After complete drainage and antibiotic treatment, the infection was resolved and the patient was alive and well 18 months post-transplant.

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 haemorrhage. Known to be a rectal carrier of carbapenem-resistant *Klebsiella pneumonia,* urine cultures turned positive two days after retrieval, however this information was not properly communicated [310]. One recipient received both kidneys, and on post-transplant day 15 he was readmitted to hospital due to high-grade fever which was confirmed to be due to carbapenem-resistant *Klebsiella pneumonia* 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 two months later due to persistent carbapenem-resistant *Klebsiella pneumonia* infection of the graft [310].

In a case reported from Israel, a donor who was an asymptomatic carrier of carbapenem-resistant *Klebsiella pneumoniae* in the respiratory tract donated kidneys, liver, and lungs to five recipients [311]. The donor had been admitted to hospital in a deep coma after a near drowning. After five days on mechanical ventilation he was declared brain dead. Routine bronchoalveolar lavage taken at the time of organ donation grew carbapenem-resistant *Klebsiella pneumoniae* two days after transplantation had taken place, with antibiotic sensitivity limited to gentamicin, colistin and tigecycline. The recipient of the liver and the two kidney recipients did not receive post-operative antibiotic treatment and none developed infectious complications. The two lung recipients both received perioperative antibiotic prophylaxis with piperacillin-tazobactam, and following the donor culture results both received intravenous colistin for five days. One of the lung recipients developed pneumonia two weeks after transplantation; *Proteus mirabilis* was cultured from sputum samples, and following treatment with intravenous 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 post-transplant, the patient developed tachypnoea and dyspnoea, 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 *Klebsiella pneumonia,* with antibiotic sensitivity profile the same as the donor. Treatment was unsuccessful and the patient died four weeks later.

In a 2007 case of carbapenem-resistant *Acinetobacter baumannii* transmission from a donor to a lung recipient in Brazil, the donor had been in the hospital for only two days prior to procurement, with partial pressure of oxygen/fraction of inspired oxygen >300, normal chest xray, and no evidence of bronchial aspiration by bronchoscopy [309]. Perioperative antimicrobial prophylaxis consisted of vancomycin plus cefepime. On day two post-transplant, 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 bronchoalveolar lavage 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 nine post-transplant, carbapenem-resistant *Acinetobacter baumannii* was isolated from the recipient's bronchoalveolar lavage and from the surgical wound specimen, and intravenous polymyxin B was substituted for meropenem, and tacrolimus dosage was reduced. By day 29 post-transplant, the patient's serum creatinine had risen to 2.1mg/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 cytomegalovirus 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 post-transplant.

Donor-derived transmission of other multidrug-resistant bacteria

Deceased donors who have undergone traumatic injury requiring abdominal packing to control major haemorrhage are at particularly high risk of nosocomial infection with bacterial or fungal pathogens, including multi-drug resistant bacteria. In a case report published in 2012, a 21 year-old male with a gunshot wound to his abdomen underwent damage control laparotomy and abdominal packing, but subsequently deteriorated and was declared brain-dead three days after admission [308]. He donated organs to four separate recipients; all four of whom subsequently developed infections with MDR *Pseudomonas aeruginosa*. The donor had received piperacillin-tazobactam and fluconazole prior to 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 prior to 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 were positive for gram-negative rods. The relevant transplant centres were contacted, and imipenem or meropenem were added to the regimens of the recipients. On the fourth day following transplantation, the pathogen isolated from the donor was confirmed to be MDR *P. aeruginosa*, with resistance to extended spectrum penicillins, ceftazidime, fluoroquinolones and tobramycin [308].

The heart recipient was hospitalized for dyspnoea approximately six weeks-post-transplant, 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 intravenous meropenem for two 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 eight post-transplant, 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 post-transplant. The recipient of the first kidney developed purulent drainage at the incision site approximately two weeks post-transplant, 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 was discovered asystolic and resuscitation was not successful. A post-mortem 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 intravenous 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 six days later developed bilateral pneumonia with cultures showing presence of *P.*

aeruginosa [312]. 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 two 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 one week post-transplant, and both recipients died within two weeks of transplantation from massive haemorrhage as a result of arterial anastomotic rupture [312].

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 [313]. The donor had developed pulmonary infiltrates and prior to procurement a bronchoscopy was performed. Cultures from the bronchoalveolar lavage 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* three 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 six weeks of polymyxin B and amikacin, consistent with the drug susceptibility profile of the isolated bacteria, and one 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 wash-out effect of prophylactic antibiotics and ineffective antibiotic coverage, leaving the potential donor susceptible to infection with multi-drug resistant bacteria [308]. 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 [312]. Negative cultures prior to organ retrieval and the absence of physical evidence of infection do not rule out the presence of pathogens capable of transmitting infection: in the two 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 [314, 315]. Temporary VAC closure for example may be associated with lower risk of infection than intra-abdominal packing with lap sponges or towel clip closure [314, 316].

Methicillin-resistant *Staphylococcus aureus* (MRSA) 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 two days of progressive confusion and somnolence [317]. 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 haemorrhage, 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 four recipients. The kidney and pancreas recipients received five doses of vancomycin prophylaxis post-transplant 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 three 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 post-transplant, 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 six days post-transplant revealed MRSA growth. Despite continued appropriate antibiotic therapy, MRSA continued to be detected on bronchoalveolar lavage cultures until 99 days post-transplant. Six months post-transplant, the patient was readmitted due to dyspnoea on exertion and a chest CT suggested extensive right-sided multifocal consolidation. Bronchoalveolar lavage cultures revealed MRSA, and vancomycin therapy was resumed for another four weeks, after which time symptoms resolved.

European guidelines recommend that organs from donors returning positive cultures for multi-drug 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 colonised [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/faecal screening with results made available prior to transplantation should be considered where not already performed. If MDR bacteria are identified prior to transplantation, the risks are highest for the bacteraemic 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.

Table 4.5: Treatment recommendations for multidrug-resistant gram-negative bacteria infections in solid organ transplant recipients [318].

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

*ceftolozane-tazobactam has become an option since this article was published

4.2.3. Recipient management

Directed antimicrobial prophylaxis in recipients has been shown to be effective in preventing transmission of multi-drug resistant gram-negative pathogens [311, 319]. In a case report from the United States, Ariza-Heredia et al. describe the use of organs from a donor known to be infected with carbapenem-resistant *K. pneumoniae* prior to organ procurement. The donor was a 21-year-old male who sustained multiple injuries in a motor vehicle accident and was hospitalised 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. pneumonia*, although blood cultures remained negative. The donor was treated with intravenous 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. pneumonia* 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 pre-transplant doses of intravenous gentamicin (4mg/kg) and tigecycline (100mg), and post transplant received a 10-day course of intravenous tigecycline (50mg every 12 hours). Surveillance cultures of the preservation fluid were negative, and five months post transplant the recipient was doing well. The heart recipient received perioperative intravenous cefepime (2g every 12 hours) and tigecycline (100mg loading does then 50mg twice daily). Antimicrobial prophylaxis received post-transplant 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 post-operative infected hematoma and peritonitis due to carbapenem-resistant *K. pneumoniae*, despite receiving prophylaxis with intravenous tigecycline (initial loading dose of 100mg, followed by 50mg every 12 hours planned for 2

weeks) [319]. On post-transplant day 10, the patient developed severe abdominal pain, tenderness and leucocytosis, and cultures of the ascetic fluid were positive for carbapenem-resistant *K. pneumoniae.* The patient underwent exploratory laparotomy and washout, and intravenous 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 (1g IV every 8 hours), amikacin (500mg IV q 12 hourly), ampicillin (1g IV every 6 hours) and fluconazole (200mg p.o. daily) for four weeks. Five months post-transplantation the recipient showed no recurrence of infection

Source control is the first priority in the treatment of multi-drug 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 multi-drug resistant colonizers in the recipient [318]. Treatment recommendations for multidrug-resistant gram-negative bacteria infections in solid organ transplant recipients are given in Table 4.5.

4.3. *Treponema pallidum*

4.3.1. 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 Aboriginal and Torres Strait Islander 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. In contrast, only 54% of infectious syphilis notifications in Aboriginal and Torres Strait Islanders 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 Aboriginal and Torres Strait Islander people living in northern Australia [37, 320]. 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 [320]. An outbreak in the western, Eyre and far north regions of South Australia was declared in March 2017 [320]. By 2016, the infectious syphilis notification rate in the Aboriginal and Torres Strait Islander 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 Aboriginal and Torres Strait Islander people - in 2016, 21% of infectious syphilis notifications in the Aboriginal and Torres Strait Islander population were in the 15-19 year age group, compared to only 2% of the non-Indigenous population [37].

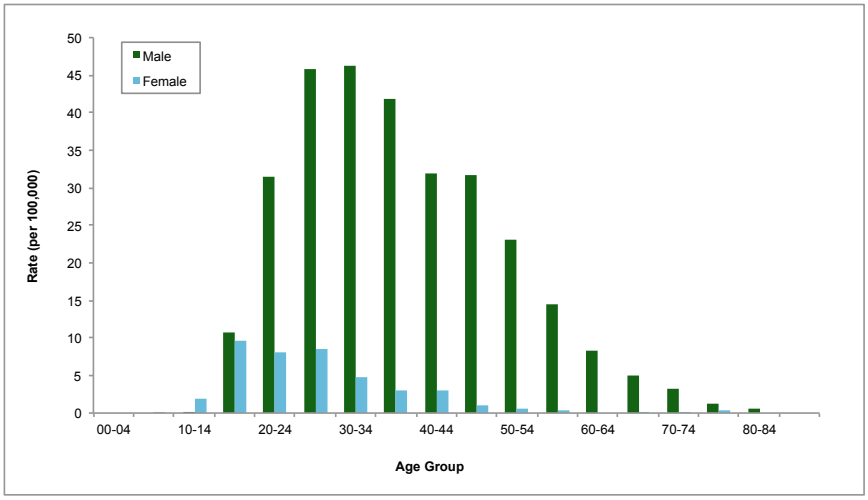


Figure 15: Age and sex distribution of the syphilis notification rate (syphilis of <2 years duration), in Australia in 2016 (Source: NNDSS).

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) [321]. As in Australia, the vast majority of cases (>90%) are in males, 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%) [321]. Cases are concentrated among males aged 20 to 34, with the biggest increase in cases since 2011 occurring among males aged 20-24 years. The Auckland region reported the highest number of infectious syphilis notifications in 2014 (61% of the total) [321].

4.3.2. Donor Screening and risk minimisation

Historically, syphilis screening has been based on non-treponemal serological tests- either the rapid plasma reagin (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 (e.g. 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 [322]. The United States Centers for Disease Control specify that a diagnosis of syphilis requires positive results on both a non-treponemal test and a treponemal-specific test [323]. Treponemal-specific tests include fluorescent treponemal antibody absorbed (FTA-ABS) tests, the T. pallidum passive particle agglutination (TP-PA) assay, various enzyme immunoassays (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 4.6.

The conventional approach to screening has been to test first with a non-treponemal 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 non-treponemal 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 enzyme immunoassay, with confirmation by a non-treponemal serological test. If the non-treponemal 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 [323]. 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, as 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.

Table 4.6: 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%

4.3.3. Transmission risk and recipient management

Only four cases of syphilis transmission via organ donation have been reported – one confirmed transmission reported to the United States Organ Procurement and Transplantation Network, and three reports in the published literature [1, 324, 325]. In a 2003 case, a homosexual male with a past history of treated syphilis donated kidneys to two recipients [324]. Donor syphilis serology, available only after transplantation had taken place, was reactive on TP-PA (titre 1:1280) and RPR (titre 1:2), which was interpreted as consistent with a history of treated infection. The two recipients were informed and were administered a single dose of 2.4g

intravenous benzyl penicillin instead of the recommended benzathine penicillin 2.4 MU administered intramuscularly. Recipient serum samples collected on day five post-transplant were reactive on treponemal enzyme immunoassay, and both recipients were then treated for early latent syphilis according to 2002 UK guidelines. After two years of follow up, both recipients had excellent kidney function, and three-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 [325]. Results of donor syphilis serology became available 24 hours after the transplant had taken place, and showed reactivity in the treponemal enzyme immunoassay 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 100mg twice a day was introduced for 28 days. There was evidence of recipient seroconversion for syphilis at one month post-transplant, however syphilis treatment was successful and the patient was well with stable graft function at nine months post-transplant [325].

The forth reported case of donor-derived syphilis transmission was in a lung transplant recipient whose donor, a 38-year-old woman who died of sub-arachnoid bleeding, returned serology test results indicating past syphilis infection one day after transplantation had occurred [326]. The recipient received penicillin G intravenously three times per day for 10 days, starting on day one post-transplant. Although immunoblot testing detected *T.pallidum*-specific newly synthesized IgG antibodies on day 29 post-transplant, the patient developed no clinical signs of syphilis infection, and by three months post-transplant the T pallidum hemagglutination titre 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 four cases of organ transplantation involving a syphilis-positive donor that did not result in transmission to the recipient after appropriate therapy [327-330]. 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 [323]. In the most recent of these cases, the enzyme immunoassay results showing that the donor was seropositive for syphilis were available only after transplantation had occurred [330]. 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 three weeks, and repeated serology at regular intervals post-transplant showed the recipient remained free of syphilis infection at three months post-transplant.

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 bacteraemic 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 (personal communication P Boan).

4.4. Bacteraemia and meningitis

There is substantial evidence that organs from bacteraemic 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 pre- and post-transplantation [5, 331]. However, it is not uncommon for bacteraemia in the donor to be unrecognised until after transplantation has occurred: in one study, 60% of bacteraemic donors were afebrile in the 24 hours prior to organ procurement [332].

A retrospective study of organ donors in Spain found that 5% of liver and heart donors had bacteraemia at the time of organ donation (including recognised and unrecognised infections) [332]. The most common microorganisms isolated from donors with bacteraemia 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 bacteraemic 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 (e.g. *E. coli*) pose a greater risk than gram-positive bacteria [333]. Given the high rates of graft loss, morbidity and mortality

associated with transmission of bactaeremia – especially in the case of infection caused by gram-negative bacilli – susceptibility testing in the donor is important [334].

Numerous other studies have demonstrated that transplant outcomes in recipients of organs from bacteraemic donors are equivalent to outcomes from non-bacteraemic 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 (e.g. improved white cell blood count, improved hemodynamics, defervescence), and tailored antibiotic treatment is initiated in the recipient in a timely manner [49, 331, 334]. Recipients should be treated with tailored antibiotic therapy for at least seven days post-transplant, or longer if the organism is difficult to treat (e.g. *S. aureus*) or if there is the potential for infection to disrupt an anastomosis or seed an endovascular source [331]. Based on existing evidence, no particular organ from a bacteraemic donor is more likely to transmit infection to the recipient than another [334].

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* [335-339]. 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 prior to transplantation [335]. Prior to 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 following only 24 hours of antibiotic therapy where blood cultures were negative on the day of donation [336]. Tailored antibiotic therapy in the recipient is recommended for at least seven days post-transplant [335, 340].

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, 341]. Similarly, meningitis caused by disseminated *M. tuberculosis* infection may be transmitted to the recipient with fatal consequences, and is a contraindication to transplantation [288]. 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 – e.g. *Staphylococcus aureus*, *P. aeruginosa*, *Salmonella* sp. – are contraindications to organ donation [342]. Lastly, the time course of infection is relevant: persistent bacteraemia caused by any organism increases the risk of metastatic infection, and in such cases organ transplantation may carry a higher risk of disease transmission [342].

European guidelines recommend that, in general, organs from donors with bacteraemia 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. Utilisation 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 prior to 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 non-reactive culture but where the bacteria are confirmed by PCR as the pathogen causing the meningitis, it can be assumed that after 48 h of antibiotic treatment, infection will not be transmitted [5].

UK guidelines state that where an organ donor has been diagnosed with bacteraemia in the five 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 who no organism is cultured should not be utilised.

Summarising these international guidelines, organs from bacteraemic donors may be utilised 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, while caution is advised where the pathogen has not been confirmed.

4.5. Pulmonary infections

Bacterial colonisation 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]. Prior to 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 bacteraemia, all other organs can be used safely. Following 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 prior to 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 [343].

A recent significant discovery has been the role of disseminated *Ureaplasma* infection in hyperammonemia syndrome after lung transplantation [344, 345]. 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 [346]. 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% [346]. A smaller retrospective cohort study of 145 lung transplant recipients found an incidence of hyperammonemia syndrome of 4% [347].

Hyperammonemia syndrome was first described in 1991 in a recipient of a bone marrow transplant [348]. The cause of the syndrome remained unknown, however, until 2015 when Bharat et al. published preliminary evidence that the syndrome may be caused by donor-derived infection with *Ureaplasma* species [345]. *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. While 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 [345].

In their initial study, Bharat et al. performed microbiologic examination (PCR, specialized culture, and molecular resistance profiling) of specimens taken from six lung transplant recipients who developed hyperammonemia syndrome post-transplantation. They found evidence of systemic infection with *U. urealyticum* or *U. parvum* in all six cases, but they found no evidence of infection in 20 control lung transplant recipients with normal ammonia concentrations [345].

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 [344]. *Ureaplasma* is able to colonise the oral cavity, with possible routes of transmission including sexual transmission from the genitourinary tract of a partner [349]. 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 [344].

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 six patients. At this time, routine donor testing for *Ureaplasma* is not suggested.

4.6. 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.

Prior to organ retrieval, the donor should be treated with antibiotics for 24-48 hours or until there is documented resolution of the infection [49]. The final decision about organ utilisation should be made at the

time of organ recovery [5]. Post-transplant 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 non-kidney organ from a deceased donor with nonbacteraemic, localised infection that does not involve the transplanted organ (excluding meningitis cases) [49].

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

5. FUNGAL, PARASITIC, AND OTHER INFECTIONS

5.1. *Toxoplasma gondii*

5.1.1. Epidemiology

Toxoplasma gondii is a protozoan (coccidian) parasite of mammals, which reproduces in cat species but has a wide intermediate host range [350]. It is one of the most common parasitic infections of humans and other warm-blooded animals [350]. Exposure is extremely common in all regions of the world, although there is substantial geographical variation in rates of *T. gondii* (see Table 5.1). It is estimated that 16-40% 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% [351]. A study of pregnant women in Australia found 35% had IgG antibodies to *T. gondii* [352]. Transmission can occur due to:

- Ingestion of undercooked meat containing *Toxoplasma* cysts;
- Ingestion of contaminated soil (e.g. via unwashed fruit or vegetables) containing cat faeces;
- Ingestion of cat faeces via cleaning a cat's litter box, gardening, contact with sandpits etc;
- Transplacental transfer from mother to foetus.

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 faeces [350]. 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 (e.g. a preference for raw or undercooked meat) [351]. When ingested, bradyzoites from tissue cysts or sporozoites from faecal 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 [350]. 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) [350]. 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.

Table 5.1: Median rate of acquired *Toxoplasma gondii* per 100,000 population by WHO region with 95% confidence intervals, 2010 [353].

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)

5.1.2. Donor Screening and risk minimisation

Organs which contain tissue cysts infected with *T. gondii* carry the risk of primary infection in a naïve and immunosuppressed recipient. Hearts are at higher risk of containing T. gondii cysts compared to other organs, and serological tests for toxoplasma are usually included among standard screening tests for heart donors in most jurisdictions [5, 354]. While 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 following recovery. NAT can be used to diagnose active infection [355, 356]; 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 (i.e. where there is clinical suspicion of acute toxoplasmosis).

5.1.3. Transmission

T. 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, 357-361]. Cases of toxoplasmosis following bowel and pancreas transplantation have also been reported [361, 362]. Presenting symptoms typically are non-specific, including fever, respiratory distress, neurological manifestations, and bone marrow suppression [361]. Cerebral toxoplasmosis, although a well-known complication in HIV patients, is extremely rare in transplant recipients [362]. 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 15-25 days post-transplant – than for reactivation of latent infection [19, 358, 360, 361, 363]. Primary toxoplasmosis is also significantly more lethal: a review of published cases of primary toxoplasmosis following 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 post transplant [363].

Mortality from toxoplasmosis post-transplantation is highest in those patients with disseminated disease, or where there is a delay in diagnosis and targeted treatment [360]. In one such case of fatal disseminated toxoplasmosis after liver transplantation from a seropositive donor to a seronegative recipient, the recipient developed symptoms 12 days post-transplant and was initially treated for methicillin-resistant *staphylococcus aureus* and then for CMV after this was detected on bronchoalveolar lavage performed on day 26 post-transplant [364]. 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 five 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 nine month post-transplant: all of these recipients were seropositive for toxoplasmosis prior to transplantation [364].

In a similar case of a fatal outcome following delayed diagnosis and treatment, a ten-year-old recipient of a small bowel transplant developed fever, bilateral frontotemporal headaches, abdominal pain, vomiting and diarrhoea three months post-transplant [361]. 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 hospitalisation 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 oedema for the lungs and patchy recent haemorrhages, and microscopic examination demonstrated small numbers of encysted *T. gondii* organisms [361]. Fatal cases of toxoplasmosis following delayed diagnosis and treatment have also been reported in heart and multi-visceral transplantation [362, 365].

Two cases of *T. gondii* transmission have been reported in Australia following kidney transplantation from a common donor [19]. Both of the Australian cases died five 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 post-transplant, and a MAG3 scan showed a lower pole infarct. He deteriorated on day 29, becoming agitated and tachypnoeic, 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 post-transplant 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 female 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 – since *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 centre where these cases occurred introduced trimethoprim-sulfamethoxazole prophylaxis for six months post-transplant as standard practice [19].

5.1.4. 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 vascularised composite allografts where muscle tissue is involved [5, 41, 354]. Trimethoprim-sulfamethoxazole is additionally effective against *Listeria monocytogenes*, *Nocardia asteroids*, and *P. jeroveci*. Trimethoprim-sulfamethoxazole prophylaxis for at least 3 months post-transplant (but usually 6 months or longer, depending on the organ) is currently standard international practice for recipients at risk of *T. gondii* transmission [366].

Serological tests have poor sensitivity for toxoplasma antibodies in immunosuppressed patients, therefore in patients with a clinical suspicion of primary toxoplasmosis post-transplant, NAT is the best diagnostic strategy [363, 364]. 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 [366].

Combination therapy with oral sulfadiazine and pyrimethamine or intravenous 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 [350].

5.2. Malaria

5.2.1. Epidemiology

There were 266 notifications of malaria in Australia in 2016, compared to 373 in the 2013/2014 season (June-July), and compared to an average annual number of cases of 434 over the five years from 2008/9 to 2012/13 [255]. This is consistent with a significant decline in malaria notifications overall in Australia since 2004-5, 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. Malaria notifications by country/region of acquisition are shown in Table 3.15. 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 following importation. There was one case of malaria acquired on Saibai Island in 2013, and seven locally acquired cases in the Torres Strait in 2011 [255].

The number and rate of malaria notifications in 2016 was highest in the 35-39 year age group (23 cases, 2.9 per 100,000 population), and the majority of cases (64%) were in males. Figure 16 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 20-39 year age group [367]. By comparison there were 26 malaria notifications in 2016, and 38 in 2015 [367]. All cases were acquired overseas, most commonly in sub-Saharan Africa countries, followed by India, then Papua New Guinea, Solomon Islands and Vanuatu [39].

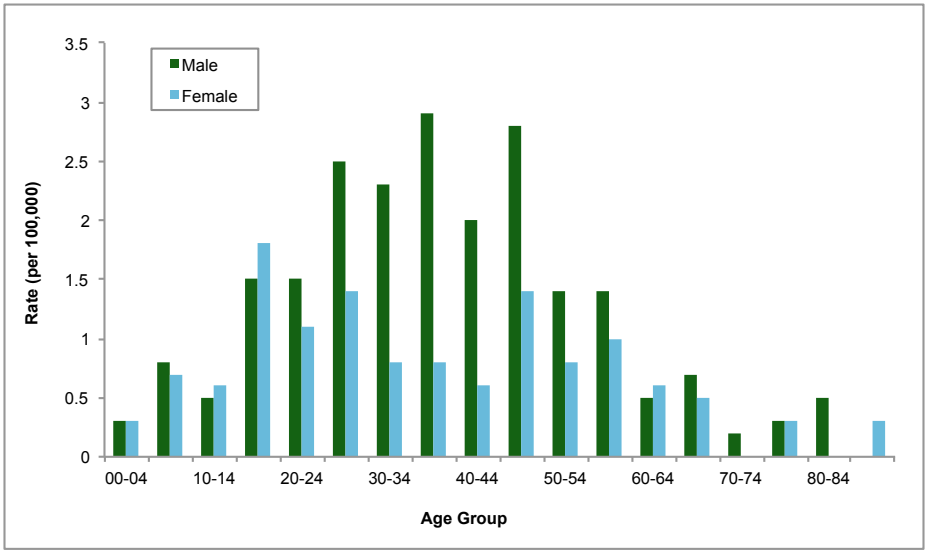


Figure 16: Notification rate of malaria in Australia in 2016, by age group at sex (NNDSS data)

5.2.2. 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 four of the main plasmodia species that infect humans – *P. ovale, P. vivax, P. malariae,* and *P. falciparum* - have been described in solid organ transplantation [354].

U.S. guidelines recommend donor testing for malaria with thick and thin blood smears if the donor is epidemiologically at high risk for infection [354]. This includes donors who have spent time in malarious regions within the previous three 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 in a malarious area for more than six months at any time of life, a validated anti-malarial 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 parasitaemia 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.

As 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.

5.2.3. Transmission

Although malaria is a rarely reported complication of organ transplantation outside of non-endemic 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) [368-374]. 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 [366].

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 [366]. Additional hypotheses for why kidney recipients fare better include longer cold ischaemia 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 prior to retrieval [368]. Donor-derived malaria is particularly fatal to liver recipients, as parasitized hepatocytes are transplanted with the allograft, resulting in high-level parasitaemia; moreover, anti-malarial therapy can be hepatotoxic, contributing to graft failure [366]. For example, in a case of fatal *P. falciparum* transmission from a donor to a liver recipient, the recipient became febrile day 20 post-transplant and blood films revealed high-level parasitaemia [371]. Quinine therapy resolved the fever and parasitaemia, however the recipient died on day 51 post-transplant. The donor in this case was an 8-year-old child from the Ivory Coast who had arrived in France two months before death. Retrospective examination of donor sera, liver and spleen samples showed high antibody titres against *P. falciparum*, malarial pigment in both organs, macrophage reactions in the spleen and a suspected intraerthrocytic trophozoite in the liver [371].

Demonstrating the different outcomes of malaria infection for kidney versus heart and liver recipients, Chiche et al. describe the outcomes for four recipients of organs from a donor who was retrospectively confirmed to be infected with *P. falciparum* [368]. Eight days post-transplantation, 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 parasitaemia. The patient was treated with 25 mg/kg/day of quinine, however an alteration of neurological status occurred and they went into a deep coma within three days. Vibramycin was added to quinine, but immunosuppressive therapy was not altered. There was an improvement in status five days after starting quinine and parasitaemia disappeared, but there was a corresponding elevation of liver function tests. Liver enzymes began to improve one month later, and after three months the patient had recovered. The heart recipient developed fever and neurological disorders on day five post-transplant, 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 post-transplant. The two recipients of the donor's kidneys showed no signs of infection when diagnosis was made in the liver and heart recipients. Prophylactic anti-malarial chemotherapy was given and both patients remained in good health [368].

P. vivax infection tends to be less severe than *P. falciparum* infection [366]. In a case of *P. vivax* transmission from a donor originally from Zaire to two Swiss kidney recipients, both recipients recovered quickly following treatment [369]. The donor had been in good health prior to death from an intracerebral haemorrahge two 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 two kidney recipients became febrile on days nine and 16 post-transplant respectively, with *P. vivax* detected on day 25. Both recipients received chloroquine treatment for three days and subsequent smears were negative [369]. In a case of *P. vivax* transmission by liver transplantation, parasitaemia was successfully cleared following anti-malarial treatment, however the patient died several months later from graft failure as a result of hepatotoxicity from chloroquine and primaquine therapy [370]. 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 sublicinical malarial infection on the basis of a positive titer for *P. vivax* 12 months after transplantation, and again at 22 and 25 months post-transplant, though without symptoms of infection. The liver recipient developed a high-grade fever on day 28 post-transplant, at which point *P. vivax* were found in a Giemsa-stained thin smear taken for blood count. The patient was treated with eight days of oral chloroquine, followed by 14 days of oral primaquine, which resolved the fever within four days although a slow rise of bilirubin and liver enzymes was noted in parallel with anti-malaria therapy. Elevation of liver function tests was progressive, and liver biopsies showed increasing centrolobular toxic parenchymal cell damage and persisting malaria pigment deposits. Following progressive cholestasis, the patient died of liver failure six months post-transplant [370]. The kidney recipient who developed malaria infection was treated with a one 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.

5.2.4. 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 [354]. Quinine can interact with cyclosporine metabolism, lowering cyclosporine blood levels [375].

Treatment of malaria requires the identification of the specific plasmodium species and knowledge of the geographical distribution of sensitivity patterns [354]. 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 [354]. Quinine and mefloquine, however, significantly interact with calcineurin inhibitors [366]. Severe cases of *P. falciparum* should be treated with intravenous 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) [354]. *P. vivax* resistant to chloroquine has been observed in Oceania [354].

5.3. *Strongyloides stercoralis*

5.3.1. 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 (e.g. farmers and miners) in parts of the United States, Europe, United Kingdom, and Australia [376, 377]. A study of Vietnam veterans resident in South Australia found *Strongyloides* seropositivity of 11.6% in this cohort [378]. 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 [379]. 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 [380, 381]. Additional risk factors for *Strongyloides* infection include individual-level low socioeconomic status, institutionalization, and alcoholism [366].

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 under five years of age [382]. 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 [383].

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 [384]. 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 [384]. 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, dyspnoea) several days later, then gastrointestinal symptoms (abdominal pain, diarrhoea, constipation, nausea and vomiting, and anorexia) approximately 2+ weeks after infection as larvae migrate to the gastrointestinal tract [384]. 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 [384, 385]. In solid organ transplant recipients, *Strongyloides* infection may initially present with vague gastrointestinal symptoms. Hyperinfection symptoms include pyrexia, gastrointestinal pain, bloody diarrhoea, ileus, anorexia, nausea, vomiting, sore throat, difficulty swallowing, dyspnoea, pneumonitis with bilateral infiltrates, and – in rare cases – intestinal or pulmonary obstruction [366, 384]. 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 [384]. 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 [366]. The defining characteristic of hyperinfection is a huge increase in the numbers of larvae in the stool or sputum. Disseminated infection occurs when the lavae migrate to organs outside of those normally involved in the pulmonary autoinfective cycle (gastrointestinal tract, peritoneum, lungs) [384]. Organs affected in reported

cases of disseminated *Strongyloides* infection include mesenteric lymph nodes, gallbladder, liver, heart, pancreas, skeletal muscle, kidneys, ovaries, and brain [384]. 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 [384]. Gram-negative sepsis is also life-threatening – moreover it may obscure the underlying diagnosis of strongyloidiasis [386]. Hyperinfection is fatal in approximately 50% of cases; the mortality rate in disseminated strongyloidiasis is up to 80% [384].

Glucocorticoids, at any dosage, are directly associated with the transformation of chronic strongyloidiasis to hyperinfection [384, 387]. The majority of cases of *Stongyloides* hyperinfection in organ transplant recipients appear to have been precipitated by increased glucocorticoid doses in response to rejection [384, 388]. Donor preconditioning with high-dose steroids may also reactivate *Stongyloides* in the latently infected donor, causing disseminated disease that may then be transmitted by solid organ transplantation [389].

Infection with HTLV-1 is associated with increased prevalence of *S. stercoralis* infection, and with a greater likelihood of hyperinfection syndrome [390, 391].

5.3.2. Donor Screening and risk minimization

U.S. 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 post-transplant [392]. 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 [384]. Eosinophilia is a common marker of helminth infections, and thus donors with unexplained eosinophilia or with gastrointestinal symptoms should also be evaluated for *Strongyloides* [354, 386].

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 [386]. Stool testing has poor sensitivity as larvae are excreted intermittently and in small quantities; the sensitivity of a single specimen is only 15-30%, 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) [393]. While useful for detecting chronic/latent infections, serological testing is less sensitive in the detection of new infections (~85%) [366] Negative serology results should be interpreted with caution in the context of the potential donor's medical and social history [386].

The New York Organ Donor Network commenced targeting screening for *Stronglyoides* in 2010 [394]. From 2010 to 2013, of 1103 potential donors, 233 (21%) were identified as being at increased risk and were tested for *Stronglyoides* antibody prior to procurement. Of this number, 10 (4.3%) tested positive of which seven became organ donors, with organs transplanted into 18 recipients. Fourteen recipients received prophylaxis; none developed strongyloidiasis [394].

5.3.3. 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) [386, 388, 389, 394-399]. 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* [384]. 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 [396].

Table 5.2 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 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 out of 20

recipients was symptomatic, with the most common symptom being gastrointestinal complaints [394, 397]. 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 [394, 395, 399]. The median time to onset of symptoms for the cases reported in Table 5.2 is 49 days, compared to a median time to diagnosis of 69 days. Out of 18 recipients with donor-derived *Stronglyoides* infection there were three reported deaths: two from bacteremia/septicemia and one 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 [399]. 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 [395].

Table 5.2: Reported cases of donor-derived *Strongyloides* transmission (deceased donors)

Reference	Donor characteristics	Transplanted organs	Onset of symptoms (days post-transplant)	Symptoms	Diagnosis (days post-transplant)	Treatment	Hyper-infection	Concomitant infections	Cause of death (day post-transplant
Hoy, 1981 [399]	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), diarrhoea (day 42), epigastric burning, nausea, vomiting, left-sided pleuritic chest pain, acidosis, hypotension	66	Thiabendazole 25 mg/kg twice daily for five 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, diarrhoea, abdominal (day 64)	68	Thiabendazole 25 mg/kg twice daily for five days	No	CMV (primary), *K. pneumoniae*	Recovered
Hamilton, 2011 [389]	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), diarrhoea, nausea, vomiting, intense abdominal cramping (day 63)	70	Ivermectin 200 ug/kg once daily for five days, then alternate days for 25 days	Yes	-	Recovered
		Kidney	-	Severe epigastric pain, hematemesis	70	Ivermectin 200 ug/kg once daily for two days, then retreated weekly for five weeks	No	-	Recovered
		Liver	-	-	70	Ivermectin 200 ug/kg once daily for two days, albendazole 400 mg daily for seven days	No	-	Recovered
Abanyie, 2015 [394]	45-year-old male from Guyana who had immigrated to the United States; cause of death was subarachnoid haemorrhage[a]	Liver	90	Diffuse abdominal pain, nausea, nonbloody emesis (day 90), altered mental status, hypoxia (day 96)	101	Ivermectin 200 ug/kg once daily for 13 days, albendazole 400 mg twice daily for 12 days	No	*P. aeruginosa,* vancomycin-resistant *E. faecalis*	Recovered
Abanyie, 2015 [394]	49-year-old US-born homeless military veteran who died from a subdural hematoma, no know international travel	Kidney	-	Respiratory symptoms	-	Ivermectin for five days followed by albendazole for seven days	No	-	Recovered
		Kidney	-	Chest pain	-	Ivermectin 200 ug/kg once daily for two days, then twice weekly for two weeks	No	-	Recovered
Abanyie, 2015 [394]	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
Abanyie, 2015 [394]	58-year-old female born in Honduras, died of respiratory failure due to asthma exacerbation	Kidney	-	-	287	-	-	-	Recovered

Reference	Donor characteristics	Transplanted organs	Onset of symptoms (days post-transplant)	Symptoms	Diagnosis (days post-transplant)	Treatment	Hyper-infection	Concomitant infections	Cause of death (day post-transplant
Roseman, 2013 [400]	46-year-old male from Honduras who had emigrated to the US seven years before, died after being struck by a car	Kidney	60	Delirium, fever, nausea, vomiting diarrhoea (day 60), odynophagia, abdominal pain (day 67)	68	Vancomycin and oral ivermectin, switched to subcutaneous ivermectin 20 ug/kg divided into 6.5mg per upper extremity every other day for eight days. Albendazole given concomitantly for three days. Tacrolimus was changed to cyclosporine.	-	*S. aureus* and coagulase negative *Staphylococcus*	Recovered
		Kidney	30	Diarrhoea (day 30), abdominal pain	68	Oral ivermectin 200ug/kg daily for seven days, albendazole 400 mg twice daily for three days	No	CMV (primary)	Recovered
Le, 2014 [401]	24-year-old Puerto Rico-born man who died from multiple gunshot wounds[c]	Heart	48	Fatigue, sore throat, hemoptysis (day 48), respiratory distress, hypotention (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, non-puritic rash	66	Ivermectin, albendazole. Immunosuppression transitioned to cyclosporine	No	MDR *E. cloacae*	Recovered
		Kidney	72	Fever, vomiting, diarrhoea, diffuse petechial rash	72	Cefepime, ivermectin, albendazole. Immunosuppression transitioned to cyclosporine, MMF and prednisone discontinued	No	-	Recovered
Rodriguez-Hernandez, 2009 [397]	47-year-old male from Ecuador	Liver	75	Asthenia, anorexia, diarrhoea, malaise (day 75), vomiting (day 79), dyspnoea, cough, whitish expectoration, fever (day 80)	88	Albendazole 400mg b.i.d. for 14 days and ivermectin 200 ug/kg/day for seven days, then intermittent prophylaxis with ivermectin for >3 weeks	Yes	*K. pneumonia,* CMV	Recovered
Brügemann, 2010 [395]	Donor originally from Suriname[d]	Heart	42	Abdominal pain, anorexia, nausea, vomiting, rash	49	Ivermectin 200 ug/kg/day for 15 days, albendazol 400 mg twice daily for 10 days		CMV (primary), novel influenza A/H1N1	Recovered
Patel, 2008 [388]	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 ug/kg daily, thiabendazole 25mg/kg twice daily, ivermectin retention enemas 15mg daily	Yes	*E. facecium*, 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* post-transplant. 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 post-transplant and was not treated.
[c]A fourth recipient underwent liver transplantation but died on day four post-transplant. No evidence of *Strongyloides* was found on autopsy.
[d]The liver and one kidney were also donated. The liver failed one week post-transplant due to haemostatic problems; evaluation of the recipient, who received a second graft, four months after the original transplant showed evidence of Strongyloides infection. The recipient of the kidney died six months post-transplant due to sepsis with *E. coli*, which could have been a complication of *Strongyloides*, although antibodies against *Stronglyoides* were not detected.

5.3.4. 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 [384]. 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 [384, 402, 403]. A reduction in immunosuppression is necessary, and it is particularly important that steroids be tapered rapidly [386]. Broad-spectrum antibiotics may be indicated if bacteraemia, meningitis or pneumonitis are suspected [366]. 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 intravenous ivermectin (3 doses of 200 ug/kg, 48 hours apart and a follow-up dose one week later) was effective [404]. The patient recovered but relapsed a month later, at which point an additional two-week course of daily oral ivermectin was administered, after which all further stool samples were negative. Treatment is recommended to continue for at least two weeks after the parasite is no longer detectable in stool or sputum [389]. In patients with hyperinfection syndrome, ivermectin is the drug of choice, and longer treatment courses may be required.

5.4. Other fungal and parasitic infections

Trypanosoma cruzi

Chagas disease, caused by the parasite *Trypanosoma cruzi,* is endemic to Central and South America. Asymptomatic parasitaemia is more common than symptomatic disease in potential donors [354]. 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 parasitaemia may be detected by PCR or the Strout-Test, but these are generally not sufficiently sensitive for screening of organs and donors because parasitaemia 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 [392]. As *T. cruzi* has a predilection for muscle, heart and neurological cells, the utilisation 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 six 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 four weeks or more.

Prophylactic treatment (benznidazole) in D+/R- combinations has had some success [405]. 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 [406, 407]. Treatment (benznidazole, nifurtimox) should be initiated promptly upon recognition of parasitaemia. Adjustments to immunosuppression may also be warranted, and certain immunosuppressive therapies (e.g. thymoglobine or mycophenolate) may need to be substituted in recipients of organs from Chagas disease-positive donors [408].

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 [366]. *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 [409]. 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 [410]. Imported cases of leishmaniasis are becoming increasingly common in non-endemic locations including Australia, North America and Northern Europe as a consequence of increased international travel and international migration [411, 412].

In the general population, visceral leishmaniasis is usually subclinical and establishes lifelong latency, with only approximately 10-20% of affected persons developing clinically overt disease [413]. 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 [413]. Leishmaniasis is rarely reported in transplant recipients, but when it does occur it is most commonly the result of reactivation of pre-existing asymptomatic leishmaniasis in the recipient [413]. Cutaneous or mucocutaneous leishmaniasis are rarely reported in organ transplant recipients [354, 366]. 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 [413].

Donor-transmitted *Leishmania* has been reported twice [366, 413]. In one case, a Macedonian kidney recipient who had purchased the organ from an Indian vendor developed visceral leishmaniasis and died [414]. In a Swiss case from 1990, visceral leishmaniasis was detected in a liver transplant recipient one year post-transplant after the patient developed fever, pancytopenia, and persistent splenomegaly [415]. She was treated with pentavalent antimony for 42 days, though while 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 [415].

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 [366]. 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 anti-leishmanial treatment, visceral leishmaniasis is a fatal disease, with death caused by intercurrent infections or bleeding [413].

Direct examination of amatigotes on bone marrow and spleen aspiration is the gold standard for diagnosis of visceral leishmaniasis [413]. 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 [366]. 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% [413].

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 [413, 416]. Antimony compounds are also used. Miltefosine has also been shown to be highly effective, but is not currently approved for use in transplant recipients [366]. As relapse is relatively common, secondary prophylaxis with intermittent amphotericin or miltefosine may be warranted [354, 366].

Given the rarity of donor-derived infection, and the poor performance, limited availability and lengthy turn-around time of non-invasive 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 one in every 1000 kidney transplants, typically as a result of contamination of the preservation fluid prior to or at the time of organ procurement [417]. Rupture of an abdominal viscus is often the likely source of the contamination [418]. Transmission from donors with candidaemia 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 – e.g. mycotic aneurysm, anastomotic rupture –

may also occur. Fluconazole is the preferred drug for treatment or prevention of donor-derived candidiasis [417]. In the absence of clinical infection, empiric antifungal therapy can be discontinued after two weeks. For patients with clinical or microbiological evidence of infection, therapy should be extended for 4-6 weeks depending on the results of imaging, cultures and clinical data. If vascular complications are present, a minimum of six weeks of antifungal treatment is recommended [417].

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. Utilisation of kidneys from donors with untreated candidemia, however, is not recommended [417].

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 [417]. 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 two 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 [417].

Candidiasis in thoracic organ transplantation

Candida species frequently colonise the oropharynx and commonly appear in respiratory tract cultures. Antifungal prophylaxis for approximately three months is commonly administered in lung transplantation [419], 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 0.3-5% of transplant recipients [420], primarily as a result of reactivated infection, although rare cases of *de novo* donor-derived cryptococcosis infection have also been described [421-423]. 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 [417]. There has been at least one case of disseminated cryptococcosis transmitted by a donor with unrecognized meningoencephalitis [421].

Risk factors for cryptococcosis in the donor include the administration of corticosteroids, iatrogenic immunosuppressants, sarcoidosis, end-stage liver or kidney disease, and rheumatologic disorders [417]. 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 [417]. 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 life-saving 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 [417]. 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 6-12 months [417].

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 [424, 425]. The first case series involved a heavily immunosuppressed liver transplant recipient who died 15 days post-transplant from

intracerebral haemorrhage and then donated their kidneys and heart [425]. Three weeks after transplantation the two 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 one 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/d) and immunosuppression reduced. Fever persisted and the patient developed progressive respiratory distress. Transplant nephrectomy was performed three weeks later and amphotericin B treatment continued for another four weeks. At month 25 post-transplant the patient was alive and well on haemodialysis. The second kidney recipient was commenced on intravenous amphotericin B (0.7 mg/kg/d) when *A. fumigatus* was detected, but fever persisted and urine cultures remained positive for *A. fumigatus*, and transplant nephrectomy was performed two months post transplant. Amphotericin B treatment was continued to a cumulative dose of 2g. At month 25 post-transplant the patient was also alive and well on haemodialysis. The heart transplant recipient had an uneventful post-operative course, and a thorough investigation prompted by the clinical course of the kidney recipients showed no sign of aspergillosis. However, five months post-transpalntation, 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 [425].

The second case, reported by Mueller et al. in 2009, involved a recipient of a heart transplant who died of cerebellar haemorrhage five days post-transplantation and subsequently donated their kidneys, liver, lungs and islet cells [424]. 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 prior to her heart transplant, although repeated tests for fungi were consistently negative. The first kidney recipient was admitted to hospital on day 40 post-transplant with weakness, symptoms of urinary tract infection, 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 post-transplant, 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 non-function of the graft, unrelated to infection [424].

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% [426].

5.5. Transmissible Spongiform Encephalopathies

Transmissible Spongiform Encephalopathies (TSEs) 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 (sCJD) and acquired (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]. While 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].

CJD 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 six months for genetic cases (range: 1.3-192 months) [427]. Of sporadic, acquired, and genetic cases respectively, 72%, 56% and 51% were deceased six months after the onset of symptoms [427].

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 cerebrospinal fluid 14-3-3 protein detection, or alternatively via personal communications from clinicians, hospitals, families or CJD-related groups, and through health record searches [427]. 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 [427]. The current annual rate of CJD deaths in the general Australian population is 1.15 per million population [312]. 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 prior to 1986 [312]. Many of those affected would have received a "Medical in Confidence" letter from the Chief Medical Officer regarding this risk.

Table 5.3: Definition of high-risk category for CJD transmission [312]

Classification of CJD	Clinical signs and risk factors
1. Sporadic TSE 1.1 Definite: Neuropathologically/immunocytochemically confirmed 1.2 Probable: 1.2.1 Clinical sign I plus at least 2/4 of signs in groups II and III 1.2.2 Possible I plus positive 14-3-3 CSF assay 1.2.3 Possible I plus 2/4 of II and duration <2 years	Clinical signs: I Rapidly progressive dementia II Myoclonus Visual or cerebellar problems Pyramidal or extrapyramidal features Akinetic mutism III Typical EEG
2. Accidentally transmitted (iatrogenic) TSE 2.1 Definite: Definite TSE with a recognized health care acquired risk factor 2.2 Probable: 2.2.1 Progressive predominant cerebellar syndrome in human pituitary hormone recipients 2.2.2 Probable TSE with recognized health care associated risk factor	Recognised health care acquired risk factors: Treatment with human cadaver-derived pituitary growth hormone, human cadaver-derived pituitary gonadotrophin or human dura mater graft. Corneal graft in which the corneal donor has been classified as definitely or probably having a human prion disease. 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 3.1 Definite 1.1.1. Definite TSE and definite or probable TSE in first-degree relative 1.1.2. Definite TSE with a pathogenic PRNP mutation 3.2 Probable 1.2.1. Progressive neuropsychiatric disorder and definite or probable TSE in first-degree relative 1.2.2. Progressive neuropsychiatric disorder and pathogeneic PRNP mutation.	Prion protein gene (PRNP) mutations PRNP mutations associated with GSS neuropathological phenotype: P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T, 192bpi 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 PRNP mutations associated with FFI neuropathological phenotype: D178N-129M PRNP mutation associated with vascular PRP amyloid: Y145S PRNP mutations associated with proven but unclassified prion disease: H187R, 216 bpi.

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 following 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 cerebrospinal fluid, magnetic resonance imaging, or direct amplification of misfolded prion protein in the cerebrospinal fluid using Real-Time-Quaking Induced Conversion [312]. In the context of deceased organ donation, minimising 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 one 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 5.3). 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 5.4). 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 [312].

Table 5.4: Definition of low-risk category for CJD transmission [312]

People with a progressive neurological illness of less than one 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 one 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 (two 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) before1986.
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.

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 [312].

UK guidelines state that organ and tissue donation is contraindicated for individuals with confirmed or suspected TSE, with a neurological disease of unknown aetiology, or anyone who is blood relatives with persons with familial CJD. Exception is made if a donor has two or more blood relatives who have developed TSE but has been informed by a genetic counsellor 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 glad 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.

6. EMERGING PATHOGENS AND OTHER PATHOGENS OF SPECIAL INTEREST

6.1. Zika

6.1.1. 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 [428]. 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, 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 2013-2014, causing disease in approximately 11% of the population, that the first link was made between Guillain Barré syndrome and Zika virus infection [429]. 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 [428]. On February 1, 2016, the Director General of the World Health Organisation 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 Concern [428]. As of July 25, 2017, 48 countries and territories have had confirmed cases of local vector-borne transmission of Zika virus, and another five countries have reported cases of sexually transmitted Zika virus [430].

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) [431]. 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 [431]. 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 [431].

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 nine [260]. 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 [432].

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 four 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 retro-ocular 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 [433]. 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 (two liver recipients and two 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 four patients was 7.25 days (range 5-10) [433]. All patients presented with complications, in particular bacterial super-infection, 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 four patients had evidence of acute liver or kidney damage, and both kidney recipients needed to have their immunosuppression regimen altered [433]. 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 [434].

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 non-steroidal anti-inflammatory drugs should be avoided until dengue can be ruled out, to reduce the risk of haemorrhage. 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. While 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 one 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 [435]. However it is unclear how infectious the virus would be infectious if these organs were to be transplanted.

6.1.2. Donor Screening and Risk Minimisation

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, West Nile virus, and chikungunya, which co-circulate with Zika and have the same vectors [436, 437]. Existing antibody-based assays are therefore labour-intensive and generally confined to research laboratories/specialist public health facilities [436]. 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 [438-440]. However, false negative NAT results are common due to the short duration of viraemia 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 [441]. For this reason, the development of accurate commercial antibody tests for the diagnosis of Zika virus has been a priority [436]. 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 >10 days post-symptom onset [442].

According to the guidelines of the Communicable Diseases Network Australia (CDNA), a case of Zika virus infection is considered confirmed only where there is laboratory definitive evidence of infection [443]. 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 titre 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 cerebrospinal fluid, in the absence of IgM to other possible infecting flaviviruses.

Zika virus NAT may be performed on blood or urine (or amniotic fluid or cerebrospinal fluid): 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 [431, 444, 445].

Table 6.1: International guidelines on Zika virus and organ donation.

Guideline	Date last updated	Recommendation
Scanditransplant[a]	15 Feb 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 viraemic 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]	8 Feb 2016	OPOs should focus on recent travel history and epidemiologic risk factors, as well as recent donor symptoms. While 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 days 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 three viruses should be performed where appropriate.

[a]Guidelines for prevention of transmission of infectious diseases from organ donors to recipients. Scandiatransplant, 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

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 three weeks prior to 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 >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 two weeks (where symptoms are present) or two months (where symptoms are absent).

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

- Fever
- Headache
- Myalgia

- Arthralgia
- Rash
- Non-purulent conjunctivitis.

International guidelines do not recommend routine screening of potential organ donors for Zika virus, but instead generally recommend targeted Zika screening for [446]:

- 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 three months prior to the sexual contact.

A summary of published international recommendations regarding Zika virus and organ transplantation is given in Table 6.1.

Table 6.2: Generalised recommendations for prevention of donor-derived Zika virus transmission in solid organ transplantation, by nature of donor exposure. Adapted from Silveira and Campos [447].

Donor exposure	Recommendation
Deceased donors	
Asymptomatic donor with travel to area of Zika transmission in the preceding four 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 four 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 six 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 six 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 four weeks after return. If no symptoms develop in four 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 four weeks	Defer donation for four 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 six months after onset of symptoms. If recipient's clinical condition does not allow the delay in transplantation, obtain Zika virus PCR four 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.

6.2. West Nile virus

6.2.1. Epidemiology

West Nile virus (WNV) 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 USA, with the location of outbreak sites corresponding with major bird migratory routes [448]. 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 [448].

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 [449]. 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 [448]. WNV infection is asymptomatic or associated with only mild-flu-like symptoms in the vast majority of cases (>99%), however in some cases WNV causes severe neuroinvasive disease, including meningitis, encephalitis and acute flaccid paralysis [448]. Immunocompromised persons have a much higher risk (~50%) of developing severe disease, and a much higher risk of death as a result [449]. 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% [450].

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 West Nile virus 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 [451]. In rare cases, infection may progress to encephalitis. There were an average of 1.6 notifications of West Nile Virus or Kunjin virus infection per year in Australia for the past decade (see Figure 17). Some of these cases were acquired internationally in endemic countries (the three 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 [255, 452-456]. 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 viraemic, 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.

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 6.3). Of 23 recipients of solid organs from eight 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 diarrhoea [457]. With the exception of one 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 West Nile virus being transmitted by organ transplantation.

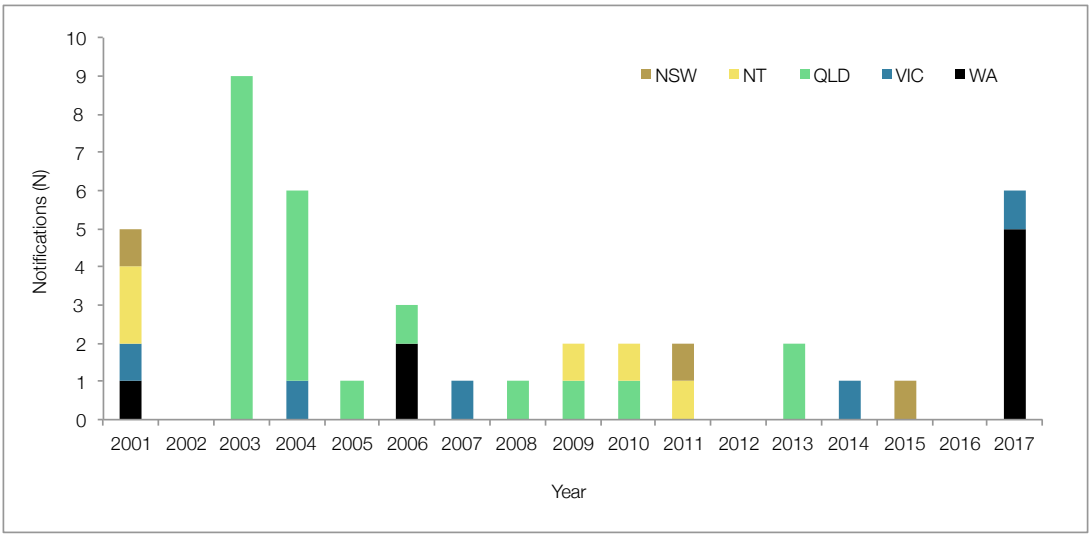


Figure 17: Number of notifications of West Nile/Kunjin virus infection received from Australian State and Territory health authorities from 2001 to 2017 [36].

Table 6.3: Donor and recipient characteristics in cases of donor-derived West Nile Virus transmission (deceased donors).

Ref	Organ	Donor			Recipient						Clinical course	Treatment	Immuno-suppression strategy	Outcome
		Serum results			Serum results			CSF results						
		PCR	IgM	IgG	PCR	IgM	IgG	PCR	IgM	IgG				
Winston, 2014 [457]	Kidney	-	+	+	+	.	.	+	-	.	Fever, myalgias, diarrhoea (day +10), lethargy, encephalopathy, tachypnoea, hypotension (day +13), left side weakness followed by coma (day +15), care withdrawn (day +23)	Polyvalent intravenous immunoglobulin (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 intravenous immunoglobulin (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	-	+	+	+	-	-	+	+	+	Dyspnoea, hypoxemia (day +13), encephalopathy, right upper-extremity weakness, respiratory distress (day +20), complete flaccid paralysis and multiple seizures, death (day +38)	Polyvalent intravenous immunoglobulin (500 mg/kg per day), subcutaneous interferon alfa-2b (6 mill units, then 3 mill units per day for three days, then 1 mill units per day for three days)	Reduced	Dead
	Liver	-	+	+	-	-	+	+	-	.	No clinical symptoms	Oral ribavirin (600 mg every 12 hours), polyvalent intravenous immunoglobulin (500 mg/kg daily for four days then every other day)	No change	Alive
Rabe, 2013 [458]	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, 2012 [459]	Kidney	-	+	+	+	+	+	+	+	+	Fever, myalgias, fatigue (day +11), tremulousness, confusion, dysarthria, mental deterioration, mechanical ventilation, coma	Fresh frozen plasma infusion containing WNV IgG (15/ml/kg/day)	.	Coma
Rhee, 2011 [460]	Liver	+	-	.	.	+	.	.	+	+	Fever (day +15), confusion, dysarthria, tremulousness, lower extremity paresis (day +3), improved mental status and motor strength (day +5)	Intravenous immune globulin (0.4g.kg)	Discontinued	Alive
Morelli, 2010 [461]	liver	+	.	.	+	.	.	.	.	.	No clinical symptoms	Fresh frozen plasma infusion containing WNV IgG	Reduced	Alive

Ref	Organ	Donor			Recipient						Clinical course	Treatment	Immuno-suppression strategy	Outcome
		Serum results			Serum results			CSF results						
		PCR	IgM	IgG	PCR	IgM	IgG	PCR	IgM	IgG				
CDC, 2009 [462]	Heart	-	(+)[a]	-	.	.	.	.	+	.	Tonic-clonic seizures requiring intubation (day +8), fever, mental deterioration	.	.	Alive
CDC, 2005 [463]	Kidney	-	+	+	+	-	+	.	.	.	No clinical symptoms	Prophylaxis with intravenous immune globulin	.	Alive
	Kidney	-	+	+	-	-	-	.	.	.	No clinical symptoms	Prophylaxis with intravenous immune globulin	.	Alive
	Liver	-	+	+	.	+	.	+	+	-	Fever, altered mental status (day +13), respiratory distress (day +18), coma, acute flaccid paralysis	High doses of intravenous immune globulin with high antibody titres against WNV	.	Coma
	Lung	-	+	+	.	+	+	-	+	+	Fever, dyspnoea (day +16), altered mental status, seizures, acute flaccid paralysis, coma	High doses of intravenous immune globulin with high antibody titres against WNV	.	Coma
Nanni Costa, 2011 [464]	Kidney	-	+	+	+	+	+	+	+	+	Fever, encephalitis	High titre West Nile intravenous immunoglobulin	.	.
	Kidney	-	+	+	+	+	+	+	+	+	Fever, encephalitis	None	.	.
Iwamoto, 2003 [465]	Kidney	+	-	.	.	+	.	.	+	+	Fever, rash, upper respiratory tract symptoms, backache, diarrhoea (day +12), decline in mental status, became unresponsive requiring mechanical ventilation (day +16), condition improved	.	.	Alive
	Kidney	+	-	.	+[b]	-	.	.	-	-	Fever, headache, myalgia, arthralgia, diarrhoea (day +17), mental deterioration, became unresponsive requiring mechanical ventilation (day +20), brain stem herniation (day +26)	.	.	Dead
	Heart	+	-	.	+	+	.	.	+	+	Fever (day +9), confusion, diarrhoea, incontinence, leg weakness (day +10), dysarthria, tremors (day +13), requiring mechanical ventilation (day+18), symptoms improved	.	.	Alive
	Liver	+	-	.	.	+	.	.	.	.	Fever (day +6), diarrhoea, 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; on of the donor's serum subsequently tested positive of WNV IgM.
[b]Quantitative PCR performed on brain tissue obtained at autopsy.

6.2.2. Donor screening and risk minimisation

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

- IgG antibody sero-conversion (or significant increase in antibody titers) in two serial specimens collected at one 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 cerebrospinal fluid and serum samples taken from WNV-infected patients who present with clinical symptoms [448]. Serum WNV IgG is produced ~3-4 days after IgM, and the presence of serum IgG confers lifelong protection against reinfection [466].

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 viraemia is transient, WNV-NAT may be negative even during the acute phase of infection [450]. 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 [457]. 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 [467]. 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, as 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 [449]. 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 [457]. 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 viraemic for WNV, European guidelines state that a transplant infectious disease expert should be consulted before such organs are utilized.

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. (see Table 6.3). 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 three post-transplant, 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 post-transplant day 45, without having developed clinical symptoms of WNV [461].

In those OPOs in the United States that test for WNV, testing is generally performed during seasons when WNV is predicted to be active in the donor service area [468]. Modelling 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 [392, 469]. The use of WNV serology or urine testing for donor screening is not recommended in the United States at this time [392]. 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 [449].

There is no effective therapy for WNV and treatment is largely supportive. Case reports of WNV in transplant recipients have described clinical improvement with intravenous immunoglobulin +/- interferon-alpha 2b (see Table 6.3). There is some evidence that early versus late administration of intravenous immunoglobulin may

improve the outcome [466]. 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 non-endemic areas where natural immunity is unlikely [449, 466].

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.

7. RECIPIENT CONSENT

It is a legal requirement in Australia and New Zealand to inform potential organ recipients of all risks associated with acceptance or non-acceptance 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 prior to an organ offer being made [44, 470]:

- 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 prior to 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 [471]. 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 [471].

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 maximise the utilisation 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 [472]. 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 to routine transplant education [472]. Although it was hypothesised 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 [472].

The Victorian and Tasmanian Renal Transplant Advisory Committee (VTRTAC) 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, which explain which donors are considered increased viral risk donors, what the risks are of catching a blood borne viral infection from an increased-risk donor, and what treatment is available in the event of disease transmission. The current VTRTAC patient information and consent form for accepting a kidney from an increased viral risk donor is given in Appendix 8.3. 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 utilisation of HCV-viraemic donors. The availability of DAAs for HCV and the use of organs from HCV-viraemic donors for HCV-non-viraemic 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, as this practice is new, there are minimal data on which to base informed consent. The potential concerns related to transplanting HCV-viraemic organs into non-viraemic 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 [473]? 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].

References

1. Ison, M.G. and M.A. Nalesnik. An update on donor-derived disease transmission in organ transplantation. Am J Transplant, 2011. 11(6): p. 1123-30.
2. Stewart, D.E., et al. Trends and Patterns in Reporting of Patient Safety Situations in Transplantation. Am J Transplant, 2015. 15(12): p. 3123-33.
3. Green, M., et al. Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee. Transplantation, 2015. 99(2): p. 282-7.
4. Garzoni, C. and M.G. Ison. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. Transplantation, 2011. 92(12): p. 1297-300.
5. European Directorate for the Quality of Medicines & Health Care: Guide to the quality and safety of organs for transplantation, 6th Edition. 2016: Strasbourg.
6. SOHO V&S Guidance for Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells. Vigilance and Surveillance of Substances of Human Origins, EU Public Health Programme. European Commission. 2013.
7. Ison, M.G., P. Grossi, and A.S.T Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 22-30.
8. Nanni Costa, A., et al. Quality and safety in the Italian donor evaluation process. Transplantation, 2008. 85(8 Suppl): p. S52-6.
9. Volk, M.L., et al. The "PHS Increased Risk" Label Is Associated With Nonutilization of Hundreds of Organs per Year. Transplantation, 2017. 101(7): p. 1666-1669.
10. Pruett, T.L., M.A. Clark, and S.E. Taranto. Deceased Organ Donors and PHS Risk Identification: Impact on Organ Usage and Outcomes. Transplantation, 2017. 101(7): p. 1670-1678.
11. White, S.L. Nudging the Organ Discard Problem. Transplantation, 2017. 101(7): p. 1518-1519.
12. Kahneman, D. and A. Tversky. Prospect Theory - Analysis of Decision under Risk. Econometrica, 1979. 47(2): p. 263-291.
13. Kucirka, L.M., et al. Landscape of Deceased Donors Labeled Increased Risk for Disease Transmission Under New Guidelines. Am J Transplant, 2015. 15(12): p. 3215-23.
14. Le Page, A.K., et al. Influenza B virus transmission in recipients of kidney and lung transplants from an infected donor. Transplantation, 2010. 90(1): p. 99-102.
15. Pilmore, H., et al. Fatal human herpesvirus-6 infection after renal transplantation. Transplantation, 2009. 88(6): p. 762-5.
16. Jensen, T.O., et al. Donor-derived tuberculosis (TB): isoniazid-resistant TB transmitted from a lung transplant donor with inadequately treated latent infection. Transpl Infect Dis, 2016. 18(5): p. 782-784.
17. Palacios, G., et al. A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med, 2008. 358(10): p. 991-8.
18. Macesic, N., et al. Herpes simplex virus-2 transmission following solid organ transplantation: Donor-derived infection and transplantation from prior organ recipients. Transpl Infect Dis, 2017.
19. Rogers, N.M., et al. Transmission of toxoplasmosis in two renal allograft recipients receiving an organ from the same donor. Transpl Infect Dis, 2008. 10(1): p. 71-4.
20. Drug overdose deaths hit record numbers in 2014. 2015 ; Available from: http://www.cdc.gov/media/releases/2015/p1218-drug-overdose.html (accessed January 2018).
21. Goldberg, D.S., et al. Improving Organ Utilization to Help Overcome the Tragedies of the Opioid Epidemic. Am J Transplant, 2016. 16(10): p. 2836-2841.
22. World Drug Report 2016 (United Nations publication, Sales No. E.16.XI.7). 2018; Available from: http://www.unodc.org/wdr2016/ (accessed 31 January 2018).
23. Stafford, J. and C. Breen. Australian Drug Trends 2016. Findings from the Illicit Drug Reporting System (IDRS). Australian Drug Trend Series. No. 163. National Drug and Alcohol Research Centre, University of New South Wales: Sydney, 2017.
24. Stafford, J. and L. Burns. Australian Drug Trends 2014. Findings from the Illicit Drug Reporting System (IDRS). Australian Drug Trend Series. No. 127. National Drug and Alcohol Research Centre, University of New South Wales: Sydney, 2015.

25. Darke, S., S. Kaye, and J. Duflou. Rates, characteristics and circumstances of methamphetamine-related death in Australia: a national 7-year study. Addiction, 2017. 112(12): p. 2191-2201.

26. AIDSinfo Indicators; Available from: http://aidsinfo.unaids.org/ (accessed February 2018).

27. Australian Vigilance and Surveillance Framework for Organ Donation For Transplantation, Version 1.0. Australian Government Organ and Tissue Authority. 2016: Canberra.

28. Vigilance and Surveillance of Substances of Human Origin Project (SOHOV&S): Vigilance Guidance Documents. Available from: http://www.notifylibrary.org/content/vigilance-and-surveillance-substances-human-origin-project-sohovs (accessed 30 January 2018).

29. Guidance on the microbiological safety of human organs, tissues and cells used in transplantation. 2011, Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), Department of Health: London, United Kingdom.

30. ODT Structure & Standards: Governance and Quality. Available from: http://www.odt.nhs.uk/odt-structures-and-standards/governance-and-quality/ (accessed 15 February 2018).

31. Ison, M.G., et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant, 2009. 9(8): p. 1929-35.

32. Policy 15: Identification of Transmissible Diseases, in Organ Procurement and Transplant Network (OPTN) Policies. 2017, Health Resources and Services Administration, U.S. Department of Health & Human Services.

33. Wolfe, C., et al. Donor Derived Transmission Events in 2015-2016: Analysis of the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC). Am J Transplant, 2017. 17(suppl 3).

34. NOTIFY: Exploring Vigilance Notification For Organs, Tissues and Cells. World Health Organization and Centro Nazionale Trapianti. Bologna, 2011.

35. Ljungman, P., Snydman, D.R., Boeckh, M (eds). Transplant Infections. Fourth Edition edition. Springer International Publishing, 2016. DOI 10.1007/978-3-319-28797-3_10

36. Notifications of a selected disease by State and Territory and year. National Notifiable Disease Surveillance System, Australian Government Department of Health. Available from: http://www9.health.gov.au/cda/source/rpt_4_sel.cfm (accessed February 2018).

37. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2017. Kirby Institute, UNSW: Sydney, Australia, 2017.

38. Notifiable Disease. New Zealand Public Health Observatory. Available from: http://www.nzpho.org.nz/NotifiableDisease.aspx (accessed February 2018).

39. Notifiable Diseases in New Zealand: Annual Report 2016. The Institute of Environmental Science and Research Ltd. Porirua, 2017.

40. Communicable Disease Control Manual 2012. New Zealand Government Ministry of Health: Wellington, 2012.

41. Fishman, J.A., M.A. Greenwald, and P.A. Grossi. Transmission of infection with human allografts: essential considerations in donor screening. Clin Infect Dis, 2012. 55(5): p. 720-7.

42. Uniform donor risk assessment interview form (donor >12 yrs old): Implementation guidance document. Eye Bank Association of America, American Association of Tissue Banks, Association of Organ Procurement Organizations, 2014.

43. Owen, S.M. Testing for acute HIV infection: implications for treatment as prevention. Curr Opin HIV AIDS, 2012. 7(2): p. 125-30.

44. Humar, A., et al. Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? A consensus conference report. Am J Transplant, 2010. 10(4): p. 889-99.

45. Policy 2: Deceased Donor Organ Procurement, in Organ Procurement and Transplant Network (OPTN) Policies. Health Resources and Services Administration, U.S. Department of Health & Human Services, 2017.

46. Levitsky, J., et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. Am J Transplant, 2017.

47. Goldberg, D.S., et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. N Engl J Med, 2017. 376(24): p. 2394-2395.

48. Kotton, C.N., et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation, 2013. 96(4): p. 333-60.

49. Fischer, S.A., K. Lu, and A.S.T. Infectious Diseases Community of Practice. Screening of donor and recipient in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 9-21.

50. Turbett, S.E. and E.S. Rosenberg. Chapter 5 - Diagnostic testing: general principles, in Transplant Infections, L. P, Editor. Springer International Publishing: Switzerland, 2016.

51. Theodoropoulos, N., et al. Improving syphilis screening in deceased organ donors. Transplantation, 2015. 99(2): p. 438-43.

52. Seem, D.L., et al. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep, 2013. 128(4): p. 247-343.

53. Ahn, J. and S.M. Cohen. Transmission of human immunodeficiency virus and hepatitis C virus through liver transplantation. Liver Transpl, 2008. 14(11): p. 1603-8.

54. Ison, M.G., et al. Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. Am J Transplant, 2011. 11(6): p. 1218-25.

55. Magiorkinis, E., et al. Renal transplantation from hepatitis B surface antigen (HBsAg)-positive donors to HBsAg-negative recipients: a case of post-transplant fulminant hepatitis associated with an extensively mutated hepatitis B virus strain and review of the current literature. Transpl Infect Dis, 2013. 15(4): p. 393-9.

56. Molina Rueda, M.J., E. Jimenez Romano, and M.A. Fernandez Sierra. De novo hepatitis B due to vaccine-escape mutants in a liver transplant recipient. Gastroenterology and Hepatology, 2013. 36(8): p. 546-7.

57. Tillmann, H.L. Lamivudine-resistant hepatitis B virus infection post-liver transplantation from a hepatitis B core antibody donor. Am J Transplant, 2006. 6(8): p. 1980; author reply p. 1981.

58. Bellandi, T., et al. Unintended transplantation of three organs from an HIV-positive donor: report of the analysis of an adverse event in a regional health care service in Italy. Transplant Proc, 2010. 42(6): p. 2187-9.

59. Clinical Guidelines for Organ Transplantation from Deceased Donors, Version 1.0. The Transplant Society of Australia and New Zealand, Sydney, 2016.

60. Chin-Hong, P.V., et al. Screening and treatment of chagas disease in organ transplant recipients in the United States: recommendations from the chagas in transplant working group. Am J Transplant, 2011. 11(4): p. 672-80.

61. Guidelines for prevention of transmission of infectious diseases from organ donors to recipients. Scandiatransplant, 2016.

62. AIDS - New Zealand, 2017. May 2017(76).

63. HIV/AIDS Statistics Overview, 2017. Available from: http://www.cdc.gov/hiv/statistics/overview/index.html (accessed February 2018).

64. Kirwan, P.D., et al. HIV in the UK - 2016 report. Public Health England, London, 2016.

65. Polaris Observatory, HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol, 2017. 2(3): p. 161-176.

66. Schweitzer, A., et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet, 2015. 386(10003): p. 1546-55.

67. Duan, K.I., M.J. Englesbe, and M.L. Volk. Centers for Disease Control 'high-risk' donors and kidney utilization. Am J Transplant, 2010. 10(2): p. 416-20.

68. NSW HIV Strategy 2016-2020: Data Report Quarter 4 & Annual 2017. NSW Health, Sydney, Australia, 2017.

69. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2015. The Kirby Institute, Sydney, 2015.

70. Jin, F., et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Sex Transm Infect, 2010. 86(1): p. 25-8.

71. Butler, T., D. Callander, and M. Simpson, National Prison Entrant's Bloodborne Virus Survey Report 2004, 2007, 2010, 2013. Kirby Institute, Sydney, 2015.

72. HIV in New Zealand. Available from: http://www.nzaf.org.nz/hiv-aids-stis/hiv-aids/hiv-in-new-zealand/ (accessed February 2018).

73. O'Connor, P., et al. Prevalence of hepatitis C among injecting drug users attending drug clinics. N Z Med J, 2016. 129(1434): p. 44-8.

74. Waller, K., et al. Donor referrals at increased risk for blood borne viruses in New South Wales, 2010-2015, in Transplantation Society of Australia and New Zealand ASM 2017. Canberra, Australia, 2017.

75. Trotter, P.B., et al., Deceased Organ Donors With a History of Increased Risk Behavior for the Transmission of Blood-Borne Viral Infection: The UK Experience. Transplantation, 2017. 101(7): p. 1679-1689.

76. Ha, J., Y. Park, and H.S. Kim. Evaluation of clinical sensitivity and specificity of hepatitis B virus (HBV), hepatitis C virus, and human immunodeficiency Virus-1 by cobas MPX: Detection of occult HBV infection in an HBV-endemic area. J Clin Virol, 2017. 96: p. 60-63.

77. Baleriola, C., et al. Organ donor screening using parallel nucleic acid testing allows assessment of transmission risk and assay results in real time. Transpl Infect Dis, 2012. 14(3): p. 278-87.

78. Baleriola, C. and W.D. Rawlinson. Chapter 6: Viral Transmission in Organ Transplantation: The Importance of Risk Assessment. Frontiers in Transplantology. Intech, 2016.

79. Fiebig, E.W., et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS, 2003. 17(13): p. 1871-9.

80. Kucirka, L.M., et al. Risk of window period HIV infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant, 2011. 11(6): p. 1176-87.

81. CSTCNTRP Increased Risk Donor Working Group. Guidance on the use of increased infectious risk donors for organ transplantation. Transplantation, 2014. 98(4): p. 365-9.

82. Kucirka, L.M., et al. Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant, 2011. 11(6): p. 1188-200.

83. Shaheen, M.A. and M. Idrees. Evidence-based consensus on the diagnosis, prevention and management of hepatitis C virus disease. World J Hepatol, 2015. 7(3): p. 616-27.

84. Northup, P.G., et al. Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis. Transpl Int, 2010. 23(10): p. 1038-44.

85. Kasprzyk, T., et al. Long-term results of kidney transplantation from HCV-positive donors. Transplant Proc, 2007. 39(9): p. 2701-3.

86. Vargas, H.E., et al. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. Gastroenterology, 1999. 117(1): p. 149-53.

87. 2017 ANZOD Annual Report. Section 4: Deceased Organ Donor Profile. Australia & New Zealand Organ Donation Registry, Adelaide, 2017.

88. Pereira, B.J., et al. A controlled study of hepatitis C transmission by organ transplantation. The New England Organ Bank Hepatitis C Study Group. Lancet, 1995. 345(8948): p. 484-7.

89. Pereira, B.J., et al. Transmission of hepatitis C virus by organ transplantation. N Engl J Med, 1991. 325(7): p. 454-60.

90. Delladetsima, I., et al. The course of hepatitis C virus infection in pretransplantation anti-hepatitis C virus-negative renal transplant recipients: a retrospective follow-up study. Am J Kidney Dis, 2006. 47(2): p. 309-16.

91. Natov, S.N. and B.J. Pereira. Transmission of viral hepatitis by kidney transplantation: donor evaluation and transplant policies (Part 1: hepatitis B virus). Transpl Infect Dis, 2002. 4(3): p. 117-23.

92. Dickson, R.C., et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology, 1997. 113(5): p. 1668-74.

93. Wachs, M.E., et al. The risk of transmission of hepatitis B from HBsAg(-), HBcAb(+), HBIgM(-) organ donors. Transplantation, 1995. 59(2): p. 230-4.

94. Yao, F., et al. The risk of HIV, HBV, HCV and HTLV infection among musculoskeletal tissue donors in Australia. Am J Transplant, 2007. 7(12): p. 2723-6.

95. Raimondo, G., et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol, 2008. 49(4): p. 652-7.

96. Torbenson, M. and D.L. Thomas. Occult hepatitis B. Lancet Infect Dis, 2002. 2(8): p. 479-86.

97. Huprikar, S., et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. Am J Transplant, 2015. 15(5): p. 1162-72.

98. Fytili, P., et al., Anti-HBc seroconversion after transplantation of anti-HBc positive nonliver organs to anti-HBc negative recipients. Transplantation, 2006. 81(5): p. 808-9.

99. Erice, A., et al., Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. Rev Infect Dis, 1991. 13(4): p. 537-47.

100. Tzakis, A.G., et al., Transplantation in HIV+ patients. Transplantation, 1990. 49(2): p. 354-8.

101. Borchi, B., et al., Case report: HIV infection from a kidney transplant. Transplant Proc, 2010. 42(6): p. 2267-9.

102. Villa, E. and A. Nanni Costa, HIV-positive organs used for transplant in Italy due to human error. Euro Surveill, 2007. 12(3): p. E070308 1.

103. Parry, J. Taiwan transplant team blamed for HIV positive organ blunder. BMJ, 2011. 343: p. d6523.

104. Miller, R., et al. Communication gaps associated with donor-derived infections. Am J Transplant, 2015. 15(1): p. 259-64.

105. Kucirka, L.M., et al. Provider response to a rare but highly publicized transmission of HIV through solid organ transplantation. Arch Surg, 2011. 146(1): p. 41-5.

106. Poli, F., et al. HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. Transplantation, 1989. 47(4): p. 724-5.

107. Briner, V., et al. HIV infection caused by kidney transplant: case report and review of 18 published cases. Schweiz Med Wochenschr, 1989. 119(30): p. 1046-52.

108. Simonds, R.J., et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. N Engl J Med, 1992. 326(11): p. 726-32.

109. Schwarz, A., et al. Human immunodeficiency virus transmission by organ donation. Outcome in cornea and kidney recipients. Transplantation, 1987. 44(1): p. 21-4.

110. Centers for Disease Control and Prevention. Human immunodeficiency virus infection transmitted from an organ donor screened for HIV antibody--North Carolina. MMWR Morb Mortal Wkly Rep, 1987. 36(20): p. 306-8.

111. Bowen, P.A., 2nd, et al. Transmission of human immunodeficiency virus (HIV) by transplantation: clinical aspects and time course analysis of viral antigenemia and antibody production. Ann Intern Med, 1988. 108(1): p. 46-8.

112. Mukhopadhyay, P., et al. Transmission of human immunodeficiency virus infection by renal transplantation. Indian J Nephrol, 2012. 22(2): p. 133-5.

113. Samuel, D., et al. Fatal acute HIV infection with aplastic anaemia, transmitted by liver graft. Lancet, 1988. 1(8596): p. 1221-2.

114. Coilly, A. and D. Samuel. Pros and Cons: Usage of organs from donors infected with hepatitis C virus - Revision in the direct-acting antiviral era. J Hepatol, 2016. 64(1): p. 226-31.

115. Huang, C.C., et al. Transmission of hepatitis C virus by renal transplantation. Transplant Proc, 1993. 25(1 Pt 2): p. 1474-5.

116. Pereira, B.J., et al. Screening and confirmatory testing of cadaver organ donors for hepatitis C virus infection: a U.S. National Collaborative Study. Kidney Int, 1994. 46(3): p. 886-92.

117. Marelli, D., et al. Hepatitis C-positive donors in heart transplantation. Am J Transplant, 2002. 2(5): p. 443-7.

118. File, E., et al. Allograft transmission of hepatitis C virus infection from infected donors in cardiac transplantation. Transplantation, 2003. 76(7): p. 1096-100.

119. Krajden, M., et al. Multi-organ donor transmission of hepatitis C virus to five solid organ transplant recipients and lack of transmission to corneal transplant recipients. Clin Diagn Virol, 1995. 3(2): p. 113-21.

120. Nampoory, M.R., et al. Organ-transmitted HCV infection in kidney transplant recipients from an anti-HCV negative donor. Transplant Proc, 1999. 31(8): p. 3207-8.

121. Centers for Disease Control and Prevention, Transmission of hepatitis C virus through transplanted organs and tissue-Kentucky and Massachusetts, 2011. MMWR Morb Mortal Wkly Rep, 2011. 60(50): p. 1697-700.

122. Suryaprasad, A., et al. Transmission of Hepatitis C Virus From Organ Donors Despite Nucleic Acid Test Screening. Am J Transplant, 2015. 15(7): p. 1827-35.

123. Choe, J., et al. Allograft transmission of hepatitis C during the window period: Weighing the new risks and costs in the era of donor shortage. Clin Transplant, 2017. 31(8).

124. Centers for Disease Control and Prevention, Potential transmission of viral hepatitis through use of stored blood vessels as conduits in organ transplantation-Pennsylvania, 2009. MMWR Morb Mortal Wkly Rep, 2011. 60(6): p. 172-4.

125. Schussler, T., et al. Severe hepatitis C infection in a renal transplant recipient following hepatitis C genotype mismatch transplant. Am J Transplant, 2004. 4(8): p. 1375-8.

126. Tugwell, B.D., et al. Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor. Ann Intern Med, 2005. 143(9): p. 648-54.

127. Levitsky, J., K. Doucette, and A.S.T. Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 147-68.

128. Fabrizio, F., S. Bunnapradist, and P. Martin. Transplanting kidneys from donors with prior hepatitis B infection: one response to the organ shortage. J Nephrol, 2002. 15(6): p. 605-13.

129. Nery, J.R., et al. Use of liver grafts from donors positive for antihepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. Transplantation, 2003. 75(8): p. 1179-86.

130. De Feo, T.M., et al. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transplant Proc, 2005. 37(2): p. 1238-9.

131. Prieto, M., et al. De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl, 2001. 7(1): p. 51-8.

132. Madayag, R.M., et al. Use of renal allografts from donors positive for hepatitis B core antibody confers minimal risk for subsequent development of clinical hepatitis B virus disease. Transplantation, 1997. 64(12): p. 1781-6.

133. Fong, T.L., et al. Impact of hepatitis B core antibody status on outcomes of cadaveric renal transplantation: analysis of United network of organ sharing database between 1994 and 1999. Transplantation, 2002. 73(1): p. 85-9.

134. Blanes, M., et al. Is there any risk of transmission of hepatitis B from heart donors hepatitis B core antibody positive? Transplant Proc, 2002. 34(1): p. 61-2.

135. Pinney, S.P., et al. Acceptable recipient outcomes with the use of hearts from donors with hepatitis-B core antibodies. J Heart Lung Transplant, 2005. 24(1): p. 34-7.

136. Ko, W.J., et al. Hepatitis B virus infection in heart transplant recipients in a hepatitis B endemic area. J Heart Lung Transplant, 2001. 20(8): p. 865-75.

137. Turik, M.A. and S.M. Markowitz. A successful regimen for the prevention of seroconversion after transplantation of a heart positive for hepatitis B surface antigen. J Heart Lung Transplant, 1992. 11(4 Pt 1): p. 781-3.

138. Lammermeier, D.E., et al. Use of potentially infected donor hearts for cardiac transplantation. Ann Thorac Surg, 1990. 50(2): p. 222-5.

139. Dhillon, G.S., et al. Impact of hepatitis B core antibody positive donors in lung and heart-lung transplantation: an analysis of the United Network For Organ Sharing Database. Transplantation, 2009. 88(6): p. 842-6.

140. Hartwig, M.G., et al. Hepatitis B core antibody positive donors as a safe and effective therapeutic option to increase available organs for lung transplantation. Transplantation, 2005. 80(3): p. 320-5.

141. Shitrit, A.B., et al. Lamivudine prophylaxis for hepatitis B virus infection after lung transplantation. Ann Thorac Surg, 2006. 81(5): p. 1851-2.

142. Pilmore, H.L. and E.J. Gane. Hepatitis B-positive donors in renal transplantation: increasing the deceased donor pool. Transplantation, 2012. 94(3): p. 205-10.

143. Wolf, J.L., et al. The transplanted kidney as a source of hepatitis B infection. Ann Intern Med, 1979. 91(3): p. 412-3.

144. Lutwick, L.I., et al. The transmission of hepatitis B by renal transplantation. Clin Nephrol, 1983. 19(6): p. 317-9.

145. Gow, P.J. and D.J. Mutimer. De novo hepatitis B infection acquired during liver transplantation. QJM, 2001. 94(5): p. 271-5.

146. Gish, R.G. and N.L. Ascher. Transmission of hepatitis B virus through allotransplantation. Liver Transpl Surg, 1996. 2(2): p. 161-4.

147. Moraleda, G., et al. De novo HBV infection caused by an anti-HBc positive donor in a vaccinated liver transplant recipient in spite of anti-HBs response. Am J Transplant, 2006. 6(2): p. 438-40.

148. Douglas, D.D., et al. The clinical course of transplantation-associated de novo hepatitis B infection in the liver transplant recipient. Liver Transpl Surg, 1997. 3(2): p. 105-11.

149. Castells, L., et al. Transmission of hepatitis B virus by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Transplant Proc, 1999. 31(6): p. 2464-5.

150. Cahlin, C., M. Olausson, and S. Friman. Severe clinical course of de novo hepatitis B infection after liver transplantation. Transplant Proc, 2001. 33(4): p. 2467-8.

151. Muller, E., et al. HIV-positive-to-HIV-positive kidney transplantation--results at 3 to 5 years. N Engl J Med, 2015. 372(7): p. 613-20.

152. Stock, P.G., et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med, 2010. 363(21): p. 2004-14.

153. Terrault, N.A., et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl, 2012. 18(6): p. 716-26.

154. Gane, E.J., et al. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology, 2007. 132(3): p. 931-7.

155. Berenguer, M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol, 2008. 49(2): p. 274-87.

156. Berenguer, M., et al. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant, 2008. 8(3): p. 679-87.

157. Levitsky, J., et al. Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent HCV infection treated with pegylated interferon. Gastroenterology, 2012. 142(5): p. 1132-1139 e1.

158. Gordon, F.D., et al. Peginterferon-alpha-2b and ribavirin for hepatitis C recurrence postorthotopic liver transplantation. J Clin Gastroenterol, 2012. 46(8): p. 700-8.

159. Xiao, N., S. Shi, and H. Zhuang. A meta-analysis that compares the use of either peginterferon-alpha2a or peginterferon-alpha2b plus ribavirin for HCV infection. Hepat Med, 2010. 2: p. 99-109.

160. Ferenci, P., et al. Randomized, double-blind, placebo-controlled study of peginterferon alfa-2a (40KD) plus ribavirin with or without amantadine in treatment-naive patients with chronic hepatitis C genotype 1 infection. J Hepatol, 2006. 44(2): p. 275-82.

161. Selzner, N., et al. Immune-mediated complications of the graft in interferon-treated hepatitis C positive liver transplant recipients. J Hepatol, 2011. 55(1): p. 207-17.

162. Bowring, M.G., et al. Changes in Utilization and Discard of Hepatitis C-Infected Donor Livers in the Recent Era. Am J Transplant, 2017. 17(2): p. 519-527.

163. Pungpapong, S., et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology, 2015. 61(6): p. 1880-6.

164. Lawitz, E., et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet, 2014. 384(9956): p. 1756-65.

165. Kwo, P.Y., et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med, 2014. 371(25): p. 2375-82.

166. Charlton, M., et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology, 2015. 149(3): p. 649-59.

167. Leroy, V., et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. Clin Gastroenterol Hepatol, 2015. 13(11): p. 1993-2001 e1-2.

168. Suarez-Benjumea, A., et al. New Antivirals for Hepatitis C Infection Among Infected Kidney Transplant Recipients: A Case Report. Transplant Proc, 2015. 47(9): p. 2672-4.

169. Durand, C., et al. EXPANDER-1: Exploring Renal Transplants Using Hepatitis-C Infected Donors for HCV-Negative Recipients. Am J Transplant, 2017. 17(suppl 3).

170. Saberi, B., et al. Utilization of hepatitis C virus RNA-positive donor liver for transplant to hepatitis C virus RNA-negative recipient. Liver Transpl, 2018. 24(1): p. 140-143.

171. Sho, T., et al. Safety and efficacy of sofosbuvir and ribavirin for genotype 2 hepatitis C Japanese patients with renal dysfunction. Hepatol Res, 2018.

172. Suda, G., et al. Safety and efficacy of daclatasvir and asunaprevir in hepatitis C virus-infected patients with renal impairment. Hepatol Res, 2017. 47(11): p. 1127-1136.

173. Roth, D., et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet, 2015. 386(10003): p. 1537-45.

174. Atsukawa, M., et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir in dialysis patients with genotype 1b chronic hepatitis C. Hepatol Res, 2017. 47(13): p. 1429-1437.

175. Reddy, K.R., et al. Elbasvir/grazoprevir does not worsen renal function in patients with hepatitis C virus infection and pre-existing renal disease. Hepatol Res, 2017. 47(12): p. 1340-1345.

176. Saxena, V., et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int, 2016. 36(6): p. 807-16.

177. Charlton, M., et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology, 2015. 148(1): p. 108-17.

178. Forns, X., et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology, 2015. 61(5): p. 1485-94.

179. Verna, E.C. and D.S. Goldberg. Hepatitis C viremic donors for hepatitis C nonviremic liver transplant recipients: Ready for prime time? Liver Transpl, 2018. 24(1): p. 12-14.

180. Martin-Davila, P., et al. Transmission of tropical and geographically restricted infections during solid-organ transplantation. Clin Microbiol Rev, 2008. 21(1): p. 60-96.

181. Einsiedel, L., K. Verdonck, and E. Gotuzzo. Chapter 6: Human T-Lymphtropic Virus 1: Clinical Aspects of a Neglected Infection among Indigenous Populations. Emerging Infections, ed. W.M. Scheld, M.L. Grayson, and J.M. Hughes. Vol. 9. Washington, DC: ASM Press, 2010.

182. Gessain, A. and O. Cassar. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Front Microbiol, 2012. 3: p. 388.

183. Einsiedel, L., et al. Human T-Lymphotropic Virus type 1 infection in an Indigenous Australian population: epidemiological insights from a hospital-based cohort study. BMC Public Health, 2016. 16: p. 787.

184. Grivas, R., K. Freeman, and R. Baird. Human T-lymphotropic virus-1 serology in the Northern Territory: 2008-2011. Pathology, 2014. 46(7): p. 644-8.

185. Einsiedel, L.J., et al. The prevalence and clinical associations of HTLV-1 infection in a remote Indigenous community. Med J Aust, 2016. 205(7): p. 305-9.

186. Tanabe, K., et al. Long-term results in human T-cell leukemia virus type 1-positive renal transplant recipients. Transplant Proc, 1998. 30(7): p. 3168-70.

187. Nakamura, N., et al. Prognosis of HTLV-I-positive renal transplant recipients. Transplant Proc, 2005. 37(4): p. 1779-82.

188. Kawano, N., et al. Adult T-cell leukemia development from a human T-cell leukemia virus type I carrier after a living-donor liver transplantation. Transplantation, 2006. 82(6): p. 840-3.

189. Soyama, A., et al. Human T-cell leukemia virus type I-associated myelopathy following living-donor liver transplantation. Liver Transpl, 2008. 14(5): p. 647-50.

190. Toro, C., et al. Rapid development of subacute myelopathy in three organ transplant recipients after transmission of human T-cell lymphotropic virus type I from a single donor. Transplantation, 2003. 75(1): p. 102-4.

191. Kaul, D.R., et al. Donor screening for human T-cell lymphotrophic virus 1/2: changing paradigms for changing testing capacity. Am J Transplant, 2010. 10(2): p. 207-13.

192. Huang, R.C. and J.A. Fishman. Screening of deceased organ donors: no easy answers. Transplantation, 2011. 91(2): p. 146-9.

193. Shames, B.D., A.M. D'Alessandro, and H.W. Sollinger. Human T-cell lymphotrophic virus infection in organ donors: a need to reassess policy? Am J Transplant, 2002. 2(7): p. 658-63.

194. Guidance for HTLV-1 screening and confirmation in potential donors and reporting potential HTLV-1 infection. Organ Procurement and Transplantation Network, U.S. Department of Health & Human Services. 2014.

195. Toro, C., et al. Infection with human T lymphotropic virus type I in organ transplant donors and recipients in Spain. J Med Virol, 2005. 76(2): p. 268-70.

196. Marvin, M.R., et al. Increasing utilization of human T-cell lymphotropic virus (+) donors in liver transplantation: is it safe? Transplantation, 2009. 87(8): p. 1180-90.

197. Bangham, C.R. The immune response to HTLV-I. Curr Opin Immunol, 2000. 12(4): p. 397-402.

198. Furukawa, Y., et al. Phylogenetic subgroups of human T cell lymphotropic virus (HTLV) type I in the tax gene and their association with different risks for HTLV-I-associated myelopathy/tropical spastic paraparesis. J Infect Dis, 2000. 182(5): p. 1343-9.

199. Jeffery, K.J., et al. HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I-associated myelopathy. Proc Natl Acad Sci U S A, 1999. 96(7): p. 3848-53.

200. Gout, O., et al. Rapid development of myelopathy after HTLV-I infection acquired by transfusion during cardiac transplantation. N Engl J Med, 1990. 322(6): p. 383-8.

201. Zanke, B.W., et al. HTLV-1 T cell lymphoma in a cyclosporine-treated renal transplant patient. Transplantation, 1989. 48(4): p. 695-7.

202. Tsurumi, H., et al. Adult T-cell leukemia developing during immunosuppressive treatment in a renal transplant recipient. Am J Hematol, 1992. 41(4): p. 292-4.

203. Nakamura, N., et al. Influence of immunosuppression in HTLV-1-positive renal transplant recipients. Transplant Proc, 1998. 30(4): p. 1324-6.

204. Cunningham, A.L., et al. Prevalence of infection with herpes simplex virus types 1 and 2 in Australia: a nationwide population based survey. Sex Transm Infect, 2006. 82(2): p. 164-8.

205. van de Laar, M.J., et al. Prevalence and correlates of herpes simplex virus type 2 infection: evaluation of behavioural risk factors. Int J Epidemiol, 1998. 27(1): p. 127-34.

206. Russell, D.B., et al. Seroprevalence of herpes simplex virus types 1 and 2 in HIV-infected and uninfected homosexual men in a primary care setting. J Clin Virol, 2001. 22(3): p. 305-13.

207. Minhas, V. and C. Wood. Epidemiology and transmission of Kaposi's sarcoma-associated herpesvirus. Viruses, 2014. 6(11): p. 4178-94.

208. Dedicoat, M., et al. Mother-to-child transmission of human herpesvirus-8 in South Africa. J Infect Dis, 2004. 190(6): p. 1068-75.

209. Luppi, M., et al. Molecular evidence of organ-related transmission of Kaposi sarcoma-associated herpesvirus or human herpesvirus-8 in transplant patients. Blood, 2000. 96(9): p. 3279-81.

210. Barozzi, P., et al. Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. Nat Med, 2003. 9(5): p. 554-61.

211. Lebbe, C., et al. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. Am J Transplant, 2013. 13(1): p. 207-13.

212. Regamey, N., et al. Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. N Engl J Med, 1998. 339(19): p. 1358-63.

213. Vijgen, S., et al. Fatal Outcome of Multiple Clinical Presentations of Human Herpesvirus 8-related Disease After Solid Organ Transplantation. Transplantation, 2016. 100(1): p. 134-40.

214. Pietrosi, G., et al. Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. Am J Transplant, 2011. 11(12): p. 2715-23.

215. Setyapranata, S., et al. Renal allograft re-use and herpetic re-infection. Nephrology (Carlton), 2015. 20 Suppl 1: p. 17-21.

216. Chiereghin, A., et al. Multicenter Prospective Study for Laboratory Diagnosis of HHV8 Infection in Solid Organ Donors and Transplant Recipients and Evaluation of the Clinical Impact After Transplantation. Transplantation, 2017. 101(8): p. 1935-1944.

217. Andreoni, M., et al. Prevalence, incidence and correlates of HHV-8/KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. J Infect, 2001. 43(3): p. 195-9.

218. Luppi, M., et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med, 2000. 343(19): p. 1378-85.

219. Luppi, M., et al. Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. Transplantation, 2002. 74(1): p. 131-2.

220. Park, Y.J., et al. Development of Kaposi sarcoma and hemophagocytic lymphohistiocytosis associated with human herpesvirus 8 in a renal transplant recipient. Korean J Intern Med, 2017. 32(4): p. 750-752.

221. Marcelin, A.G., et al. Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. Liver Transpl, 2004. 10(2): p. 295-300.

222. Balfour, H.H., Jr., et al. Age-specific prevalence of Epstein-Barr virus infection among individuals aged 6-19 years in the United States and factors affecting its acquisition. J Infect Dis, 2013. 208(8): p. 1286-93.

223. Lai, P.K., E.M. Mackay-Scollay, and M.P. Alpers. Epidemiological studies of Epstein-Barr herpesvirus infection in Western Australia. J Hyg (Lond), 1975. 74(3): p. 329-37.

224. Dollard, S.C., et al. National prevalence estimates for cytomegalovirus IgM and IgG avidity and association between high IgM antibody titer and low IgG avidity. Clin Vaccine Immunol, 2011. 18(11): p. 1895-9.

225. Seale, H., et al. National serosurvey of cytomegalovirus in Australia. Clin Vaccine Immunol, 2006. 13(11): p. 1181-4.

226. Sampaio, M.S., et al. Impact of Epstein-Barr virus donor and recipient serostatus on the incidence of post-transplant lymphoproliferative disorder in kidney transplant recipients. Nephrol Dial Transplant, 2012. 27(7): p. 2971-9.

227. Sullivan, S.G., et al. A brief overview of influenza surveillance systems in Australia, 2015. Commun Dis Intell Q Rep, 2016. 40(3): p. E351-E355.

228. Newall, A.T., J.G. Wood, and C.R. Macintyre. Influenza-related hospitalisation and death in Australians aged 50 years and older. Vaccine, 2008. 26(17): p. 2135-41.

229. Dalton, C.B., et al. Flutracking weekly online community survey of influenza-like illness: 2013 and 2014. Commun Dis Intell Q Rep, 2015. 39(3): p. E361-8.

230. Meylan, P.R., J.D. Aubert, and L. Kaiser. Influenza transmission to recipient through lung transplantation. Transpl Infect Dis, 2007. 9(1): p. 55-7.

231. O'Callaghan, G. Guideline for assessing and managing the possible risk of transmission of influenza (including H1N1 2009). Australian Organ & Tissue Authority, Canberra ACT, 2009.

232. Kumar, D., et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant, 2005. 5(8): p. 2031-6.

233. Noureddin, M. and R. Gish. Hepatitis delta: epidemiology, diagnosis and management 36 years after discovery. Curr Gastroenterol Rep, 2014. 16(1): p. 365.

234. Farci, P. and G.A. Niro. Clinical features of hepatitis D. Semin Liver Dis, 2012. 32(3): p. 228-36.

235. Hughes, S.A., H. Wedemeyer, and P.M. Harrison. Hepatitis delta virus. Lancet, 2011. 378(9785): p. 73-85.

236. Hepatitis D Fact Sheet. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/hepatitis-d/en/ (accessed 31 January 2018).

237. Alfaiate, D., P. Deny, and D. Durantel. Hepatitis delta virus: From biological and medical aspects to current and investigational therapeutic options. Antiviral Res, 2015. 122: p. 112-29.

238. Rizzetto, M. and A. Ciancio. Epidemiology of hepatitis D. Semin Liver Dis, 2012. 32(3): p. 211-9.

239. Heidrich, B., et al. Virological and clinical characteristics of delta hepatitis in Central Europe. J Viral Hepat, 2009. 16(12): p. 883-94.

240. Shadur, B., J. MacLachlan, and B. Cowie. Hepatitis D virus in Victoria 2000-2009. Intern Med J, 2013. 43(10): p. 1081-7.

241. Lempp, F.A. and S. Urban. Hepatitis Delta Virus: Replication Strategy and Upcoming Therapeutic Options for a Neglected Human Pathogen. Viruses, 2017. 9(7).

242. Heidrich, B., M.P. Manns, and H. Wedemeyer. Treatment options for hepatitis delta virus infection. Curr Infect Dis Rep, 2013. 15(1): p. 31-8.

243. Khuroo, M.S., M.S. Khuroo, and N.S. Khuroo. Hepatitis E: Discovery, global impact, control and cure. World J Gastroenterol, 2016. 22(31): p. 7030-45.

244. Matsubayashi, K., et al. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. Transfusion, 2008. 48(7): p. 1368-75.

245. Boxall, E., et al. Transfusion-transmitted hepatitis E in a 'nonhyperendemic' country. Transfus Med, 2006. 16(2): p. 79-83.

246. Colson, P., et al. Transfusion-associated hepatitis E, France. Emerg Infect Dis, 2007. 13(4): p. 648-9.

247. Teshale, E.H., D.J. Hu, and S.D. Holmberg. The two faces of hepatitis E virus. Clin Infect Dis, 2010. 51(3): p. 328-34.

248. Khuroo, M.S. and M.S. Khuroo. Hepatitis E: an emerging global disease - from discovery towards control and cure. J Viral Hepat, 2016. 23(2): p. 68-79.

249. Schlosser, B., et al. Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. J Hepatol, 2012. 56(2): p. 500-2.

250. Tan, H.H., et al. Chronic hepatitis e infection resulting in graft failure in a liver transplant tourist. Case Rep Transplant, 2011. 2011: p. 654792.

251. Ijaz, S., et al. Indigenous hepatitis E in England and wales from 2003 to 2012: evidence of an emerging novel phylotype of viruses. J Infect Dis, 2014. 209(8): p. 1212-8.

252. Ijaz, S., et al. Indigenous hepatitis E virus infection in England: more common than it seems. J Clin Virol, 2009. 44(4): p. 272-6.

253. Hewitt, P.E., et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet, 2014. 384(9956): p. 1766-73.

254. McPherson, S., et al. Summary of the British Transplantation Society UK Guidelines for Hepatitis E and Solid Organ Transplantation. Transplantation, 2018. 102(1): p. 15-20.

255. Knope, K.E., et al. Arboviral diseases and malaria in Australia, 2013-14: Annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2016. 40(3): p. E400-E436.

256. Harley, D., A. Sleigh, and S. Ritchie. Ross River virus transmission, infection, and disease: a cross-disciplinary review. Clin Microbiol Rev, 2001. 14(4): p. 909-32.

257. Hoad, V.C., et al. First reported case of transfusion-transmitted Ross River virus infection. Med J Aust, 2015. 202(5): p. 267-70.

258. Cordova, S.P., et al. Murray Valley encephalitis in Western Australia in 2000, with evidence of southerly spread. Commun Dis Intell, 2000. 24(12): p. 368-72.

259. Mackenzie, J.S., et al. Australian encephalitis in Western Australia, 1978-1991. Med J Aust, 1993. 158(9): p. 591-5.

260. Summary information about overseas-acquired vectorborne disease notifications in Australia: fortnight ending 24 February 2018. Australian Government Department of Health. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-vectorborne-overseas-acquired.htm (accessed March 2018).

261. Tan, F.L., et al. Dengue haemorrhagic fever after living donor renal transplantation. Nephrol Dial Transplant, 2005. 20(2): p. 447-8.

262. Mitchell, A.B., B.G. Oliver, and A.R. Glanville. Translational Aspects of the Human Respiratory Virome. Am J Respir Crit Care Med, 2016. 194(12): p. 1458-1464.

263. Wylie, K.M., et al. Sequence analysis of the human virome in febrile and afebrile children. PLoS One, 2012. 7(6): p. e27735.

264. Young, J.C., et al. Viral metagenomics reveal blooms of anelloviruses in the respiratory tract of lung transplant recipients. Am J Transplant, 2015. 15(1): p. 200-9.

265. Zoll, J., et al. Direct multiplexed whole genome sequencing of respiratory tract samples reveals full viral genomic information. J Clin Virol, 2015. 66: p. 6-11.

266. TT viruses: The still elusive human pathogens. Berlin, Heidelberg: Springer, 2009.

267. Kaul, D.R., et al. Solid organ transplant donors with central nervous system infection. Transplantation, 2014. 98(6): p. 666-70.

268. Guidance for recognizing central nervous system infections in potential deceased organ donors. Organ Procurement and Transplant Network, United States, 2018. Available from: https://optn.transplant.hrsa.gov/resources/guidance/guidance-for-recognizing-central-nervous-system-infections-in-potential-deceased-organ-donors/ (accessed 20 January 2018).

269. Srinivasan, A., et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med, 2005. 352(11): p. 1103-11.

270. Fischer, S.A., et al. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med, 2006. 354(21): p. 2235-49.

271. Peters, C.J. Arenavirus diseases. In Porterfield, J. S., ed. Exotic viral infections. London: Chapman & Hall Medical, 1995.

272. Toms, C., et al. Tuberculosis notifications in Australia, 2012 and 2013. Commun Dis Intell Q Rep, 2015. 39(2): p. E217-35.

273. Lumb, R., et al. Tuberculosis in Australia: bacteriologically-confirmed cases and drug resistance, 2011. A report of the Australian Mycobacterium Reference Laboratory Network. Commun Dis Intell Q Rep, 2014. 38(4): p. E369-75.

274. Coll, E., et al. Incidence of tuberculosis in deceased-organ donors and transmission risk to recipients in Spain. Transplantation, 2013. 96(2): p. 205-10.

275. Singh, N. and D.L. Paterson. *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis, 1998. 27(5): p. 1266-77.

276. Morris, M.I., et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. Am J Transplant, 2012. 12(9): p. 2288-300.

277. Benito, N., et al. Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: a retrospective matched cohort study. Clin Microbiol Infect, 2015. 21(7): p. 651-8.

278. Centers for Disease Control and Prevention, Transplantation-transmitted tuberculosis-Oklahoma and Texas, 2007. MMWR Morb Mortal Wkly Rep, 2008. 57(13): p. 333-6.

279. Lee, J., et al. Multidrug-resistant tuberculosis in a lung transplant recipient. J Heart Lung Transplant, 2003. 22(10): p. 1168-73.

280. Ridgeway, A.L., et al. Transmission of *Mycobacterium tuberculosis* to recipients of single lung transplants from the same donor. Am J Respir Crit Care Med, 1996. 153(3): p. 1166-8.

281. Winthrop, K.L., et al. Transmission of *mycobacterium tuberculosis* via lung transplantation. Am J Transplant, 2004. 4(9): p. 1529-33.

282. Edathodu, J., et al. Multi-recipient donor-transmitted tuberculosis. Int J Tuberc Lung Dis, 2010. 14(11): p. 1493-5.

283. Malone, A., et al. *Mycobacterium tuberculosis* in a renal transplant transmitted from the donor. Ir J Med Sci, 2007. 176(3): p. 233-5.

284. Mortensen, E., et al. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. Transpl Infect Dis, 2014. 16(1): p. 67-75.

285. Kumar, D., et al. Donor-derived tuberculosis (TB) infection in lung transplant despite following recommended algorithm. Am J Transplant, 2013. 13(8): p. 2225-6.

286. Weile, J., et al. First case of *Mycobacterium tuberculosis* transmission by heart transplantation from donor to recipient. Int J Med Microbiol, 2013. 303(8): p. 449-51.

287. Mourad, G., et al. Transmission of *Mycobacterium tuberculosis* with renal allografts. Nephron, 1985. 41(1): p. 82-5.

288. Peters, T.G., C.G. Reiter, and R.L. Boswell. Transmission of tuberculosis by kidney transplantation. Transplantation, 1984. 38(5): p. 514-6.

289. Boedefeld, R.L., et al. Fatal *Mycobacterium tuberculosis* infection in a lung transplant recipient. J Heart Lung Transplant, 2008. 27(10): p. 1176-8.

290. Wong, C.F., et al. Lung transplantation in Hong Kong: 12 years of experience. Respirology, 2008. 13(6): p. 903-7.

291. Shitrit, D., et al. Multidrug resistant tuberculosis following lung transplantation: treatment with pulmonary resection. Thorax, 2004. 59(1): p. 79-80.

292. Schulman, L.L., et al. Pulmonary tuberculosis after lung transplantation. Chest, 1997. 111(5): p. 1459-62.

293. Miller, R.A., et al. *Mycobacterium tuberculosis* in lung transplant recipients. Am J Respir Crit Care Med, 1995. 152(1): p. 374-6.

294. Carlsen, S.E. and C.J. Bergin. Reactivation of tuberculosis in a donor lung after transplantation. AJR Am J Roentgenol, 1990. 154(3): p. 495-7.

295. Adamu, B., et al. Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis. Cochrane Database Syst Rev, 2014(3): p. CD008597.

296. Coombs, G.W., et al. Australian Group on Antimicrobial Resistance Hospital-onset *Staphylococcus aureus* Surveillance Programme annual report, 2011. Commun Dis Intell Q Rep, 2013. 37(3): p. E210-8.

297. Coombs, G.W., et al. Australian Group on Antimicrobial Resistance Australian *Staphylococcus aureus* Sepsis Outcome Programme annual report, 2014. Commun Dis Intell Q Rep, 2016. 40(2): p. E244-54.

298. Coombs, G.W., et al. Australian Group on Antimicrobial Resistance Australian Enterococcal Sepsis Outcome Programme annual report, 2014. Commun Dis Intell Q Rep, 2016. 40(2): p. E236-43.

299. Mahony, A.A., et al. Vancomycin-resistant *Enterococcus* faecium sequence type 796 - rapid international dissemination of a new epidemic clone. Antimicrob Resist Infect Control, 2018. 7: p. 44.

300. van Hal, S.J., et al. Polyclonal emergence of vanA vancomycin-resistant *Enterococcus* faecium in Australia. J Antimicrob Chemother, 2017. 72(4): p. 998-1001.

301. Lee, A.S., et al. Defining the Role of the Environment in the Emergence and Persistence of vanA Vancomycin-Resistant *Enterococcus* (VRE) in an Intensive Care Unit: A Molecular Epidemiological Study. Infect Control Hosp Epidemiol, 2018: p. 1-8.

302. Bell, J.M., et al. Australian Group on Antimicrobial Resistance Australian Enterobacteriaceae Sepsis Outcome Programme annual report, 2014. Commun Dis Intell Q Rep, 2016. 40(2): p. E229-35.

303. European Centre for Disease Prevention and Control. Annual epidemiological report antimicrobial resistance and healthcare-associated infections, 2014.

304. Sheng, W.H., et al. Distribution of extended-spectrum beta-lactamases, AmpC beta-lactamases, and carbapenemases among *Enterobacteriaceae* isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother, 2013. 57(7): p. 2981-8.

305. Lanini, S., et al. Incidence of carbapenem-resistant gram negatives in Italian transplant recipients: a nationwide surveillance study. PLoS One, 2015. 10(4): p. e0123706.

306. European Centre for Disease Prevention and Control. Carbapenemase-producing bacteria in Europe: Interim results from the European survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE) project 2013. ECDC, Stockholm, 2013.

307. Wu, T.J., et al. Suspect the donor with potential infection in the adult deceased donor liver transplantation. Transplant Proc, 2008. 40(8): p. 2486-8.

308. Watkins, A.C., et al. The deceased organ donor with an "open abdomen": proceed with caution. Transpl Infect Dis, 2012. 14(3): p. 311-5.

309. Martins, N., et al. Severe infection in a lung transplant recipient caused by donor-transmitted carbapenem-resistant *Acinetobacter baumannii*. Transpl Infect Dis, 2012. 14(3): p. 316-20.

310. Mularoni, A., et al. Outcome of Transplantation Using Organs From Donors Infected or Colonized With Carbapenem-Resistant Gram-Negative Bacteria. Am J Transplant, 2015. 15(10): p. 2674-82.

311. Goldberg, E., et al. Organ transplantation from a donor colonized with a multidrug-resistant organism: a case report. Transpl Infect Dis, 2012. 14(3): p. 296-9.

312. Orlando, G., et al. Fatal hemorrhage in two renal graft recipients with multi-drug resistant *Pseudomonas aeruginosa* infection. Transpl Infect Dis, 2009. 11(5): p. 442-7.

313. Simkins, J. and V. Muggia. Favorable outcome in a renal transplant recipient with donor-derived infection due to multidrug-resistant *Pseudomonas aeruginosa*. Transpl Infect Dis, 2012. 14(3): p. 292-5.

314. Subramonia, S., et al. Vacuum-assisted closure of postoperative abdominal wounds: a prospective study. World J Surg, 2009. 33(5): p. 931-7.

315. Abikhaled, J.A., et al. Prolonged abdominal packing for trauma is associated with increased morbidity and mortality. Am Surg, 1997. 63(12): p. 1109-12; discussion 1112-3.

316. Barker, D.E., et al. Vacuum pack technique of temporary abdominal closure: a 7-year experience with 112 patients. J Trauma, 2000. 48(2): p. 201-6; discussion 206-7.

317. Wendt, J.M., et al. Transmission of methicillin-resistant Staphylococcus aureus infection through solid organ transplantation: confirmation via whole genome sequencing. Am J Transplant, 2014. 14(11): p. 2633-9.

318. van Duin, D., C. van Delden, and A.S.T. Infectious Diseases Community of Practice. Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 31-41.

319. Ariza-Heredia, E.J., et al. Outcomes of transplantation using organs from a donor infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*. Transpl Infect Dis, 2012. 14(3): p. 229-36.

320. Infectious syphilis outbreak. Australian Government Department of Health. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-infectious-syphilis-outbreak.htm (accessed March 2018).

321. Sexually Transmitted Infections in New Zealand: Annual Surveillance report 2014. The Institute of Environmental Science and Research Limited: Porirua, New Zealand, 2015.

322. Sena, A.C., White B.L., and Sparling P.F. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis, 2010. 51(6): p. 700-8.

323. 2015 Sexually Transmitted Diseases Treatment Guidelines: Syphilis. Division of STD prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. Atlanta, Georgia (last updated July 27, 2016).

324. Cortes, N.J., et al. Transmission of syphilis by solid organ transplantation. Am J Transplant, 2006. 6(10): p. 2497-9.

325. Tariciotti, L., et al. Asymptomatic transmission of *Treponema pallidum* (syphilis) through deceased donor liver transplantation. Transpl Infect Dis, 2012. 14(3): p. 321-5.

326. Steinmann, J., et al. Syphilis-specific immunoglobulin G seroconversion after double-lung transplantation. J Heart Lung Transplant, 2009. 28(8): p. 857-9.

327. Gibel, L.J., et al. Is serological evidence of infection with syphilis a contraindication to kidney donation? Case report and review of the literature. J Urol, 1987. 138(5): p. 1226-7.

328. Caballero, F., et al. Successful transplantation of organs retrieved from a donor with syphilis. Transplantation, 1998. 65(4): p. 598-9.

329. Ko, W.J., et al. Successful prevention of syphilis transmission from a multiple organ donor with serological evidence of syphilis. Transplant Proc, 1998. 30(7): p. 3667-8.

330. Marek, A. and T. Inkster. A syphilis-positive organ donor - management of the cardiac transplant recipient: a case report and review of the literature. Sex Transm Dis, 2012. 39(6): p. 485-6.

331. Kovacs, C.S., Jr., et al. Selecting suitable solid organ transplant donors: Reducing the risk of donor-transmitted infections. World J Transplant, 2014. 4(2): p. 43-56.

332. Lumbreras, C., et al. Clinical significance of donor-unrecognized bacteremia in the outcome of solid-organ transplant recipients. Clin Infect Dis, 2001. 33(5): p. 722-6.

333. Singh, N. Impact of donor bacteremia on outcome in organ transplant recipients. Liver Transpl, 2002. 8(10): p. 975-6.

334. Freeman, R.B., et al. Outcome of transplantation of organs procured from bacteremic donors. Transplantation, 1999. 68(8): p. 1107-11.

335. Bahrami, T., et al. Intrathoracic organ transplantation from donors with meningitis: a single-center 20-year experience. Ann Thorac Surg, 2008. 86(5): p. 1554-6.

336. Caballero, F., et al. Successful transplantation of organs from a donor with postneurosurgical meningitis caused by *Escherichia coli*. Transplantation, 2012. 93(3): p. e11-3.

337. Satoi, S., et al. The use of liver grafts from donors with bacterial meningitis. Transplantation, 2001. 72(6): p. 1108-13.

338. Lopez-Navidad, A., et al. Successful transplantation of organs retrieved from donors with bacterial meningitis. Transplantation, 1997. 64(2): p. 365-8.

339. Paig i, J.M., et al. Organ donors with adequately treated bacterial meningitis may be suitable for successful transplantation. Transplant Proc, 2000. 32(1): p. 75-7.

340. Quagliarello, V.J. and W.M. Scheld. Treatment of bacterial meningitis. N Engl J Med, 1997. 336(10): p. 708-16.

341. Skogberg, K., et al. Clinical presentation and outcome of listeriosis in patients with and without immunosuppressive therapy. Clin Infect Dis, 1992. 14(4): p. 815-21.

342. Issa, N.C. and R. Patel. Potential for expansion of the donor pool using liver allografts from donors with bacterial meningitis. Liver Transpl, 2002. 8(10): p. 977-9.

343. Ruiz, I., et al. Donor-to-host transmission of bacterial and fungal infections in lung transplantation. Am J Transplant, 2006. 6(1): p. 178-82.

344. Fernandez, R., et al. *Ureaplasma* Transmitted From Donor Lungs Is Pathogenic After Lung Transplantation. Ann Thorac Surg, 2017. 103(2): p. 670-671.

345. Bharat, A., et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med, 2015. 7(284): p. 284re3.

346. Chen, C., et al. Hyperammonemia Syndrome After Lung Transplantation: A Single Center Experience. Transplantation, 2016. 100(3): p. 678-84.

347. Lichtenstein, G.R., et al. Fatal hyperammonemia after orthotopic lung transplantation. Ann Intern Med, 2000. 132(4): p. 283-7.

348. Tse, N., S. Cederbaum, and J.A. Glaspy. Hyperammonemia following allogeneic bone marrow transplantation. Am J Hematol, 1991. 38(2): p. 140-1.

349. Nakashima, K., et al. Prevalence of human papillomavirus infection in the oropharynx and urine among sexually active men: a comparative study of infection by papillomavirus and other organisms, including *Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma spp., and Ureaplasma spp*. BMC Infect Dis, 2014. 14: p. 43.

350. Hill, D.E., S. Chirukandoth, and J.P. Dubey. Biology and epidemiology of *Toxoplasma gondii* in man and animals. Anim Health Res Rev, 2005. 6(1): p. 41-61.

351. Dubey, J.P. and C.P. Beattie. Toxoplasmosis of Animals and Man. 1988, Boca Raton, FL: CRC Press.

352. Walpole, I.R., N. Hodgen, and C. Bower, Congenital toxoplasmosis: a large survey in western Australia. Med J Aust, 1991. 154(11): p. 720-4.

353. Torgerson, P.R., et al. World Health Organization Estimates of the Global and Regional Disease Burden of 11 Foodborne Parasitic Diseases, 2010: A Data Synthesis. PLoS Med, 2015. 12(12): p. e1001920.

354. Schwartz, B.S., Mawhorter, S.D., and A.S.T. Infectious Diseases Community of Practice, Parasitic infections in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 280-303.

355. Lewis, J.S., Jr., et al. PCR for the diagnosis of toxoplasmosis after hematopoietic stem cell transplantation. Expert Rev Mol Diagn, 2002. 2(6): p. 616-24.

356. Joseph, P., et al. Optimization and evaluation of a PCR assay for detecting toxoplasmic encephalitis in patients with AIDS. J Clin Microbiol, 2002. 40(12): p. 4499-503.

357. Giordano, L.F., et al. Toxoplasmosis transmitted via kidney allograft: case report and review. Transplant Proc, 2002. 34(2): p. 498-9.

358. Renoult, E., et al. Toxoplasmosis in kidney transplant recipients: report of six cases and review. Clin Infect Dis, 1997. 24(4): p. 625-34.

359. Mason, J.C., et al. Toxoplasmosis in two renal transplant recipients from a single donor. Transplantation, 1987. 44(4): p. 588-91.

360. Fernandez-Sabe, N., et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis, 2012. 54(3): p. 355-61.

361. Campbell, A.L., et al. First case of toxoplasmosis following small bowel transplantation and systematic review of tissue-invasive toxoplasmosis following noncardiac solid organ transplantation. Transplantation, 2006. 81(3): p. 408-17.

362. Hommann, M., et al. Cerebral toxoplasmosis after combined liver-pancreas-kidney and liver-pancreas transplantation. Transplant Proc, 2002. 34(6): p. 2294-5.

363. Martina, M.N., et al. *Toxoplasma gondii* primary infection in renal transplant recipients. Two case reports and literature review. Transpl Int, 2011. 24(1): p. e6-12.

364. Botterel, F., et al. Disseminated toxoplasmosis, resulting from infection of allograft, after orthotopic liver transplantation: usefulness of quantitative PCR. J Clin Microbiol, 2002. 40(5): p. 1648-50.

365. Hermanns, B., et al. Fulminant toxoplasmosis in a heart transplant recipient. Pathol Res Pract, 2001. 197(3): p. 211-5.

366. Coster, L.O. Parasitic infections in solid organ transplant recipients. Infect Dis Clin North Am, 2013. 27(2): p. 395-427.

367. Annual Notifiable Disease Tables. New Zealand Ministru of Health and The Institute of Environmental Science and Research Ltd. Available from: https://surv.esr.cri.nz/surveillance/annual_diseasetables.php (accessed 9 May 2018).

368. Chiche, L., et al. Posttransplant malaria: first case of transmission of Plasmodium falciparum from a white multiorgan donor to four recipients. Transplantation, 2003. 75(1): p. 166-8.

369. Holzer, B.R., et al. Transmission of malaria by renal transplantation. Transplantation, 1985. 39(3): p. 315-6.

370. Fischer, L., et al. Transmission of malaria tertiana by multi-organ donation. Clin Transplant, 1999. 13(6): p. 491-5.

371. Crafa, F., et al. Possible transmission of malaria by liver transplantation. Transplant Proc, 1991. 23(5): p. 2664.

372. Babinet, J., et al. Transmission of *Plasmodium falciparum* by heart transplant. BMJ, 1991. 303(6816): p. 1515-6.

373. Yenen, O.S., et al. A case of *Plasmodium vivax* infection transmitted by renal allograft. Nephrol Dial Transplant, 1994. 9(12): p. 1805-6.

374. Johnston, I.D. Possible transmission of malaria by renal transplantation. Br Med J (Clin Res Ed), 1981. 282(6266): p. 780.

375. Tan, H.W. and S.L. Ch'ng. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. Singapore Med J, 1991. 32(3): p. 189-90.

376. Beknazarova, M., H. Whiley, and K. Ross. Strongyloidiasis: A Disease of Socioeconomic Disadvantage. Int J Environ Res Public Health, 2016. 13(5).

377. Liu, L.X. and P.F. Weller. Strongyloidiasis and other intestinal nematode infections. Infect Dis Clin North Am, 1993. 7(3): p. 655-82.

378. Rahmanian, H., et al. Seroprevalence of *Strongyloides stercoralis* in a South Australian Vietnam veteran cohort. Aust N Z J Public Health, 2015. 39(4): p. 331-5.

379. Grove, D.I. Strongyloidiasis in Allied ex-prisoners of war in south-east Asia. Br Med J, 1980. 280(6214): p. 598-601.

380. Caruana, S.R., et al. Undiagnosed and potentially lethal parasite infections among immigrants and refugees in Australia. J Travel Med, 2006. 13(4): p. 233-9.

381. de Silva, S., et al. Chronic *Strongyloides stercoralis* infection in Laotian immigrants and refugees 7-20 years after resettlement in Australia. Epidemiol Infect, 2002. 128(3): p. 439-44.

382. Fisher, D., F. McCarry, and B. Currie. Strongyloidiasis in the Northern Territory. Under-recognised and under-treated? Med J Aust, 1993. 159(2): p. 88-90.

383. Prociv, P. and R. Luke. Observations on strongyloidiasis in Queensland aboriginal communities. Med J Aust, 1993. 158(3): p. 160-3.

384. Keiser, P.B. and T.B. Nutman. *Strongyloides stercoralis* in the Immunocompromised Population. Clin Microbiol Rev, 2004. 17(1): p. 208-17.

385. Schwartz, B.S., et al. Organ donor screening practices for *Trypanosoma cruzi* infection among US Organ Procurement Organizations. Am J Transplant, 2011. 11(4): p. 848-51.

386. Roxby, A.C., G.S. Gottlieb, and A.P. Limaye. Strongyloidiasis in transplant patients. Clin Infect Dis, 2009. 49(9): p. 1411-23.

387. Thomas, M.C. and S.A. Costello. Disseminated strongyloidiasis arising from a single dose of dexamethasone before stereotactic radiosurgery. Int J Clin Pract, 1998. 52(7): p. 520-1.

388. Patel, G., et al. Strongyloides hyperinfection syndrome after intestinal transplantation. Transpl Infect Dis, 2008. 10(2): p. 137-41.

389. Hamilton, K.W., et al. Donor-derived *Strongyloides stercoralis* infections in renal transplant recipients. Transplantation, 2011. 91(9): p. 1019-24.

390. Gotuzzo, E., et al. *Strongyloides stercoralis* hyperinfection associated with human T cell lymphotropic virus type-1 infection in Peru. Am J Trop Med Hyg, 1999. 60(1): p. 146-9.

391. Hayashi, J., et al. Correlation between human T cell lymphotropic virus type-1 and *Strongyloides stercoralis* infections and serum immunoglobulin E responses in residents of Okinawa, Japan. Am J Trop Med Hyg, 1997. 56(1): p. 71-5.

392. Theodoropoulos, N. and M. Ison. Donor-Derived Infections: Incidence, Prevention, and Management. Transplant Infections, ed. P. Ljungman. Switzerland: Springer, 2016.

393. Sato, Y., et al. Efficacy of stool examination for detection of Strongyloides infection. Am J Trop Med Hyg, 1995. 53(3): p. 248-50.

394. Abanyie, F.A., et al. Donor-derived *Strongyloides stercoralis* infection in solid organ transplant recipients in the United States, 2009-2013. Am J Transplant, 2015. 15(5): p. 1369-75.

395. Brugemann, J., et al. Two donor-related infections in a heart transplant recipient: one common, the other a tropical surprise. J Heart Lung Transplant, 2010. 29(12): p. 1433-7.

396. Palau, L.A. and Pankey G.A. Strongyloides hyperinfection in a renal transplant recipient receiving cyclosporine: possible *Strongyloides stercoralis* transmission by kidney transplant. Am J Trop Med Hyg, 1997. 57(4): p. 413-5.

397. Rodriguez-Hernandez, M.J., et al. *Strongyloides stercoralis* hyperinfection transmitted by liver allograft in a transplant recipient. Am J Transplant, 2009. 9(11): p. 2637-40.

398. Ben-Youssef, R., et al. *Stronglyoides stercoralis* infection from pancreas allograft: case report. Transplantation, 2005. 80(7): p. 997-8.

399. Hoy, W.E., et al. Transmission of strongyloidiasis by kidney transplant? Disseminated strongyloidiasis in both recipients of kidney allografts from a single cadaver donor. JAMA, 1981. 246(17): p. 1937-9.

400. Roseman, D.A., et al. *Strongyloides stercoralis t*ransmission by kidney transplantation in two recipients from a common donor. Am J Transplant, 2013. 13(9): p. 2483-6.

401. Le, M., et al. Single donor-derived strongyloidiasis in three solid organ transplant recipients: case series and review of the literature. Am J Transplant, 2014. 14(5): p. 1199-206.

402. Gann, P.H., F.A. Neva, and A.A. Gam. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. J Infect Dis, 1994. 169(5): p. 1076-9.

403. Datry, A., et al. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. Trans R Soc Trop Med Hyg, 1994. 88(3): p. 344-5.

404. Marty, F.M., et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. Clin Infect Dis, 2005. 41(1): p. e5-8.

405. Salvador, F., et al. Safety of liver transplantation with Chagas disease-seropositive donors for seronegative recipients. Liver Transpl, 2011. 17(11): p. 1304-8.

406. Chagas' Disease Argentine Collaborative Transplant Consortium and Casadei, D. Chagas' disease and solid organ transplantation. Transplant Proc, 2010. 42(9): p. 3354-9.

407. Cura, C.I., et al. Early molecular diagnosis of acute Chagas disease after transplantation with organs from *Trypanosoma cruzi*-infected donors. Am J Transplant, 2013. 13(12): p. 3253-61.

408. Pinazo, M.J., et al. Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas. Transplant Rev (Orlando), 2011. 25(3): p. 91-101.

409. Leishmaniasis: Epidemiological Situation. World Health Organization, 2018 Available from: http://www.who.int/leishmaniasis/burden/en/ (accessed January 2018).

410. Roberts, T., et al. Molecular epidemiology of imported cases of leishmaniasis in Australia from 2008 to 2014. PLoS One, 2015. 10(3): p. e0119212.

411. Bart, A., et al. Imported leishmaniasis in the Netherlands from 2005 to 2012: epidemiology, diagnostic techniques and sequence-based species typing from 195 patients. Euro Surveill, 2013. 18(30): p. 20544.

412. Alvar, J., et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One, 2012. 7(5): p. e35671.

413. Antinori, S., et al. Leishmaniasis among organ transplant recipients. Lancet Infect Dis, 2008. 8(3): p. 191-9.

414. Ivanovski, N., et al. Living-unrelated (paid) renal transplantation--ten years later. Transplant Proc, 2005. 37(2): p. 563-4.

415. Horber, F.F., et al. Visceral leishmaniasis after orthotopic liver transplantation: impact of persistent splenomegaly. Transpl Int, 1993. 6(1): p. 55-7.

416. Murray, H.W. Leishmaniasis in the United States: treatment in 2012. Am J Trop Med Hyg, 2012. 86(3): p. 434-40.

417. Singh, N., et al. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. Am J Transplant, 2012. 12(9): p. 2414-28.

418. Albano, L., et al. Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. Clin Infect Dis, 2009. 48(2): p. 194-202.

419. Dummer, J.S., et al. A survey of anti-fungal management in lung transplantation. J Heart Lung Transplant, 2004. 23(12): p. 1376-81.

420. Sun, H.Y., M.M. Wagener, and N. Singh. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis, 2009. 48(11): p. 1566-76.

421. Baddley, J.W., et al. Transmission of *Cryptococcus neoformans* by Organ Transplantation. Clin Infect Dis, 2011. 52(4): p. e94-8.

422. Kanj, S.S., et al. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. Medicine (Baltimore), 1996. 75(3): p. 142-56.

423. Ooi, B.S., et al. Survival of a patient transplanted with a kidney infected with *Cryptococcus neoformans*. Transplantation, 1971. 11(4): p. 428-9.

424. Mueller, N.J., et al. Donor-derived aspergillosis from use of a solid organ recipient as a multiorgan donor. Transpl Infect Dis, 2010. 12(1): p. 54-9.

425. Keating, M.R., et al. Transmission of invasive aspergillosis from a subclinically infected donor to three different organ transplant recipients. Chest, 1996. 109(4): p. 1119-24.

426. Shoham, S., et al. Invasive filamentous fungal infections associated with renal transplant tourism. Transpl Infect Dis, 2010. 12(4): p. 371-4.

427. Klug, G.M., et al. Creutzfeldt-Jakob disease surveillance in Australia: update to December 2015. Commun Dis Intell Q Rep, 2016. 40(3): p. E368-E376.

428. Kindhauser, M.K., et al. Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ, 2016. 94(9): p. 675-686C.

429. Aubry, M., et al. Seroprevalence of arboviruses among blood donors in French Polynesia, 2011-2013. Int J Infect Dis, 2015. 41: p. 11-2.

430. Pan American Health Organization/World Health Organization. Zika-Epidemiological Update, 26 July 2017. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=40945&lang=en.

431. Lessler, J., et al. Times to key events in Zika virus infection and implications for blood donation: a systematic review. Bull World Health Organ, 2016. 94(11): p. 841-849.

432. Zika virus infection weekly report: 27 February 2017. New Zealand Ministry of Health and the Institute of Environmental Science and Research Ltd. Available from https://surv.esr.cri.nz/surveillance/WeeklyZikaFever.php

433. Nogueira, M.L., et al. Zika Virus Infection and Solid Organ Transplantation: A New Challenge. Am J Transplant, 2017. 17(3): p. 791-795.

434. Kotton, C.N. Zika Virus and Solid Organ Transplantation: Significant Pathogen or Harbinger of Things to Come? Transplantation, 2016. 100(5): p. 970-2.

435. Epidemiological Alert: Neurological syndrome, congenital malformations, and Zika virus infections. Implications for public health in the Americas. 2015, Pan American Health Organization and World Health Organization. Available from http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32405&lang=en

436. Landry, M.L. and K. St George. Laboratory Diagnosis of Zika Virus Infection. Arch Pathol Lab Med, 2017. 141(1): p. 60-67.

437. Priyamvada, L., et al. Human antibody responses after dengue virus infection are highly cross-reactive to Zika virus. Proc Natl Acad Sci U S A, 2016. 113(28): p. 7852-7.

438. Charrel, R.N., et al. Background review for diagnostic test development for Zika virus infection. Bull World Health Organ, 2016. 94(8): p. 574-584D.

439. Galel, S.A., et al. First Zika-positive donations in the continental United States. Transfusion, 2017. 57(3pt2): p. 762-769.

440. Williamson, P.C., et al. First cases of Zika virus-infected US blood donors outside states with areas of active transmission. Transfusion, 2017. 57(3pt2): p. 770-778.

441. Brasil, P., et al. Zika Virus Outbreak in Rio de Janeiro, Brazil: Clinical Characterization, Epidemiological and Virological Aspects. PLoS Negl Trop Dis, 2016. 10(4): p. e0004636.

442. Balmaseda, A., et al. Antibody-based assay discriminates Zika virus infection from other flaviviruses. Proc Natl Acad Sci USA, 2017. 114(31): p. 8384-8389.

443. Policy and guidelines: Revised surveillance case definitions. Flavivirus infection (unspecified) including Zika virus. CDI, 2016. 40(2): p. E285-E288.

444. Corman, V.M., et al. Assay optimization for molecular detection of Zika virus. Bull World Health Organ, 2016. 94(12): p. 880-892.

445. Gourinat, A.C., et al. Detection of Zika virus in urine. Emerg Infect Dis, 2015. 21(1): p. 84-6.

446. Zika virus and safety of substances of human origin - a guide for preparedness activities in Europe. European Centre for Disease Prevention and Control (EDC): Stockholm, 2016.

447. Silveira, F.P. and S.V. Campos, The Zika epidemics and transplantation. J Heart Lung Transplant, 2016. 35(5): p. 560-3.

448. West Nile Virus: Fact sheet #354. World Health Organization, Geneva, 201; Available from: http://www.who.int/mediacentre/factsheets/fs354/en/ [accessed 4 January 2018).

449. West Nile Virus and Solid Organ Transplantation. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO): United Kingdom, 2013.

450. Yango, A.F., et al. West Nile virus infection in kidney and pancreas transplant recipients in the Dallas-Fort Worth Metroplex during the 2012 Texas epidemic. Transplantation, 2014. 97(9): p. 953-7.

451. Murray Valley encephalitis and Kunjin viruses. Government of Western Australia Department of Health. Available from: http://healthywa.wa.gov.au/Articles/J_M/Murray-Valley-encephalitis-and-Kunjin-viruses (accessed February 2018).

452. Knope, K.E., et al. Arboviral diseases and malaria in Australia, 2011-12: annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2014. 38(2): p. E122-42.

453. Knope, K., et al. Arboviral diseases and malaria in Australia, 2010-11: annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2013. 37(1): p. E1-20.

454. Wright, P., et al. Arboviral diseases and malaria in Australia, 2009-10: annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2012. 36(1): p. 70-81.

455. Fitzsimmons, G.J., et al. Arboviral diseases and malaria in Australia, 2008-09: annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2010. 34(3): p. 225-40.

456. Fitzsimmons, G.J., et al. Arboviral diseases and malaria in Australia, 2007/08: annual report of the National Arbovirus and Malaria Advisory Committee. Commun Dis Intell Q Rep, 2009. 33(2): p. 155-69.

457. Winston, D.J., et al. Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. Transplantation, 2014. 97(9): p. 881-9.

458. Rabe, I.B., et al. Fatal transplant-associated west nile virus encephalitis and public health investigation-california, 2010. Transplantation, 2013. 96(5): p. 463-8.

459. Inojosa, W.O., et al. West Nile virus transmission through organ transplantation in north-eastern Italy: a case report and implications for pre-procurement screening. Infection, 2012. 40(5): p. 557-62.

460. Rhee, C., et al. West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature. Transpl Infect Dis, 2011. 13(3): p. 312-7.

461. Morelli, M.C., et al. Absence of neuroinvasive disease in a liver transplant recipient who acquired West Nile virus (WNV) infection from the organ donor and who received WNV antibodies prophylactically. Clin Infect Dis, 2010. 51(4): p. e34-7.

462. Centers for Disease Control and Prevention. West Nile virus transmission via organ transplantation and blood transfusion - Louisiana, 2008. MMWR Morb Mortal Wkly Rep, 2009. 58(45): p. 1263-7.

463. Centers for Disease Control and Prevention. West Nile virus infections in organ transplant recipients--New York and Pennsylvania, August-September, 2005. MMWR Morb Mortal Wkly Rep, 2005. 54(40): p. 1021-3.

464. Costa, A.N., et al. West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011. Euro Surveill, 2011. 16(41).

465. Iwamoto, M., et al. Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med, 2003. 348(22): p. 2196-203.

466. Singh, N., M.E. Levi, and A.S.T. Infectious Diseases Community of Practice, Arenavirus and West Nile virus in solid organ transplantation. Am J Transplant, 2013. 13 Suppl 4: p. 361-71.

467. Gomez, A.J., et al. Fatal West Nile Virus Encephalitis in a Heart Transplant Recipient. J Clin Microbiol, 2015. 53(8): p. 2749-52.

468. Nett, R.J., et al. Current practices and evaluation of screening solid organ donors for West Nile virus. Transpl Infect Dis, 2012. 14(3): p. 268-77.

469. Kiberd, B.A. and Forward, K. Screening for West Nile virus in organ transplantation: a medical decision analysis. Am J Transplant, 2004. 4(8): p. 1296-301.

470. Organ Donation and Transplantation - Managing Risks of Transmission of HIV, HCV and HBV. Ministry of Health, NSW: Sydney, 2013.

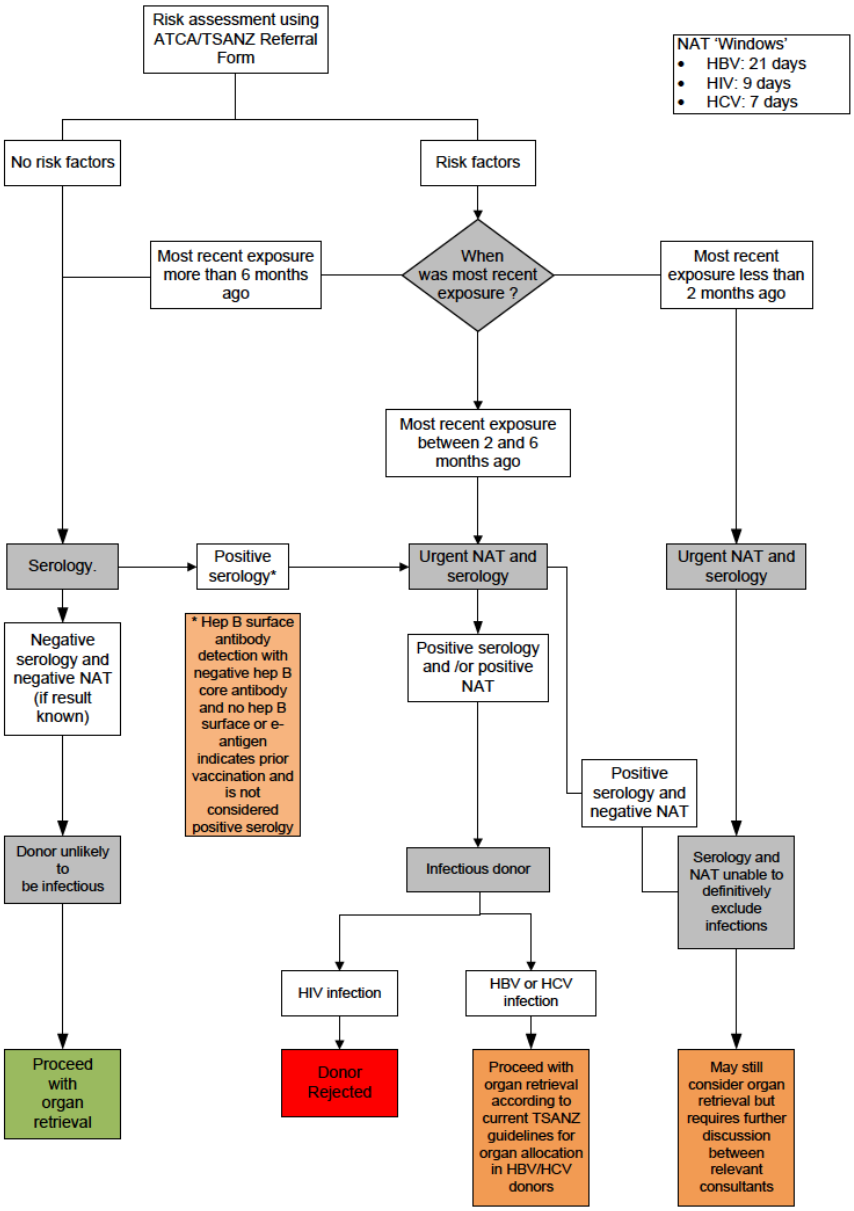
471. Consent to Medical Treatment - Patient Information. Ministry of Health, New South Wales: Sydney, 2005.

472. Gordon, E.J., et al., Effect of a Mobile Web App on Kidney Transplant Candidates' Knowledge About Increased Risk Donor Kidneys: A Randomized Controlled Trial. Transplantation, 2017. 101(6): p. 1167-1176.

473. Reese, P.P., et al. Transplanting Hepatitis C-Positive Kidneys. N Engl J Med, 2015. 373(4): p. 303-5.

8. APPENDICES

8.1. NSW blood borne virus testing algorithm



Source: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2013_029.pdf (last accessed 14 May 2018)

8.2. Search strategies

Search strategies

Pathogen-related search terms	
Viral pathogens	1. exp HIV/ 2. (human immunodeficiency virus$ or hiv).tw 3. exp hepatitis b/ or exp hepatitis c/ or exp hepadnaviridae infections/ 4. (hepatits b or hepatitis c or hbv or hcv or hepadnaviridae.tw) 5. exp Human T-lymphotropic virus 1/ 6. (t cell leuk?emia virus 1 or t cell leuk?emia virus I or htlv 1 or htlv i).tw 7. (t adj3 lymphotropic virus 1 or t adj3 lymphotropic virus i).tw 8. exp Influenza, Human/ 9. (influenza or flu).tw 10. exp herpesvirus 1, human/ or exp herpesvirus 2, human/ 11. (hsv 1or hhv 1).tw 12. (herpes$ adj4 virus).tw 13. exp Cytomegalovirus/ 14. (hhv 5 or herpesvirus 5 or cytomegalovirus$).tw 15. (salivary gland adj3 virus$).tw 16. exp Herpesvirus 4, Human/ 17. ("e$ b$ virus$" or ebv or epstein barr).tw 18. (hhv 4 or herpes$ 4 or mononucleosis adj virus$).tw 19. (burkitt$ adj2 herpes$ or burkitt$ adj2 lymphoma).tw 20. exp exp Arenavirus/ 21. (lcm virus$ or lcmv or lymphocytic choriomeningitis virus$ or arenavirus).tw 22. exp Rabies virus/ or exp West Nile virus/ or exp Parvoviridae/ or exp Zika Virus/ 23. exp West Nile Fever/ or exp Zika Virus Infection/ 24. (rabies or west nile virus or parvovirus or zika).tw.
Bacterial pathogens	1. exp Mycobacterium tuberculosis/ 2. (tuberculosis or mycobacterium).tw. 3. exp Enterococcus/ 4. enterococc$.tw. 5. exp Staphylococcus/

	6. staphylococc$.tw. 7. exp Escherichia coli/ 8. (escherichia coli or e? coli).tw. 9. exp Drug Resistance, Bacterial/ 10. (mrsa or mdro or vre or vancomycin?resistant enterococc$ or vancomycin resistant enterococc$ or methicillin? resistant staphylococc$).tw. 12. exp Gram-Negative Bacteria/ 13. (acinetobacter or brucella or ehrlichia or klebsiella or legionella or pseudomonas or veillonella or L? pneumophila or P? aeruginosa).tw. 14. exp Treponema pallidum/ 15. (treponema pallidum or t? pallidum).tw. 16. exp Neisseria meningitidis/ 17. (n$ meningitidis or meningococc$).tw. 18. exp Listeria/ or exp Nocardia/ or exp Streptococcus/ 19. (listeria or nocardia or streptococc$).tw. 20. or/1-19 21. limit 20 to humans
Fungi	1. exp Aspergillus/ 2. aspergill$.tw. 3. exp Candida/ 4. candida.tw. 5. exp Cryptococcus neoformans/ 6. cryptococc$.tw. 7. exp Histoplasma/ 8. histoplasm$.tw. 9. exp Scopulariopsis/ 10. exp Scopulariopsis/ 11. exp Zygomycosis/ 12. zygomycetes.tw. 13. exp entomophthorales/ or exp mucorales/ 14. or/1-13 15. limit 14 to humans
Parasites	1. exp Toxoplasma/ 2. toxoplasma gondi$.tw. 3. exp plasmodium falciparum/ or exp plasmodium malariae/ or exp plasmodium ovale/ or exp plasmodium vivax/ 4. (plasmodium falciparum or malaria$ or plasmodium ovale or plasmodium vivax).tw 5. exp Strongyloides/ or exp Naegleria fowleri/ or exp Scedosporium/ or exp Schistosomiasis/ or exp Trypanosoma cruzi/ or exp Balamuthia mandrillaris/ or exp Babesia/ 6. (strongyloides or naegleria fowleri or scedosporium or schistosom$ or

	trypanosom$ or b$ mandrillaris or babesi$ or nuttallia).tw 7. or/1-6 8. limit 7 to humans
Prions	1. exp Prions/ 2. exp creutzfeldt-jakob syndrome/ or exp gerstmann-straussler-scheinker disease/ or exp insomnia, fatal familial/ or exp kuru/ or exp wasting disease, chronic/ 3. creutzfeldt jakob.tw. 4. gerstmann straussler.tw. 5. spongiform encephalopath$.tw. 6. fatal familial insomnia.tw. 7. kuru.tw. 8. or/1-7 9. limit 8 to humans

SEARCH STRATEGY: Case reports of transmission of pathogens from donors to recipients of solid organ transplants
1. viral/bacterial/fungi/parasite/prion search terms above 2. exp Virus Diseases/ or exp Bacterial Infections/ and Mycoses or exp Parasitic Diseases/ 3. 1 and 2 4. exp Organ Transplantation/ 5. (recipient$ adj5 transplant$).tw 6. (organ adj3 don$).tw 7. (organ adj3 transplant$).tw 8. (donor adj5 deriv$).tw 9. (transmi$ adj5 donor$).tw 10. or/4-9 11. 3 and 10 12. limit 11 to humans

8.3. VTRTAC consent form: increased viral risk donors

Information and Consent for Accepting a Kidney Transplant from an Increased Viral Risk Donor

People with kidney failure waiting for a deceased donor kidney transplant can choose to be added to a second waiting list, in addition to the standard waiting list. This second waiting list is for patients who have decided to accept kidney transplants from donors who are at increased risk of having viral infections. These infections include the hepatitis B, hepatitis C and human immunodeficiency (HIV) viruses. HIV is the virus that causes acquired immune deficiency syndrome (AIDS).

Choosing to go onto this increased viral risk donor waiting list is entirely your personal decision. This decision will depend on the level of risk you are willing to accept. If you choose not to accept a kidney transplant from these donors, your place on the standard waiting list and your care by the transplant team will not be affected. Even if you sign this consent form, you will still have the opportunity to decline a kidney transplant from an increased viral risk donor at the time it is offered to you.

Which donors are increased viral risk donors?

Increased viral risk donors have had behaviours before their death which increase their risk of having hepatitis B, hepatitis C or HIV infections. Some examples of these increased risk behaviours include injecting non-medical drugs and higher risk sexual behaviours.

Routinely, increased viral risk donors have screening tests performed for hepatitis B, hepatitis C and HIV before donation. One of the tests is called a nucleic acid test (NAT). This test allows earlier detection of these infections when they are active in donors. If active infection from these viruses is detected in a donor using this test, transplant will not proceed. Only donors with negative NAT tests will be offered to the increased viral risk donor waitlist. Even though the NAT must be negative for the kidneys to be offered, there is still a small chance that these infections may be missed and transmitted from the donor to the recipient of the transplant.

What is the risk of catching blood borne viral infections from increased viral risk donors?

In international studies, the risk of hepatitis C infection from increased viral risk donors with negative screening tests is less than 1 in 100, and the risk of HIV infection is less than 1 in 1000. In the United States between 2009 and 2015, the risk of being infected with hepatitis B, hepatitis C or HIV after a transplant from these donors was 1 in 1150. There is also a risk of these infections being transmitted from standard risk donors (1 in 2780). If you receive a transplant from a donor with an active infection, it is almost certain that you will be infected with that virus. The risk in Australia is not known, but it is likely to be similar.

What are the potential benefits?

Increased viral risk donors are often younger than many of the standard donors. They may provide a kidney transplant with better than average function that may function for longer. These potential benefits may outweigh the increased risk of getting an infection from the donor. You should discuss this with your transplant team.

What tests are needed after the transplant?

Once you have received a kidney transplant from an increased viral risk donor, you will have blood tests within the first month to detect possible transmitted infections. Most transmitted infections are detected within the first month after the transplant.

What treatment is available if a virus is transmitted?

Medications to treat these infections are available. Hepatitis B infection can be controlled with long-term antiviral tablets. Most hepatitis C infections can now be cured with minimal side effects. HIV infection can usually be controlled with long-term medications. However, even with treatment, the outcome of kidney transplants in HIV infected patients tends to be less favourable than those without HIV infection. Removing the transplanted kidney does not cure the infection.

Online educational material

We strongly encourage you to visit Inform Me, a website developed by Northwestern University in Chicago (United States), for additional information and resources concerning increased viral risk donors. This will help you make an informed decision about whether this is the right decision for you.

The Inform Me website address is: https://informme.cbits.northwestern.edu/system/index.html

Some of the information presented by Inform Me does not apply in Australia. Specifically, in Australia:

The proportion of increased viral risk donors is likely to be lower than 20%.

Accepting a kidney from an increased viral risk donor may not allow you an earlier kidney transplant.

Hepatitis B, hepatitis C and HIV nucleic acid test (NAT), which allows earlier detection of these infections, will always be performed on donors.

The risk of being infected with Hepatitis C on haemodialysis is likely to be lower.

Please inform your transplant team if you have any questions or cannot access the website. Your transplant team may ask you if you have completed this education tool.

Can I remove myself from the increased viral donor waiting list?

If you agree to be added to the increased viral risk donor kidney transplant waiting list but later change your mind, you can request that the transplant team remove you from this waiting list. This will not affect your position on the standard waiting list.

PATIENT OR LEGAL REPRESENTATIVE CERTIFICATION

Dr _____ has discussed with me the potential risks and benefits of accepting a kidney transplant from an increased viral risk deceased donor. I have had the opportunity to ask any questions and these have been answered to my satisfaction. I understand that my place on the standard risk donor waiting list will not be affected by my decision to accept or decline a kidney transplant from an increased viral risk donor.

I, _____, consent to be placed on the waiting list for a kidney transplant from an increased viral risk deceased donor.

Signature of Patient/ Legal Representative _____ Date _____

Relationship to Patient (if consent is given by other than patient) _____

□ I have been given a copy of this consent form for my records.

Signature of Doctor _____ Date _____

Interpreter's name (if used) _____ Signature _____