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MAJOR ARTICLE

Notifiable Infectious Diseases Among Organ Transplant Recipients: A Data-Linked Cohort Study, 2000–2015

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Background. Infections, including common communicable infections such as influenza, frequently cause disease after organ transplantation, although the quantitative extent of infection and disease remains uncertain.

Methods. A cohort study was conducted to define the burden of notifiable infectious diseases among all solid organ recipients transplanted in New South Wales, Australia, 2000–2015. Data linkage was used to connect transplant registers to hospital admissions, notifiable diseases, and the death register. Standardized incidence ratios (SIRs) were calculated relative to general population notification rates, accounting for age, sex, and calendar year. Infection-related hospitalizations and deaths were identified.

Results. Among 4858 solid organ recipients followed for 39 183 person-years (PY), there were 792 notifications. Influenza was the most common infection (532 cases; incidence, 1358 [95% CI, 1247–1478] per 100 000 PY), highest within 3 months posttransplant. Next most common was salmonellosis (46 cases; incidence, 117 [95% CI, 87–156] per 100 000 PY), then pertussis (38 cases; incidence, 97 [95% CI, 71–133] per 100 000 PY). Influenza and invasive pneumococcal disease (IPD) showed significant excess cases compared with the general population (influenza SIR, 8.5 [95% CI, 7.8–9.2]; IPD SIR, 9.8 [95% CI, 6.9–13.9]), with high hospitalization rates (47% influenza cases, 68% IPD cases) and some mortality (4 influenza and 1 IPD deaths). By 10 years posttransplant, cumulative incidence of any vaccine-preventable disease was 12%, generally similar by transplanted organ, except higher among lung recipients. Gastrointestinal diseases, tuberculosis, and legionellosis had excess cases among transplant recipients, although there were few sexually transmitted infections and vector-borne diseases.

Conclusions. There is potential to avoid preventable infections among transplant recipients with improved vaccination programs, health education, and pretransplant donor and recipient screening.

Keywords. solid organ transplantation; immunosuppression; vaccine-preventable infections; gastrointestinal infections; sexually transmitted infections.

Infections are a significant cause of morbidity [1] and mortality among organ transplant recipients, causing the death of nearly 20% of kidney recipients [2]. Solid organ recipients have the highest infection risk for 6 months posttransplant and are closely monitored for opportunistic infections (eg, *Pneumocystis jirovecii*), donor-derived infections (eg, hepatitis C), latent infections reactivating (eg, cytomegalovirus), and site-specific infections (eg, urinary tract infections post–kidney transplant) [3]. However, particularly long-term, infections that are common in the general population are also important for recipients. Common communicable pathogens, such as influenza [4], *Streptococcus pneumoniae* [5], or gastrointestinal organisms [6], can cause disease more frequently or severely among transplant recipients than the general population, with associated impacts on health systems [7, 8]. Rates of infections beyond 6–12 months posttransplant are inadequately described.

International [9], national [10], and local public health authorities conduct case surveillance of diseases of public significance in order to track diseases and target prevention efforts. In Australia, a National Notifiable Disease Surveillance System (NNDSS) collates state-based registers including the New South Wales (NSW) notifiable conditions information management system (NCIMS). Registers collect mandatory pathology or clinician reports of >50 communicable diseases [11], including selected blood-borne diseases, gastrointestinal diseases, quarantinable diseases, sexually transmitted infections (STIs), vaccine-preventable diseases, vector-borne disease, zoonoses, and other bacterial infections.

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Although most (94%) hospitalizations and deaths due to communicable diseases in Australia are from nonnotifiable diseases [12], notifiable conditions are of public health importance and often have known preventive strategies. Understanding the epidemiology of notifiable infectious diseases within the vulnerable transplant recipient population informs the relative importance of these preventive strategies, including the potential to reduce hospitalizations and deaths. For instance, while vaccinations are internationally recommended for transplant recipients [13, 14], optimum vaccination strategies are still being refined given suboptimal immune responses to standard-dose vaccines [15]. In Australia, recommended vaccinations for solid organ recipients include hepatitis B, human papillomavirus, influenza (twice in first year posttransplant then yearly), pneumococcus (13-valent conjugate vaccine, then 2 doses of 23-valent polysaccharide vaccine), and diphtheria-tetanus-pertussis [16], Poor uptake of vaccinations has been documented among organ recipients internationally [17, 18]. For other preventable infections, guidance on lifestyle measures to reduce infection risk is less evidence-based for transplant recipients [19, 20]. Both the provision of information to patients and patient adherence to recommendations vary [21, 22].

Data linkage of all transplant recipients to routinely collected health administrative data allows a long period of follow-up, to inform knowledge gaps about the epidemiology of infections posttransplant. We aimed to quantify the burden of notifiable infectious diseases in an Australian cohort of transplant recipients compared with the general population.

METHODS

A cohort study was performed among all solid organ recipients in NSW, Australia, transplanted from 2000 to 2015. This was used to estimate the burden of notifiable infectious diseases compared to the general population.

Study Design

Prospectively collected data in several state-based datasets were linked to form a comprehensive database of solid organ transplant recipients. The NSW Ministry of Health Biovigilance Public Health Register (SAFEBOD), described elsewhere [23], links transplant registers to administrative health data for all solid organ recipients in NSW (Supplementary Figure 1). SAFEBOD was initiated under the NSW Public Health Act and has ethical oversight from the University of Sydney Human Research Ethics Committee (project number 2016/758). In brief, deterministic and probabilistic data linkage were undertaken by the Centre for Health Record Linkage using best-practice privacy-preserving protocols. Matching was based on identifiers including name, sex, date of birth, postcode, and treating hospital. The error rate of linkage was estimated at <0.5% (maximum 5/1000 false positive or false negatives) [24]. Only de-identified data were available to researchers.

Study Population

Organ transplantation in Australia is coordinated at the state level. NSW, the most populous state, has 6 kidney transplant centers, 1 liver transplant center, and 1 lung/heart transplant center. In 2020, 379 organs were transplanted [25]. This study included all solid organ recipients resident in NSW transplanted between 1 January 2000 and 31 December 2015. Donor organs came from NSW and other states. Living and deceased donor transplants were included.

Characteristics of recipients included date of birth, sex, transplant date, and organs transplanted. Administrative health data of recipients were available until 31 December 2016 and included diagnostic codes, hospital and intensive care (ICU) admission dates, and dates and causes of death. To ascertain notifiable diseases occurring in recipients, the NSW-based NCIMS was used. All notifiable disease cases are reported under mandate by community and hospital pathology laboratories (who provide 99% of reports) and/or by doctors. Defined case criteria are applied, with duplicate records continuously sought and removed. Completeness of case ascertainment is expected to vary with disease type, severity, and diagnostic method (eg, mild influenza cases that do not seek medical attention will not be notified). Case data included infection type and site, disease onset date, and diagnosis method. Data for the general population were collated from publicly available NNDSS summary data [11]. Vaccination status was reported by NCIMS for some cases. However, full recipient vaccination data were unavailable as vaccines are typically administered in primary care and these data are not routinely collected.

Outcomes

The primary outcome was the incidence of notifiable infectious diseases. Secondary outcomes included hospitalizations, ICU admissions, and deaths following these infections.

Definitions

Notifiable infectious diseases reported between 2000 and 2016 were included, covering specified vaccine-preventable diseases, gastrointestinal diseases, STIs, vector-borne diseases, zoonoses, listed human diseases, and other bacterial infections (Table 1). Diseases that were not reportable in NSW or within the study period were excluded (campylobacteriosis, varicella zoster virus infection, respiratory syncytial virus) as case data were not available. Hepatitis B, hepatitis C, and human immunodeficiency virus were excluded as we have previously analyzed and reported these infections among this population [26]. Notified conditions not related to infectious diseases were excluded (lead poisoning).

Confirmed cases of notifiable disease were identified among recipients after transplant. To attribute a hospitalization or death to a specific infectious disease, the diagnosis codes for the healthcare episode listed a relevant infection *International*

Statistical Classification of Diseases and Related Health Problems, Tenth Edition, Australian Modification (*ICD-10-AM*) code (Supplementary Table 1). Hospitalizations were counted when notifications occurred within the hospitalization period or in the preceding 14 days.

Statistical Analyses

Demographic and clinical characteristics were compared between recipients with at least 1 notifiable disease and those without any notifiable diseases using χ^2 tests for categorical outcomes and Wilcoxon rank-sum test for continuous outcomes.

Infectious disease incidence rates per 100 000 person-years (PY) were estimated using multiple event survival analysis for each disease notification; recipients were observed from date of first transplant to date of death or end of follow-up (31 December 2016). Cumulative incidence was reported for disease groups with at least 50 notifications. Disease incidence among transplant recipients was compared with the general population using standardized incidence ratios (SIRs), estimated for each infection using indirect standardization, by age, sex, and calendar year. Statistical analyses were conducted in Stata 14.2 software (StataCorp, College Station, Texas).

Table 1. Infectious Diseases Included in Our Cohort Study That Were Notifiable by Mandate for at Least Some of the Time Period 2000–2016[a]

Category	Infections (Years of Mandated Notification)
Vaccine-preventable diseases	Diphtheria, Hib (invasive), influenza (2001+), measles, mumps, pertussis, poliomyelitis, IPD (2001+), rubella, and tetanus
Gastrointestinal diseases	Botulism, cryptosporidiosis (2001+), cholera, hepatitis A, hepatitis E, giardiasis[b], listeriosis, rotavirus infection (2010+), salmonellosis, STEC infection/HUS, shigellosis, and typhoid fever
Sexually transmitted infections	Chlamydia, chancroid, donovanosis, gonococcal infection, lymphogranuloma venereum (2001+), and syphilis (2004+)
Vector-borne diseases and zoonoses	Anthrax (2001+), Barmah Forest virus infection, brucellosis (2015+), chikungunya virus infection (2008+), dengue virus infection, *Flavivirus* infection, Hendra virus infection (2012+)[b], Japanese encephalitis virus infection (2001+), Kunjin virus infection (2001+), leptospirosis, *Lyssavirus* infection (2001+), malaria, Murray Valley encephalitis virus infection (2001+), psittacosis/ornithosis, Q fever, Ross River virus infection, tularemia (2003+), Zika virus
Listed human diseases	Creutzfeldt-Jakob disease (2004+), MERS-CoV, plague, SARS, smallpox (2003+), viral hemorrhagic fevers, and yellow fever
Other bacterial infections	Acute rheumatic fever (2001+)[b], legionellosis, leprosy, invasive meningococcal disease, rheumatic heart disease (<35 years old)[b], and tuberculosis

Notifiable conditions not included in this study were blood-borne viruses (hepatitis B, C, and D, reported elsewhere [26]); conditions only monitored from 2017 onward (eg, respiratory syncytial virus); conditions not reportable in New South Wales (campylobacteriosis, varicella zoster virus); and noninfectious notifiable conditions (lead poisoning).

Abbreviations: Hib, *Haemophilus influenzae* type b; HUS, hemolytic uremic syndrome; IPD, invasive pneumococcal disease; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome; STEC, Shiga-toxigenic *Escherichia coli*.

[a]Indicated by bracketed dates when notification was for part of the period only.

[b]Conditions indicated are reportable in New South Wales but not nationally and were included in this study.

RESULTS

Cohort Characteristics

There were 4858 solid organ recipients of 4968 organs during 2000–2015, followed for 39 183 PY (median, 7.5 PY). Most were males (63%) and kidney recipients (65%) (Table 2). The median age at transplant was 50 years (interquartile range [IQR], 36–58 years), with only 352 (7%) recipients <18 years of age.

At least 1 notifiable infectious disease was reported for 663 of 4858 recipients (14%). Recipients with notifiable diseases were younger than recipients without a notifiable disease (median age, 42 vs 50 years; $P < .001$). Although lung recipients formed only 11% of the total cohort, they were overrepresented (22%) among recipients with notifiable infections. Some transplant recipients had >1 infection notified; there were 792 notifications among these 663 recipients. Most notifications were vaccine-preventable diseases, predominantly influenza, followed by gastrointestinal diseases. There were few cases of STIs, vector-borne diseases, or other bacterial infections.

Table 2. Participant Characteristics by Recipients With and Without Notifiable Infectious Disease

Characteristic	Recipients With At Least 1 Notification (Column %)	Recipients Without Notifiable Infectious Disease (Column %)	All Recipients (Column %)
No. (row %)	663 (14)	4195 (86)	4858 (100)
Sex			
Male	380 (57)	2673 (64)	3053 (63)
Female	283 (43)	1522 (36)	1805 (37)
Age at transplant, y			
Median (IQR)	42 (25–55)	50 (37–59)	50 (36–58)
<18	112 (17)	240 (6)	352 (7)
18–34	143 (22)	628 (15)	771 (16)
35–44	106 (16)	673 (16)	779 (16)
45–54	124 (19)	1074 (26)	1198 (25)
55–64	142 (21)	1175 (28)	1317 (27)
≥65	36 (5)	405 (10)	441 (9)
Organ type			
Kidney	373 (56)	2767 (66)	3140 (65)
Liver	99 (15)	782 (19)	881 (18)
Lung	145 (22)	388 (9)	533 (11)
Heart	56 (8)	286 (7)	342 (7)
Pancreas	11 (2)	61 (1)	72 (1)
Year transplanted			
2000–2003	147 (22)	786 (19)	933 (19)
2004–2007	169 (26)	927 (22)	1096 (23)
2008–2011	198 (30)	1101 (26)	1299 (27)
2012–2015	149 (22)	1381 (33)	1530 (31)

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range.

Table 3. Incidence of Notifiable Infectious Diseases Among Solid Organ Transplant Recipients

Disease	Notifications/ Recipients, no./ No.[a]	Age, y, Median (IQR)	Incidence Rate per 100 000 PY (95% CI)	SIR (95% CI)	Hospitalization, No. (% Notification)	ICU Admission, No. (% Hospitalization)	LOS,d, Median (IQR)	Deaths, No. (% Notification)
Vaccine-preventable diseases								
Influenza[b]	532/461	45 (27–59)	1358 (1247–1478)	8.5 (7.8–9.2)	250 (47)	29 (12)	4 (3–9)	4 (1)
Mumps	1/1	63 (NA)	2.6 (.4–18.1)	2.5 (.3–17.5)	0 (0)	…	…	0 (0)
Pertussis	38/38	46 (32–57)	97 (71–133)	1.4 (1.0–1.9)	4 (11)	0 (0)	6 (4–10)	0 (0)
Pneumococcal disease[b,c]	31/28	45 (29–45)	79 (56–113)	9.8 (6.9–13.9)	21 (68)	6 (29)	6 (4–10)	1 (3)
Gastrointestinal diseases								
Cryptosporidiosis[b]	32/31	36 (21–50)	81 (57–115)	12.0 (8.5–17.0)	14 (44)	1 (7)	9 (3–14)	0 (0)
Giardiasis	33/33	46 (36–61)	84 (60–118)	3.4 (2.4–4.7)	11 (33)	0 (0)	4 (3–11)	0 (0)
Listeriosis	5/5	61 (57–64)	13 (5–31)	34.1 (14.2–82.0)	0 (0)	…	…	0 (0)
Rotavirus (2010+)	26/25	10 (4–38)	66 (45–97)	11.0 (7.5–16.2)	14 (54)	0 (0)	4 (2–9)	0 (0)
Salmonellosis	46/46	45 (29–56)	117 (87–156)	2.8 (2.1–3.7)	0 (0)	…	…	0 (0)
Shigellosis[b]	2/2	55 (39–71)	5.1 (1.3–20.3)	1.6 (.4–6.6)	0 (0)	…	…	0 (0)
Sexually transmitted infections								
Chlamydia	5/4	34 (22–49)	13 (5–30)	0.1 (.0–.2)	0 (0)	…	…	0 (0)
Gonococcal infection	4/4	40 (35–46)	10 (4–27)	0.2 (.1–.6)	0 (0)	…	…	0 (0)
Syphilis (2004+)	7/7	54 (42–66)	18 (9–37)	2.0 (1.0–4.3)	2 (29)	0 (0)	10 (9–11)	0 (0)
Vector-borne diseases and zoonoses								
Ross River virus infection	4/4	57 (53–62)	10 (4–27)	0.4 (.1–.9)	0 (0)	…	…	0 (0)
Psittacosis	2/2	52 (45–58)	5.1 (1.3–20.3)	9.0 (2.3–36.1)	0 (0)	…	…	0 (0)
Other bacterial infections								
Legionellosis	8/8	56 (53–64)	20 (10–41)	7.5 (3.7–15.0)	5 (63)	1 (20)	16 (13–19)	0 (0)
Meningococcal disease[c]	1/1	58 (NA)	2.5 (.4–18.0)	3.7 (.5–26.1)	0 (0)	…	…	0 (0)
Tuberculosis	15/15	59 (32–66)	38 (23–63)	6.8 (4.1–11.2)	8 (53)	2 (25)	16 (14–33)	1 (7)

% notification: percentage of all notifications for that infection; % hospitalization: percentage of all hospitalizations for that infection.

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; PY, person-years; SIR, standardized incidence ratio.

[a]Each recipient may have multiple case notifications.

[b]All diseases reported from 2000 to 2016 unless otherwise specified, except where "b" indicates no data were collected for 2000.

[c]Refers to invasive pneumococcal disease and invasive meningococcal disease.

Vaccine-Preventable Diseases

Influenza had by far the highest incidence of all notifiable infectious diseases posttransplant at 1358 (95% confidence interval [CI], 1247–1478) per 100 000 PY (Table 3). Most recipients (399/461) with influenza only had it once, but 55 of 461 were affected twice, and 7 recipients 3–4 times. Pertussis was the second most common vaccine-preventable disease with an incidence of 97 (95% CI, 71–133) cases per 100 000 PY, followed by invasive pneumococcal disease (IPD) at 79 (95% CI, 56–113) cases per 100 000 PY. There was only 1 case of mumps, and no cases of diphtheria, invasive *Haemophilus influenzae* type b infection, measles, poliomyelitis, rubella, or tetanus.

Compared with the general population, organ recipients were 8.5 times as likely to be diagnosed with influenza (SIR, 8.5 [95% CI, 7.8–9.2]) and 9.8 times as likely to be diagnosed with IPD (SIR, 9.8 [95% CI, 6.9–13.9]) (Figure 1). Many influenza (47%) and IPD (68%) cases were hospitalized, with the median length of stay 4 days for influenza and 6 days for IPD. Hospitalizations were sometimes associated with an ICU admission (12% influenza, 29% IPD). There were 4 deaths due to influenza (1% of cases) and 1 death (3% of cases) due to IPD. Recipients also experienced excess pertussis cases, occurring at a rate closer to the general population (SIR, 1.4 [95% CI, 1.0–1.9]), with an 11% hospitalization rate.

Excess cases of influenza dropped substantially over time, with the SIR reducing from 40.4 (95% CI, 22.4–73.0) in 2001–2004 to 6.6 (95% CI, 5.9–7.4) in 2013–2016 (Figure 2). Excess cases of pertussis also decreased over time and reached

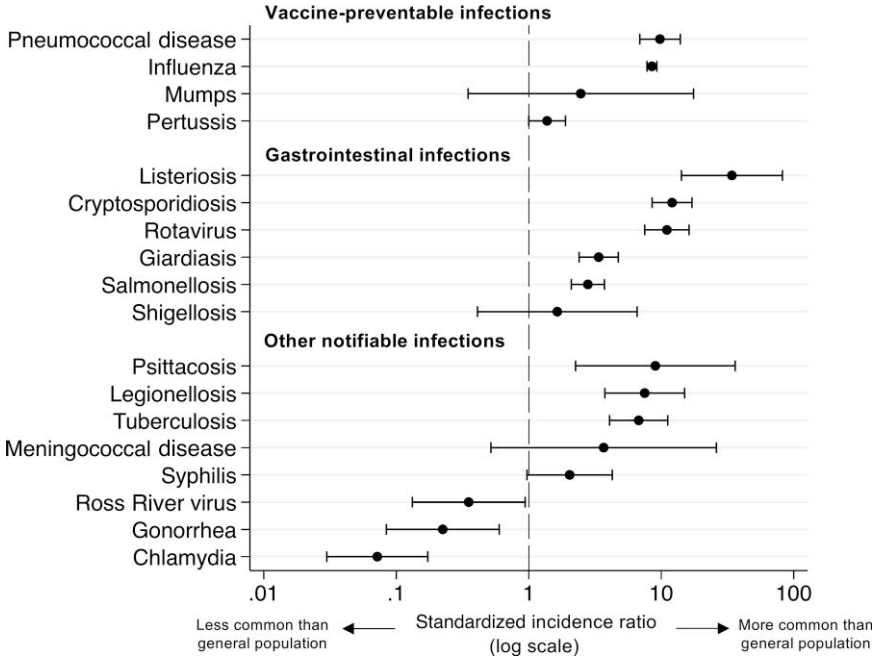


Figure 1. Standardized incidence ratios with 95% confidence intervals of infections after transplant.

general population rates from 2009 to 2012. Change in excess cases over time was less evident for IPD.

Vaccination status was poorly available (unknown for >95% cases). However, vaccination status was recorded for 16 of 28 (57%) patients with IPD, with 18 infections; only 44% (7/16) were vaccinated. The 11 infections in 9 unvaccinated recipients were associated with higher hospitalization rates than the 7 infections in vaccinated recipients (82% vs 29%; $P = .03$).

Influenza incidence was highest in the first 3 months posttransplant (3047 [95% CI, 2208–4205] per 100 000 PY) (Figure 3). However, the cumulative incidence of vaccine-preventable diseases continued to increase with time (Figure 4*A*). By 10 years, 12% of recipients had experienced at least 1 vaccine-preventable disease. Influenza incidence was higher among lung transplant recipients than other organ recipients (Supplementary Table 2). Nearly 30% of lung recipients experienced a vaccine-preventable disease (mainly influenza) by 10 years posttransplant (Figure 4*B*). Younger organ recipients (≤29 years) had both higher influenza incidence and SIR than older recipients. Influenza type was poorly recorded (58% not otherwise specified), but influenza A was more common than influenza B (35% vs 6%).

Gastrointestinal Diseases

Salmonellosis was the second most common notifiable infectious disease and most common infectious gastrointestinal disease (incidence, 117 [95% CI, 87–156] per 100 000 PY). There were no cases of botulism, cholera, hepatitis A or E, Shiga-toxigenic *Escherichia coli*/hemolytic uremic syndrome, or typhoid fever.

All reported gastrointestinal diseases occurred more commonly than in the general population, except shigellosis, which was rare (Figure 1). Listeriosis had the highest SIR of any notifiable infectious disease (SIR, 34.1 [95% CI, 14.2–81.9]), followed by cryptosporidiosis (SIR, 12.1 [95% CI, 8.5–17.1]) and rotavirus infection (SIR, 11.0 [95% CI, 7.5–16.2]). The median age of rotavirus infection was low at 10 (IQR, 4–38). Giardiasis, cryptosporidiosis, and rotavirus infection had high hospitalization rates (33%–54%), but rarely resulted in ICU admissions and caused no deaths. By 10 years posttransplant, 3.4% of recipients (95% CI, 2.8–4.3) experienced a notifiable gastrointestinal infection (Figure 4*A*). Rates did not vary substantially by organ type.

Sexually Transmitted Infections

Sexually transmitted infections were rare, with few cases of chlamydia, gonorrhea, and syphilis. There was no chancroid, donovanosis, or lymphogranuloma venereum. Chlamydia and gonorrhea occurred less often than expected (chlamydia: SIR, 0.1 [95% CI, .0–.2]; gonorrhea: SIR, 0.2 [95% CI, .1–.6]); however, syphilis showed a slight excess in cases (SIR, 2.0 [95% CI, 1.0–4.3]). Many syphilis cases (29%) were associated with hospitalization, with significant lengths of stay (median, 10 days). Reactivation vs newly acquired syphilis could not be distinguished, as all cases were of unknown duration when notified.

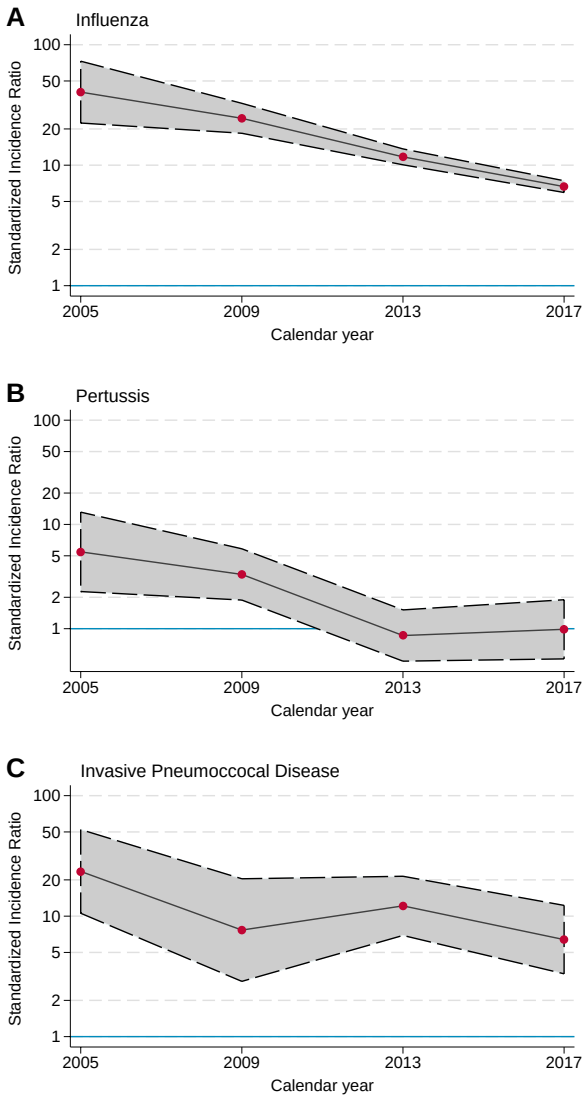


Figure 2. Standardized incidence ratio by calendar year (preceding 4-year periods) for influenza (*A*), pertussis (*B*), and invasive pneumococcal disease (*C*). Blue line indicates the comparable to expected rate in general population.

Vector-Borne Diseases, Zoonoses, and Listed Human Diseases

Vector-borne diseases and zoonoses were also uncommon, with only 2 cases of psittacosis and 4 cases of Ross River virus infection recorded. Despite the few events, psittacosis occurred more often than expected (SIR, 9.0 [95% CI, 2.3–36.1]).

There were no cases of anthrax, Barmah Forest virus infection, brucellosis, chikungunya virus infection, dengue virus infection, *Flavivirus* infection, Hendra virus infection, Japanese encephalitis virus infection, Kunjin virus infection, leptospirosis, *Lyssavirus* infection, malaria, Murray Valley encephalitis virus infection, Q fever, tularemia, Zika virus infection, Creutzfeldt-Jakob disease, Middle East respiratory syndrome coronavirus, plague, severe acute respiratory syndrome, smallpox, viral hemorrhagic fevers, or yellow fever.

Other Bacterial Infections

Tuberculosis and legionellosis occurred infrequently but more commonly than in the general population (tuberculosis: SIR, 6.8 [95% CI, 4.1–11.2]; legionellosis: SIR, 7.5 [95% CI, 3.7–15.0]). Both were associated with high hospitalization rates (53%–63%), with median lengths of stay of 16 days, and some ICU admissions (20%–25%). There was 1 death attributed to tuberculosis. There was 1 case of invasive meningococcal disease and no cases of acute rheumatic fever, leprosy, or rheumatic heart disease (<35 years of age).

DISCUSSION

This study describes excess cases and health system impacts of notifiable infections among transplant recipients, including some rarely described elsewhere, and highlights opportunities for health promotion in this vulnerable group.

The excess burden of influenza and IPD highlights the importance of vaccinations for transplant recipients. Influenza risk was high immediately after transplant, but continued thereafter, suggesting the importance of ongoing vaccinations. Those at highest risk of influenza, hence the groups to target for prevention, were lung recipients and younger recipients, as in other studies [7, 27]. Higher rates of influenza among lung recipients may reflect increased testing for respiratory pathogens. Age-related differences may reflect vaccination rates, given that among "at risk" Australians aged 18–49 years in 2014, only 9.4% were vaccinated against influenza, compared with 45.3% of those aged >65 years [28]. Strategies for influenza vaccination posttransplant are debated, including high-dose or 2-dose vaccination regimens, as recipients may not mount adequate immune responses [15]. Pneumococcal vaccination recommendations also require further study [13, 29]. Our limited data suggest vaccination reduced IPD hospitalizations. Interestingly, the overall influenza case fatality rate was lower than reported elsewhere (0.75% vs 3.2%) [30]. This may reflect the relatively high proportion of cases in younger patients, differences in case identification (with this data-linkage study likely identifying less severe cases than those recruited from tertiary centers prospectively), and differences in attribution of death (our study uses *ICD-10-AM* codes to define deaths related to infection, rather than all-cause mortality).

Although already recommended by guidelines [31], our work adds emphasis to pertussis vaccination posttransplant, which is likely underreported elsewhere among organ recipients [32]. The reduction in excess influenza and pertussis cases over time could indicate improved vaccination, but this needs dedicated study. Changes in diagnostic techniques over time (from rapid antigen testing/viral culture to molecular testing) may increase the sensitivity or uptake of background community testing. Transplant recipient adherence to vaccination recommendations elsewhere are variable but have not been

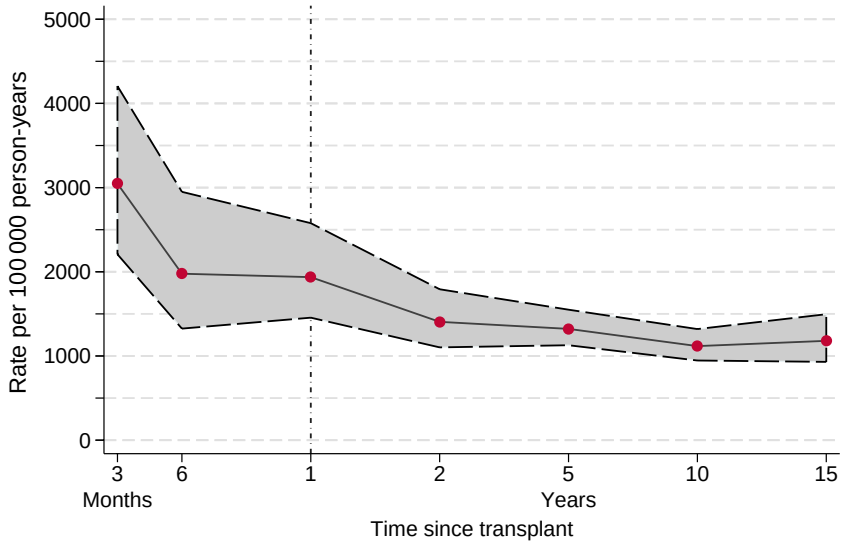


Figure 3. Incidence rates of influenza at time posttransplantation.

reported in Australia [18]. Strategies to improve adherence to vaccinations among recipients include infectious diseases consultation [33], vaccination clinics [34], and improved communication [17, 35]. Understanding vaccination uptake and effectiveness in this cohort is of increasing relevance with the coronavirus disease 2019 pandemic, and transplant clinicians should be attentive to the full range of vaccines during follow-up.

We describe excess recipient gastrointestinal disease from viral, parasitic, and bacterial pathogens. High SIRs of foodborne bacterial diseases, including salmonellosis, were recently identified in another recipient cohort [36]. Interestingly, this occurs despite recommendations for trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* pneumonia prophylaxis, which may impact infection rates [37]. For intestinal parasites or viruses, specific stool testing is required for diagnosis. Rotavirus is likely underestimated elsewhere as a cause of posttransplant diarrhea [38, 39] and affects more than infants. Health education could reduce incidence of infectious diarrhea [20], but there is currently no strong emphasis on food hygiene and hand hygiene in most clinical guidelines or patient information for solid organ recipients [19, 22]. A recent study on listeriosis notifications, mostly among immunocompromised persons, showed that most infected persons had recent exposure to high-risk foods, and few recalled receiving prior health education regarding food safety, suggesting room to improve health communication [40].

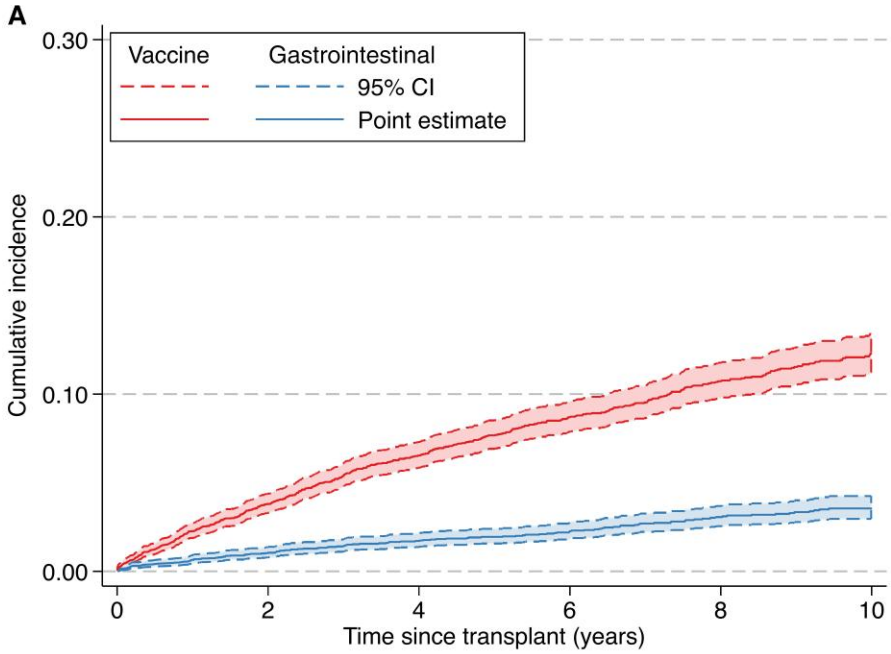
Legionellosis has known excess burden posttransplant [41], but psittacosis posttransplant has not been described. Recipients should be made aware of sources of and preventive behaviors for these infections, such as avoiding potting mix, evaporative air conditioners, spa baths, and birds [42].

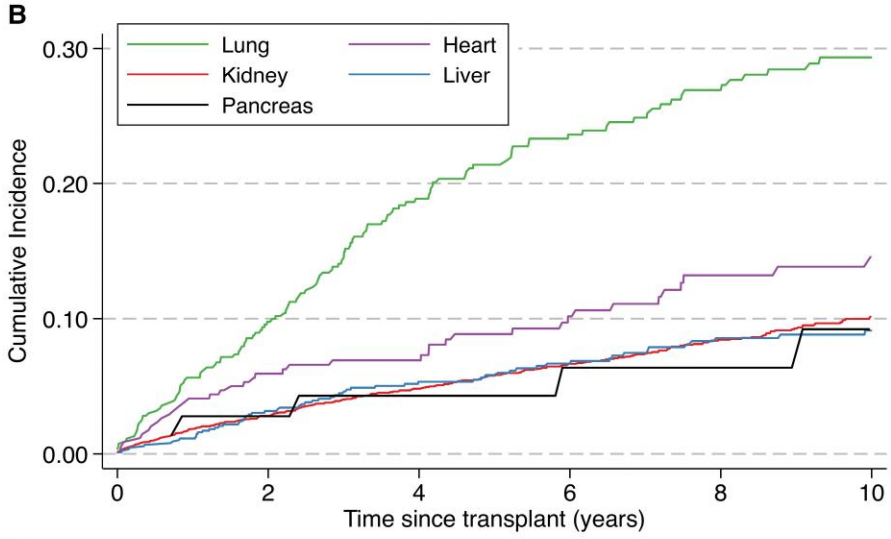
Excess tuberculosis (well-described posttransplant) and syphilis cases (no prior rate estimates posttransplant) may relate to latent disease that has reactivated, although new and donor-derived infections are also possible [43–45]. Screening of donors and recipients for latent or active infection prior to transplantation enables recipient pretransplant treatment or posttransplant chemoprophylaxis [46, 47].

Low rates of chlamydia and gonorrhea, among the 5 most common notifiable diseases in Australia, are also remarkable [12]. Some case series detected increased asymptomatic STIs among recipients [48]. Relatively low notification rates could reflect lack of asymptomatic testing. Other explanations could include risk-reduction behavior (safer sex) or reduced exposure from sexual dysfunction associated with underlying disease or transplantation itself [49].

This study gives important insights into the relative incidence and severity of preventable infections among solid organ transplant recipients. Such diseases are frequently underreported in the literature, typically limited to case studies with severe outcomes. Prospective registries provide detailed infection data but lack a control population for comparison [27, 50]. In contrast, this work is a population-based sample observed over a long time frame, with objective detection measures standardized to a control population that considers change over time.

Limitations include that notification rates are a surrogate for true incidence, as they only reflect detected incidence of infections from those who seek medical attention and are subsequently diagnosed. Higher notification rates among transplant recipients could reflect more symptomatic disease rather than higher incidence, which remains of clinical significance. Notification rates in transplant recipients may also be





C

At risk

All	4858	4246	3431	2788	2155	1634
Kidney	3140	2775	2246	1845	1421	1075
Liver	881	766	625	503	395	304
Lung	533	437	334	257	196	148
Heart	342	297	248	200	156	118
Pancreas	72	65	57	44	37	30

Figure 4. Cumulative incidence of infection after transplant. *A*, Vaccine-preventable and gastrointestinal infection among all recipients, with 95% confidence interval. *B*, Vaccine-preventable infections among recipients of each organ type. *C*, Numbers at risk for vaccine-preventable infections.

influenced by systematic differences in detection between recipients and the general population, due to higher rates of seeking medical care and test administration. Similarly, hospitalization rates may reflect more severe disease, more cautious medical care for immunosuppressed patients, or higher rates of hospitalization for other reasons. The nature of this study means some details of interest were not available, including vaccination status, education on risk factors, and specific exposures. Point estimates of incidence should be interpreted cautiously where case numbers were low. As infection

prevalence varies internationally, the incidences reported here are likely to vary from studies overseas; however, relative increases in incidence among transplant recipients compared with the general population rates would be expected to follow similar trends where immunosuppression and preventive strategies were similar. Importantly, nonnotifiable infectious diseases were not measured in this study, and notifiable infections are likely a minority of total recipient infectious disease burden [12, 50].

This study highlights areas where infection prevention may be improved for transplant recipients. We suggest a focus on improving vaccination rates and targeted research on optimum vaccination strategies, as well as education on food safety and other lifestyle modifications for immunosuppressed patients. Future studies should assess implementation of these strategies and develop clinician- and patient-focused interventions for improvement. Capturing all infections (including nonnotifiable infections) and assessing changes over time and across Australia would also be of interest.

There is potential to prevent burdensome infections among transplant recipients with improved vaccination programs (especially influenza and *Streptococcus pneumoniae*), health education (food and lifestyle safety), and donor and recipient screening for latent diseases.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. The design of this work has been approved by local ethics committees under the NSW Public Health Act and via the University of Sydney Human Research Ethics Committee (project number 2016/758). Written consent was waived due to the nature of this study.

Data availability. The data that support the findings of this study are not publicly available due to privacy and ethical restrictions. Reasonable requests to the corresponding author for access to data will be considered in conjunction with the relevant data custodians.

Disclaimer. Some of the data reported here have been supplied by ANZDATA. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of ANZDATA.

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