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Incidence of Hospitalization for Vaccine-Preventable Infections in Children Following Solid Organ Transplant and Associated Morbidity, Mortality, and Costs

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IMPORTANCE Pediatric transplant recipients are at risk for vaccine-preventable infections owing to immunosuppression, suboptimal response to vaccines before and after transplant, and potential underimmunization if transplant occurred early in life. However, the incidence and burden of illness from vaccine-preventable infections in this population is unknown.

OBJECTIVES To evaluate in pediatric solid organ transplant recipients the number of hospitalizations for vaccine-preventable infections in the first 5 years after transplant and to determine the associated morbidity, mortality, and costs.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study from January 1, 2004, to December 31, 2011, with 5 years of follow-up per participant (unless they died during the study period). The participants of this multicenter study through the Pediatric Health Information System were solid organ transplant recipients who were younger than 18 years at the time of transplant. Analysis began in July 2017.

EXPOSURES Transplant.

MAIN OUTCOMES AND MEASURES Hospitalizations for a vaccine-preventable infection during the first 5 years after transplant were ascertained using *International Classification of Diseases, Ninth Revision*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, clinical modification diagnosis codes. Data were collected on clinical care, outcomes, and costs during these hospitalizations.

RESULTS Of 6980 transplant recipients identified, there were 3819 boys (54.7%), and the mean (SD) age at transplant was 8 (6.2) years. Overall, 1092 patients (15.6%) had a total of 1490 cases of vaccine-preventable infections. There were 195 of 1490 cases (13.1%) that occurred during transplant hospitalization. The case fatality rate was 1.7% for all infections. Excluding infections that occurred during transplant hospitalization (when all patients go to the intensive care unit), 213 of 1257 patients (17.0%) were hospitalized with a vaccine-preventable infection requiring intensive care. In multivariable analysis, age younger than 2 years at time of transplant and receipt of a lung, heart, intestine, or multivisceral organ were positively associated with increased risk of a hospitalization from a vaccine-preventable infection.Transplant hospitalizations complicated by vaccine-preventable infections were $120 498 more expensive (median cost) than transplant hospitalizations not complicated by vaccine-preventable infections.

CONCLUSIONS AND RELEVANCE Hospitalization for vaccine-preventable infections occurred in more than 15% of solid organ transplant recipients in the first 5 years after transplant at a rate of up to 87 times higher than in the general population. There was significant morbidity, mortality, and costs from these infections, demonstrating the importance of immunizing all transplant candidates and recipients. Further research on improving immunization delivery, preventing nosocomial infections, and monitoring response to vaccines in the transplant population is needed.

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Supplemental content

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Infectious diseases are a well-known cause of morbidity and mortality in immunocompromised transplant recipients.[1] Some of these infections are potentially preventable by vaccines.[2-11] Unfortunately, many pediatric transplant recipients are not fully immunized at the time of transplant.[12-18] Additionally, transplant candidates with end-stage organ disease and transplant recipients taking immunosuppressive medications may not mount equal immune responses to immunizations as healthy individuals[19-22] and may also have a more rapid decrease in antibody titers than control populations.[23-28] For these reasons, pediatric solid organ transplant recipients are likely to be at increased risk for vaccine-preventable infections (VPIs).[10] However, the true incidence, morbidity, mortality, and costs of VPIs in pediatric solid organ transplant recipients remain unknown.

To address this critical gap in knowledge, we used the Pediatric Health Information System (PHIS) database to determine the incidence of hospitalizations for VPIs in the solid organ transplant population. As in our prior study focused on liver transplant recipients,[10] we chose to include respiratory syncytial virus (RSV) in patients younger than 2 years in this study. Although RSV is not truly a VPI (as there is no vaccine to prevent RSV), given that it is one of the most common infectious causes for hospitalization in children and that a monoclonal antibody (palivizumab) exists, which can reduce risk in select populations,[29] we felt it was important to include.

The goals of this study were to determine (1) the number of hospitalizations from RSV or a VPI in the pediatric solid organ transplant population in the first 5 years following transplant; (2) the morbidity, mortality, and costs associated with these hospitalizations; and (3) demographic and health factors that are associated with the number of infections (RSV or VPI) in the 5 years following transplant. We hypothesized that there would be a substantial number of hospitalizations for RSV or a VPI posttransplant with substantial morbidity, mortality, and costs and that certain subgroups of solid organ transplant recipients would be at greatest risk for RSV or a VPI.

Key Points

Question Are vaccine-preventable infections a common cause for hospitalization after pediatric solid organ transplant?

Findings In this multicenter cohort study of 6980 pediatric solid organ transplant recipients at a Pediatric Health Information System center, 16% of individuals had at least 1 hospitalization for a vaccine-preventable infection in the first 5 years after transplant. Children who received transplants when they were younger than 2 years and transplant recipients of lung, intestine, heart, and multivisceral organs were at increased risk for hospitalization with a vaccine-preventable infection.

Meaning Vaccine-preventable infections are common after pediatric transplant; therefore, maximal efforts must be made to ensure complete immunization of transplant candidates and recipients.

Methods

Pediatric Health Information System

We conducted a multicenter retrospective cohort study of pediatric solid organ transplant recipients using data from the PHIS. The PHIS (Children's Hospital Association, Kansas City, Kansas) is an administrative database that contains inpatient billing data from 45 not-for-profit tertiary care pediatric hospitals in the United States and includes data for more than 6 million children. On entry into the database, patients are deidentified and subsequently assigned a unique identification number allowing for longitudinal analyses across hospitalizations. The PHIS database includes patient demographics; *International Classification of Diseases, Clinical Modification, (ICD-CM)* diagnoses and Clinical Transaction Classification procedure codes; discharge disposition; and hospital charges. Data quality and reliability are assured jointly by the Children's Hospital Association and the participating hospitals.[30,31] In accordance with the Common Rule (45 CFR 46.102[f]) and the policies of the University of Colorado institutional review board, this study using a deidentified data set was not subject to institutional review board approval, and the need for informed consent was waived.

Study Participants

This analysis included all patients who were younger than age 18 years when they underwent a heart, lung, liver, kidney, intestine, or multivisceral transplant at a PHIS center between January 1, 2004, and December 31, 2011. Analysis began in July 2017. Transplant recipients were identified using *ICD-9-CM* procedural codes for transplant (eTable 1 in the Supplement). *ICD-9* codes were used for all hospital days that occurred before October 1, 2015; thereafter, *ICD-10* codes were used. All patients in the data set had the potential for 5 years of follow-up (unless they died during the 5-year period). Although we had data on child ethnicity (Hispanic/not Hispanic/unknown), given the large proportion of unknown (3077 [44%]), we did not include it in our analysis or modeling.

Outcome Variable

The primary outcome was hospitalization for RSV or a VPI in the first 5 years after transplant. Respiratory syncytial virus infections that occurred in children 2 years or older were excluded from the analysis. Hospitalizations for RSV/VPI (RSV, influenza, pneumococcus, meningococcus, *Haemophilus influenzae*, human papillomavirus, varicella, pertussis, rotavirus, measles, mumps, and hepatitis A) were defined using specific *ICD-9* and *ICD-10 CM* diagnosis codes as reported in eTable 1 in the Supplement. Secondary outcomes included length of hospital stay, need for intensive care unit management ("ICU Flag" coded by PHIS), need for mechanical ventilation ("Ventilation Flag" coded by PHIS), and median adjusted hospitalization costs (using the PHIS variable "Adj Total RCC Costs").[32]

Statistical Analysis

Descriptive statistics were used to characterize the individuals by age, sex, ethnicity, race, and organ transplanted. Comparisons, using independent *t* tests and Wilcoxon tests as appropriate, were made between the group of patients who never

had a hospitalization for RSV/VPI and those who did. To capture different exposure times in the transplant population (as some transplant recipients may die within the first 5 years after transplant), we calculated the mean cumulative function (number of cases per total person-year) for each individual infection and for RSV/VPI as a combined group. We used the Wilcoxon rank sum test to compare median adjusted hospitalization cost and length of hospitalization for individuals with an initial transplant hospitalization complicated by an RSV/VPI with individuals whose initial transplant hospitalizations were not complicated by RSV/VPI.

To account for the possibility of repeated infections within a child, as well as varying lengths of follow-up time for each child, we used a recurrent events analysis with a random effect for patient and a random effect for hospital (R version 3.5.1 frailty pack package [R Project for Statistical Computing]). Because death appeared informative for recurrent hospitalizations, we considered a joint model for hospitalizations and death (or censoring) but were unable to fit such a model (eMethods in the Supplement). Thus, to minimize biases,[33,34] we fit 2 separate models: a model for the recurrent hospitalizations among those individuals who survived the entire follow-up period and a model for death as a binary outcome. Variables included in the initial model included patient sex, race, age at transplant, organ transplanted, calendar quarter of transplant, and year of transplant. Because there was an association between the organ transplanted and the age of the child at transplant, we tested for an interaction between these 2 variables. We removed nonsignificant variables 1 at a time, removing the least significant variable at each iteration, until all effects were significant at $P < .05$. We kept year of transplant in the model to account for any temporal trend but did not report hazard ratios (HRs) by year. Analyses were performed using SAS 9.4 (SAS Inc) and R version 3.5.1 (R Project for Statistical Computing).

Results

We identified 6980 children (3819 boys [54.7%], mean [SD] age at transplant was 8 [6.2] years) who underwent solid organ transplant at a PHIS center between January 1, 2004, and December 31, 2011. Of these, 2583 (37.0%) were kidney recipients; 2095 (30.0%), liver; 1691 (24.2%), heart; 287 (4.1%), lung; 230 (3.3%), multivisceral; and 94 (1.3%), intestinal. Of the 230 multivisceral recipients, 151 (65.7%) were liver/intestine; 31 (13.5%), liver/kidney; 25 (10.9%), heart/lung; 8 (3.5%), heart/kidney; and 15 (6.5%), other combinations. In the first 5 years after transplant, 1092 individuals (15.6%) had a hospitalization for RSV/VPI, 173 (15.8%) of which occurred during the initial transplant hospitalization. These 1092 individuals had 1490 total cases of RSV/VPI. Excluding cases of RRSV/VPI that occurred during initial transplant hospitalization (where primary diagnosis code was transplantation), 1136 of 1257 remaining cases (90.4%) of RSV/VPI had a primary diagnosis code consistent with RSV/VPI (eg, septicemia, fever) as opposed to a primary diagnosis code inconsistent with RSV/VPI (eg, transplant rejection, gastrostomy complication). Patients who had a hospitalization for RSV/VPI were more likely to be younger than 2 years at time of transplant compared with those who were 2 years or older at time of transplant (25.0% vs 12.0%; 13.1% difference; 95% CI, 11.0%-15.2%; $P < .001$; **Table 1**).

RSV/VPIs Resulting in Hospitalizations After Transplant

The most common RSV/VPIs following solid organ transplant were influenza (518 of 6980 [7.4%]), rotavirus (260 of 6980 [3.7%]), varicella (144 of 6980 [2.1%]), pneumococcus (142 of 6980 [2.0%]), and RSV (129 of 6980 [1.8%]). Respiratory syncytial virus/VPIs occurred a mean (SD) of 1.5 (1.4) years (median [interquartile range {IQR}], 1.1 [0.3-2.5] years) posttransplant. Overall, 195 RSV/VPI cases (13.1%) occurred during the initial transplant hospitalization, and 700 RSV/VPI cases (47.0%) occurred within the first year posttransplant (**Table 2** and **Figure**).

Morbidity, Mortality, and Costs From RSV/VPIs

Table 3 displays the morbidity and mortality from RSVs/VPIs in the first 5 years after transplant. The overall case fatality rate for all RSVs/VPIs was 1.7%. Excluding RSVs/VPIs that occurred during initial transplant hospitalization, the mean (SD) and median (IQR) lengths of stay for RSV/VPI hospitalizations were 9 (19) and 4 (2-9) days, respectively, 101 of 1257 patients (8.0%) required mechanical ventilation, and 213 patients (17.0%) required intensive care unit–level care.

Transplant hospitalizations complicated by RSV/VPI were $120 498 more expensive (median cost) than transplant hospitalizations not complicated by RSV/VPI (median [IQR], $268 626 [$136 162-$507 187] vs $148 128 [$80 494-$262 137]; $P < .001$). In addition, transplant hospitalizations complicated by RSV/VPI had a longer median length of stay than transplant hospitalizations not complicated by RSV/VPI (median [IQR], 55 [30-109] days vs 16 [9-38] days; $P < .001$).

Risk Factors for Being Hospitalized With RSV/VPI in the First 5 Years After Transplant

Age younger than 2 years at time of transplant (HR, 2.2; 95% CI, 1.9-2.5) and intestinal (HR, 2.8; 95% CI, 1.8-4.4), multivisceral (HR, 2.2; 95% CI, 1.6-3.1), lung (HR, 2.1; 95% CI, 1.5-2.9), and heart (HR, 1.4; 95% CI, 1.2-1.7) transplant were associated with an increased HR for hospitalization with RSV/VPI after controlling for year of transplant and accounting for repeated hospitalizations on the same individual and hospital variability. There was no interaction between age group and organ transplanted (**Table 4**). Additional details about the hospitalization model and death model are reported in eTable 2, eTable 3, eFigure 1, and eFigure 2 in the Supplement.

Discussion

In this national multicenter cohort analysis of almost 7000 pediatric solid organ transplant recipients, we found that at least 15% of transplant recipients were hospitalized in the first 5 years after transplant with RSV/VPI. Overall, influenza, rotavirus, varicella, pneumococcus, and RSV were the most common VPIs resulting in posttransplant hospitalization. Transplant hospitalizations complicated by RSV/VPI were significantly more

Table 1. Characteristics of 6980 Pediatric Patients Who Underwent Solid Organ Transplant

Variable	No. (%) Overall (N = 6980)	No RSV/VPI (n = 5888)[a]	Any RSV/VPI (n = 1092)[a]	*P* Value for Any RSV/VPI
Age at transplant, y				
<2	1970 (28.2)	1477 (75.0)	493 (25.0)	<.001
≥2	5010 (71.8)	4411 (88.0)	599 (12.0)	
Sex				
Male	3819 (54.7)	3224 (84.4)	595 (15.6)	.87
Female	3161 (45.3)	2664 (84.3)	497 (15.7)	
Race				
Other[b]	1203 (17.2)	994 (82.6)	209 (17.4)	.08
White	4681 (67.1)	3980 (85.0)	701 (15.0)	
Black	1096 (15.7)	914 (83.4)	182 (16.6)	
Organ transplanted				
Liver	2095 (30.0)	1753 (83.7)	342 (16.3)	<.001
Lung	287 (4.1)	227 (79.1)	60 (20.9)	
Heart	1691 (24.2)	1382 (81.7)	309 (18.3)	
Intestine	94 (1.4)	64 (68.1)	30 (31.9)	
Kidney	2583 (37.0)	2292 (88.7)	291 (11.3)	
Multivisceral	230 (3.3)	170 (73.9)	60 (26.1)	
Quarter of transplant				
January to March	1675 (24.0)	1384 (82.6)	291 (17.4)	.10
April to June	1791 (25.7)	1506 (84.1)	285 (15.9)	
July to September	1878 (26.9)	1601 (85.3)	277 (14.8)	
October to December	1636 (23.4)	1397 (85.4)	239 (14.6)	
Year of transplant				
2004	775 (11.1)	665 (85.8)	110 (14.2)	.004
2005	791 (11.3)	662 (83.7)	129 (16.3)	
2006	872 (12.5)	740 (84.9)	132 (15.1)	
2007	736 (10.5)	696 (83.3)	140 (16.8)	
2008	910 (13.0)	744 (81.8)	166 (18.2)	
2009	974 (14.0)	798 (81.9)	176 (18.1)	
2010	942 (13.5)	824 (87.5)	118 (12.5)	
2011	880 (12.6)	759 (86.3)	121 (13.8)	
Died during transplant hospitalization	254 (3.6)	246 (96.9)	8 (3.2)	NA
Died at any point during 5 y follow-up	540 (7.7)	470 (87.0)	70 (13.0)	NA
Had a VPI during transplant hospitalization	173 (2.5)	NA	173 (100.0)	NA

Abbreviations: NA, not applicable; RSV, respiratory syncytial virus; VPI, vaccine-preventable infection.

[a] Percentages were calculated using the overall study population (N = 6980).

[b] Other includes Asian (3.4%), Pacific Islander/other (11.2%), and missing (2.7%).

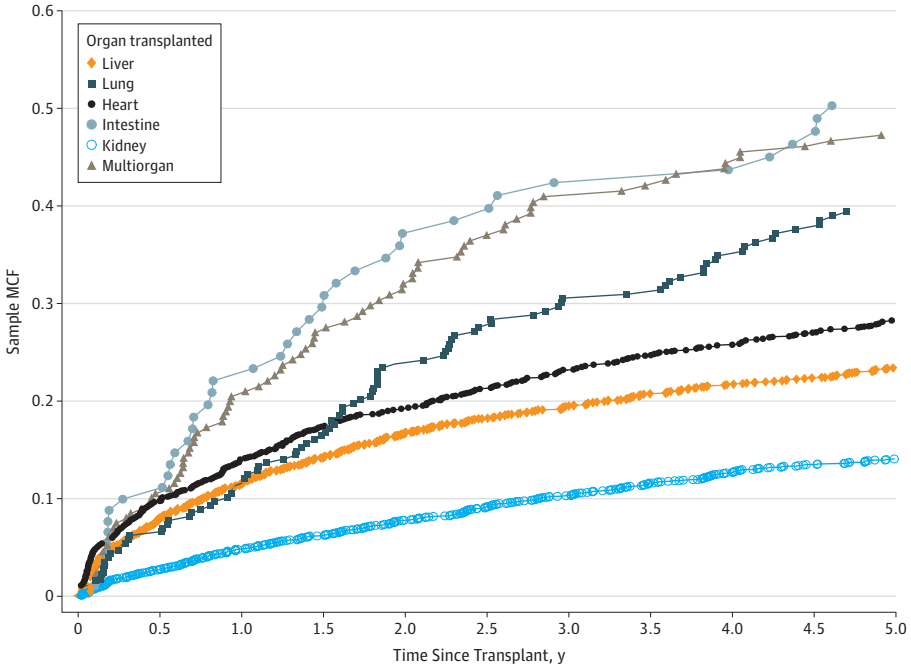
Table 2. Infections During Hospitalizations for Respiratory Syncytial Virus or a Vaccine-Preventable Infection in the First 5 Years After Transplant

Infection	Years Posttransplant Mean (SD)	Median (IQR)	Cases, No.	Individuals, No.	Total Cases, No. (%) Occurred During Transplant Hospitalization	Occurred During First Posttransplant Year	MCF at 1 y Posttransplant
Influenza	1.9 (1.4)	1.7 (0.6-2.9)	614	518	52 (8.5)	218 (35.5)	0.03
Rotavirus	1.0 (1.1)	0.6 (0.1-1.3)	286	260	38 (13.3)	181 (63.3)	0.03
Varicella	2.0 (1.3)	1.9 (0.8-3.1)	163	144	6 (3.7)	46 (28.2)	0.007
Pneumococcus	1.5 (1.4)	1.1 (0.3-2.6)	151	142	33 (21.9)	72 (47.7)	0.01
RSV	0.4 (0.4)	0.3 (0-0.8)	143	129	25 (17.5)	126 (88.1)	0.02
All RSVs/VPIs	1.5 (1.4)	1.1 (0.3-2.5)	1490	1092	195 (13.1)	700 (47.0)	0.1

Abbreviations: IQR, interquartile range; MCF, mean cumulative function; RSV, respiratory syncytial virus; VPI, vaccine-preventable infection.

expensive and resulted in longer lengths of stay than transplant hospitalizations not complicated by RSV/VPI. Children who received transplants before age 2 years and children who received lung, heart, intestine and multivisceral transplants were most likely to be hospitalized for RSV/VPI in the 5 years after transplant. This is consistent with the fact that children

Figure. Incidence of Respiratory Syncytial Virus (RSV)/Vaccine-Preventable Infection (VPI) by Organ Type



The mean cumulative function of RSV or a VPI by days alive per transplanted organ type. Each mark represents an infection. MCF indicates mean cumulative function.

who receive transplants before their second birthday are less likely to have received their full set of immunizations by the time of transplant, and children who undergo lung, heart, intestine, and multivisceral transplant receive high levels of immunosuppression to prevent graft rejection.

Although there are case series discussing the morbidity from individual infections in pediatric transplant recipients,[2-9,35] to our knowledge this is the first study to assess the burden of illness from all VPIs across the entire pediatric solid organ transplant population. We found that the morbidity and mortality from VPIs was much greater than that reported in the literature on the general pediatric population. For RSV, the rate of hospitalization in the first year after transplant was 6 times greater than the expected annual rate of hospitalization in the general pediatric population of children younger than 5 years (1.8% vs 0.3%),[36] and the death rate was 53 times greater than in the general pediatric population (2.1% vs 0.04%).[29] For influenza, the rate of hospitalization in the first year after transplantation was 52 times greater than the expected annual rate of hospitalization for influenza in individuals younger than 19 years (3.1% vs 0.06%),[37] and the death rate was 4 times greater (1.6% vs 0.4%).[38,39] For pneumococcus, the rate of hospitalization in the first year after transplant was 2 times greater than the expected annual rate of hospitalization in the general pediatric population (1% vs 0.5%),[40] and the death rate was 17 times greater (3.3% vs 0.2%).[40] For rotavirus, the rate of hospitalization in the first year after transplant was 87 times greater than the expected annual rate of hospitalization in the general pediatric population (2.6% vs 0.03%),[41] and the death rate was 23 times greater (1.4% vs 0.06%).[42]

In the present study, we found that 13.1% of RSV/VPI cases occurred during the initial transplant hospitalization and resulted in significant morbidity and mortality. This is consistent with literature that suggests that early infections posttransplant are important causes of morbidity, mortality, and graft loss in adult patients.[43,44] Infections during the transplant hospitalization can arise if a child (1) enters transplant with an active infection (less likely as unless a child has acute organ failure, transplant is usually delayed until the patient is free from active infection); (2) enters transplant with colonization or an asymptomatic infection that becomes symptomatic with initiation of immunosuppression; (3) acquires a donor-derived infection from the allograft; or (4) acquires a nosocomial infection in the peritransplant period.[1,44,45]

Interestingly, in our study, there were 163 cases of varicella. Currently, the Infectious Diseases Society of America recommends that posttransplant "the measles, mumps and rubella (MMR) vaccine and the varicella vaccine should generally not be administered except for in children without evidence of immunity who are renal or liver transplant recipients, are receiving minimal or no immunosuppression, and have no recent graft rejection."[46] These recommendations are based on concerns that (1) administration of live vaccines may result in life-threatening infection with the viral strain pathogen in immunocompromised patients and (2) immunosuppression could prevent development of a protective immune response. However, there are studies that demonstrate that in certain transplant recipients on lower levels of immunosuppression, live immunizations can be safely and effectively administered.[47,48] Among the transplant community, there continues to be variability in practice about use of live vaccines posttransplant. In a 2016 survey of pediatric hepatologists, 26% of respondents sometimes/always recommended live vaccines posttransplant.[49] In an era of decreasing herd immunity owing to vaccine refusal, it will be important to conduct multicenter large studies to understand under what circumstances live

Table 3. Inpatient Morbidity and Mortality From Respiratory Syncytial Virus or a Vaccine-Preventable Infection

Infection	Total Hospitalizations	LOS, d		No. (%)		
		Mean (SD)	Median (IQR)	Intensive Care Unit	Mechanical Ventilation	Deaths During Hospitalization
Influenza						
All	614	13 (33)	3 (1-8)	NA	NA	10 (1.6)
Tx hosp	52	82 (69)	61 (30-108)	NA	NA	3 (5.8)
Non-tx hosp	562	7 (16)	3 (1-6)	85 (15.1)	40 (7.1)	7 (1.2)
Varicella						
All	163	9 (24)	4 (2-6)	NA	NA	1 (0.6)
Tx hosp	6	91 (74)	70 (30-133)	NA	NA	1 (16.7)
Non-tx hosp	157	6 (12)	4 (2-6)	7 (4.5)	2 (1.3)	0 (0.0)
Pneumococcal						
All	151	26 (39)	10 (6-31)	NA	NA	5 (3.3)
Tx hosp	33	70 (57)	49 (35-85)	NA	NA	2 (6.1)
Non-tx hosp	118	13 (18)	8 (5-14)	40 (33.9)	26 (22.0)	3 (2.5)
Rotavirus						
All	286	26 (54)	9 (4-22)	NA	NA	4 (1.4)
Tx hosp	38	101 (102)	66 (41-118)	NA	NA	0 (0.0)
Non-tx hosp	248	15 (28)	8 (4-15)	43 (17.3)	19 (7.7)	4 (1.6)
RSV						
All	143	24 (52)	6 (3-18)	NA	NA	3 (2.1)
Tx hosp	25	101 (90)	69 (35-132)	NA	NA	1 (4.0)
Non-tx hosp	118	8 (8)	5 (3-10)	27 (22.8)	9 (7.6)	2 (1.7)
All RSVs/VPIs						
All	1430	18 (41)	5 (2-14)	NA	NA	24 (1.7)
Tx hosp	173	84 (80)	55 (30-109)	NA	NA	8 (4.6)
Non-tx hosp	1257	9 (19)	4 (2-9)	213 (17.0)	101 (8.0)	16 (1.3)

Abbreviations: IQR, interquartile range; LOS, length of stay; NA, not applicable; non-tx hosp, hospitalizations that occurred after patient was discharged from initial hospitalization when the transplant was performed; RSV, respiratory syncytial virus; VPI, vaccine-preventable infection; tx hosp, the hospitalization during which transplant occurred.

Table 4. Model Hospitalizations of Respiratory Syncytial Virus or a Vaccine-Preventable Infection Among Survivors in the 5 Years After Pediatric Solid Organ Transplant[a]

Variable	HR (95% CI)
Age at transplant, y	
<2	2.2 (1.9-2.5)
≥2	1 [Reference]
Organ	
Heart	1.4 (1.2-1.7)
Intestine	2.8 (1.8-4.4)
Liver	1.1 (0.9-1.3)
Lung	2.1 (1.5-2.9)
Multivisceral	2.2 (1.6-3.1)
Kidney	1 [Reference]

Abbreviation: HR, hazard ratio.

[a] Controlled for calendar year of transplant (fixed). See eMethods, eTables 2 and 3, and eFigures 1 and 2 in the Supplement for more details.

vaccines can be safely and effectively administered posttransplant.

Unlike in the adult population where postoperative nosocomial infections are well studied through the National Surgical Quality Improvement Program, data on pediatric posttransplant nosocomial infections are limited to single-center case studies.[2-9,35] Prospective studies in pediatric transplant recipients are needed to understand the epidemiology, risk factors (including impact of immunosuppressive regimens), and outcomes of nosocomial VPIs in the immediate posttransplant period.[44,50,51] These data could be collected by expanding information collected by the current Scientific Registry of Transplant Recipients, through the National Surgical Quality Improvement Program, or through development of a novel national transplant prospective open cohort study (perhaps modeled after the Swiss Transplant Cohort Study or the Spanish Research Network of Infection in Transplantation).[52,53] These data would be critical to help guide pretransplant and posttransplant policies on infectious disease screening, prophylaxis, and medical practices (such as isolation or reverse isolation).

Overall, the huge burden of illness from VPIs shown in this article should stress to specialty and primary care physicians the critical importance of ensuring that all transplant patients receive age-appropriate immunizations. Unfortunately, underimmunization of transplant patients remains a significant problem with less than half of all transplant recipients reported being up to date for age on immunizations at the time of transplant.[49] Subspecialists and primary care physicians will need to partner together to develop new strategies and tools to increase immunization rates in this highly at-risk population.[49,54]

Strengths and Limitations

Our findings must be interpreted in light of the strengths and weaknesses of our data source, the PHIS data set. The strengths of PHIS are (1) it is a geographically diverse database that represents a large portion of inpatient pediatric care in the United States, (2) it allows tracking of individual patients over time and multiple hospitalizations, and (3) the database contains demographic, diagnosis, procedural, and disposition information. However, as with all administrative databases, the accuracy of the data are dependent on proper diagnostic and procedural coding. To improve the validity of our study, we chose not to include broad diagnostic codes that may potentially have represented individuals with a non-vaccine-preventable infection (ie, pneumonia or bronchiolitis) and only included *ICD* codes that specifically identified a VPI (ie, pneumococcal pneumonia or RSV bronchiolitis). Our study likely underestimates the true incidence, morbidity, mortality, and costs that result from RSV/VPI as (1) PHIS does not capture outpatient data, (2) PHIS does not include every transplant center in the United States and is more likely to represent large tertiary care centers (for example, during 2010-2012, PHIS centers performed 56% of all pediatric liver transplants done in the United States[55]), (3) PHIS does not capture data on patients who received transplants at a PHIS center but were subsequently hospitalized with RSV/VPI at a non-PHIS center, and (4) we were conservative in our inclusion factors and did not include individuals with broad diagnosis codes (such as pneumonia), which may have potentially represented a VPI.

The largest limitation of this study is that PHIS in its current form does not capture immunization delivery or markers of immune response to vaccines (ie, antibody titers). Therefore, it is not possible for us to determine whether individuals hospitalized for RSV/VPI had received vaccines against the infection for which they were hospitalized nor to know whether their immunity had waned secondary to immunosuppressive medications. Currently, this data only exist at the individual-center level. In future studies, it will be important to set up multicenter vaccine registries for transplant candidates and recipients to follow (1) pretransplant and posttransplant immune responses to vaccine administration, (2) posttransplant markers of immune memory on different levels of immunosuppressive medications (eg, antibodies, B-cell and T-cell markers), and (3) occurrence of VPIs (including outpatient cases).

Finally, we are not definitively able to say that morbidity, mortality, and costs of hospitalization were due specifically to RSV/VPI. However, 90% of the patients hospitalized with RSV/VPI outside of initial transplant hospitalization had a primary diagnosis code consistent with RSV/VPI as opposed to allograft dysfunction or a vascular problem; therefore, we feel confident that most of these hospitalizations were due to RSVs/VPIs (not RSVs/VPIs).

Conclusions

Hospitalizations for RSV/VPIs are common after pediatric solid organ transplantation. These hospitalizations result in morbidity, mortality, and increased hospital costs. Young age at transplant and heart, lung, intestine, and multivisceral transplant increase the risk of RSV/VPI in the first 5 years after transplant. Further research is necessary to understand and prevent RSVs/VPIs in the transplant population including development of tools to improve immunization rates in the transplant population, practices to decrease nosocomial infectious spread during hospitalizations, and establishment of best methods to monitor response to immunization in the transplant population.

ARTICLE INFORMATION

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