

Original Article



Incidence and Risk of Common Vaccine Preventable Diseases among Transplant Recipients in Korea: A Nationwide Population-Based Study (2009-2020)

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ABSTRACT

Background: Infection remains a leading cause of mortality among transplant recipients. Studies on vaccine-preventable diseases (VPDs) among transplant recipients in Asia are lacking. This study aimed to investigate the incidence and risk of VPD in transplant recipients in Korea.

Materials and Methods: Individuals who underwent transplantation were retrospectively recruited using data from the Korea National Health Insurance system from 2008 to 2020. We selected four major VPDs—varicella, invasive

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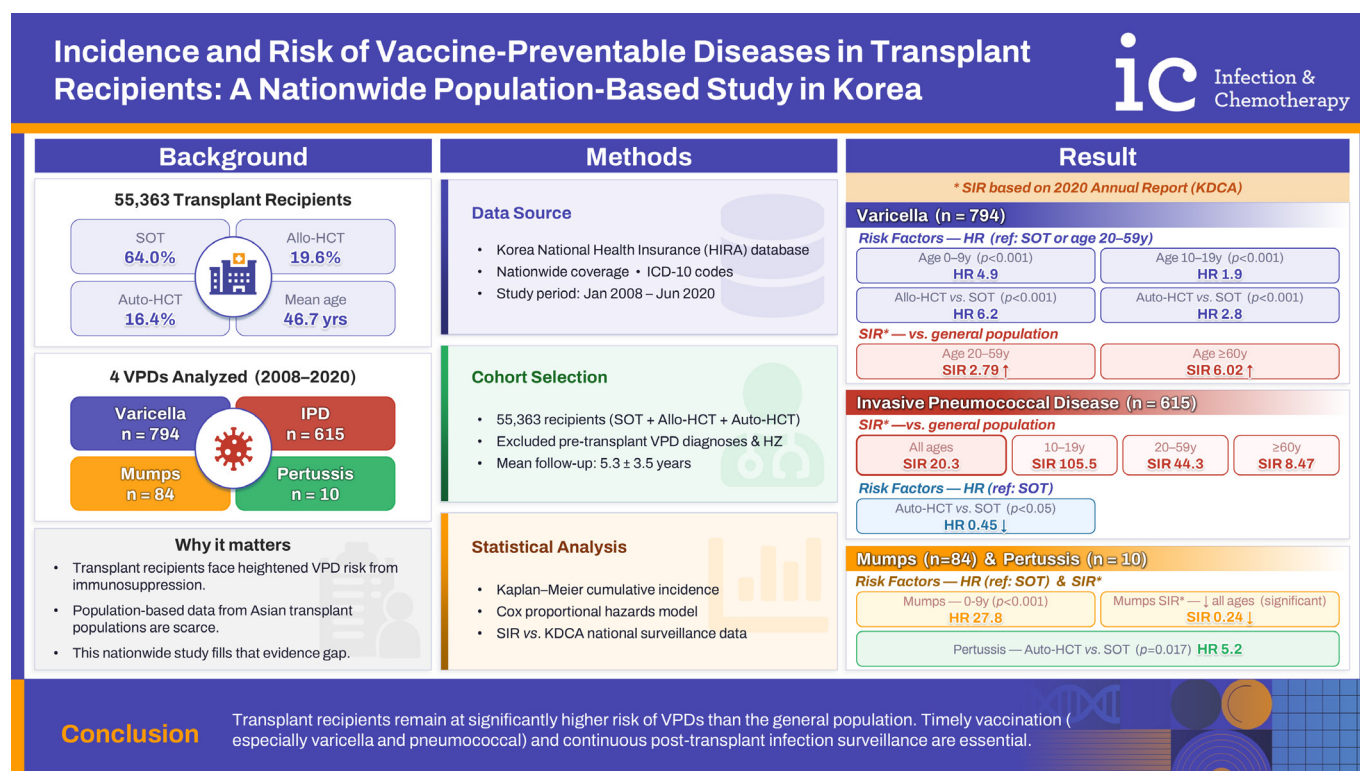
pneumococcal disease (IPD), mumps, and pertussis—and evaluated the cumulative incidence rate and standardized incidence ratio (SIR), comparing it to that of the general population.

Results: A total of 55,363 transplant recipients were included. Among these, 1,503 cases of the four VPDs were identified. Multivariable analysis revealed a significantly higher risk of varicella in children and allogeneic hematopoietic stem cell transplantation recipients. Conversely, for IPD, the risk was higher among individuals aged ≥ 60 years and in solid organ transplantation recipients; however, the difference was not significant. The SIR for varicella was notably higher in adult recipients aged ≥ 20 years (SIR, 2.79; 95% confidence interval [CI], 2.53–3.06; SIR, 6.02; 95% CI, 4.89–7.33), while for IPD, the SIR for all ages was notably increased at 20.3 (95% CI, 18.72–21.96). For mumps, the SIR was significantly lower at 0.24 (95% CI, 0.19–0.30) across all age groups. Conversely, for pertussis, the SIR was 0.67 (95% CI, 0.32–1.24), but the difference was not significant.

Conclusion: These findings underscore that transplant recipients are still at higher risk of getting VPDs than is the general population, emphasizing the importance of surveillance and vaccination efforts.

Keywords: Vaccine-preventable diseases; Transplant recipients; Chickenpox; Mumps; Pneumococcal infections

GRAPHICAL ABSTRACT



INTRODUCTION

Post-transplantation infections, including those after solid organ transplantation (SOT) and allogeneic and autologous hematopoietic stem cell transplantation (HCT), remain a significant burden [1, 2]. In the early post-transplantation period, recipients face the risk of surgery-related and/or opportunistic infections due to profound immunosuppression. Typically, 6–12 months post-

transplantation, as recipients gradually reintegrate into social activity, they may encounter communicable diseases similar to those seen in the general population. However, they have a heightened risk of contracting infections and are more susceptible to developing severe cases [3–6].

Vaccination may be an effective infection preventive strategy in recipients post-transplantation [7]. However, vaccination recommendations vary by transplantation

type. Revaccination against vaccine-preventable diseases (VPDs) is recommended for HCT recipients. In contrast, SOT recipients who take immunosuppressive agents over their lifetime often follow the vaccination schedules of their age group in the general population. However, exceptions exist for some infectious diseases, such as influenza and coronavirus disease 2019 (COVID-19) [8]. Furthermore, pediatric SOT recipients who underwent transplantation at a young age and did not receive or incompletely received live vaccines, such as measles, mumps, rubella (MMR), and varicella vaccines, might have insufficient immunogenicity compared to that of the general pediatric population [9].

Epidemiological studies on the incidence of VPDs post-transplantation, and the extent of the increased risk compared with the general population, are scarce for adult and pediatric recipients. Therefore, we aimed to examine the incidence of significant VPDs in pediatric and adult transplant recipients by integrating data from nationwide population-based databases and surveillance data on infectious diseases in Korea. Additionally, we assessed the relative risk of VPDs in transplant recipients compared with that of the general population.

MATERIALS AND METHODS

1. Data source

The Health Insurance Review and Assessment (HIRA) database was used, with details described previously [10]. We used national surveillance data from the Korea Disease Control and Prevention Agency (KDCA) to calculate the standardized incidence ratio (SIR). The KDCA designated 66 infectious diseases as notifiable, and healthcare workers who detect these pathogens or diagnose infectious diseases are legally obliged to report them within 24 hours. The KDCA provides this information in real time through the infectious disease portal (www.kdca.go.kr). To calculate the SIR, population data for Koreans, stratified by age and sex, were obtained from the Korean Statistical Information Service (<http://kosis.kr>).

2. Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2020-0018) and the requirement for informed consent was waived due to the retrospective nature of the study.

3. Study design and participants

This retrospective cohort study used data from nationwide databases. The primary outcome is the cumulative incidence rate (CIR) of major VPDs in transplant recipients. Secondary outcomes include the SIR and risk factors for major VPDs. Individuals with procedure codes for HCT or SOT between January 2008 and June 2020 were included as recipients. Transplant recipients and VPD cases were identified using International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes and procedure codes recorded in the HIRA database. Those with procedure codes for washout in 2008 were excluded. Additionally, recipients with a pre-transplant diagnosis code for VPDs, or a diagnosis code for varicella or herpes zoster (HZ) infections, were excluded. To avoid diagnostic ambiguity, recipients with a diagnosis code for HZ were explicitly excluded, and only cases coded as varicella were included as study outcomes. The detailed inclusion and exclusion criteria have been outlined previously [11], and procedural codes for transplantation and ICD-10 diagnostic codes used to define each VPD are provided in **Supplementary Table 1 and 2**.

4. Selection of VPDs

First, we selected 11 VPDs (diphtheria, pertussis, tetanus, varicella, measles, mumps, rubella, polio, *Haemophilus influenzae* type B, invasive pneumococcal disease (IPD), and Japanese encephalitis) that are included in the National Immunization Program (NIP) in Korea. Active tuberculosis, influenza, and human papillomavirus were excluded because a separate surveillance system was either in operation or the national surveillance system was unavailable. Second, among these 11 VPDs, we selected major VPDs for the final analysis based on predefined criteria: (1) an annual incidence of more than 100 cases nationwide over the preceding five years (2016-2020), according to the KDCA annual reports, and (2) the availability of stable diagnostic definitions within administrative claims data. Based on these criteria, varicella, invasive pneumococcal disease, mumps, and pertussis were selected for the final analysis. Patients with hepatitis A and B were excluded because of possible underlying pre-transplant conditions and etiology prior to transplantation, such as liver transplantation, rather than post-transplant complications. VPD diagnoses were made using the diagnostic criteria presented in the KDCA Annual Report (**Supplementary Table 2**).

5. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) and were compared using the independent *t*-test. Categorical variables, including age, sex, type of transplantation, cause of HCT, and comorbidities, are presented as frequencies and percentages, and were compared using the chi-square test or Fisher's exact test. We followed the participants from the date of transplantation to the date of each VPD diagnosis, date of death, or conclusion of the study (December 31, 2020), whichever came first. Using the Kaplan-Meier method, we estimated the cumulative incidence of each VPD by age group and transplant type using a log-rank test. The Cox proportional hazards model was used to explore risk factors associated with VPDs. In the multivariable analysis, we considered the following variables as risk factors: age, sex, transplantation type, and Charlson Comorbidity Index score. SIRs were calculated to compare the risk of VPDs in patients who underwent transplantation with that in the general population in Korea. For comparison, we used the number of reported cases of infectious diseases in the general population from the 2019 and 2020 Infectious Disease Surveillance Yearbooks [12, 13]. The 95% confidence intervals (CIs) of the SIRs were calculated

using a Poisson distribution. All statistical tests were two-sided, and *P*-values <0.05 were considered significant. SAS Enterprise Guide (version 7.1, SAS Institute, Cary, NC, USA) was used for statistical analysis.

6. Validation of diagnostic criteria

To assess the validity of our diagnostic criteria, we performed a validation substudy using medical records from Severance Hospital. We identified patients diagnosed with Varicella, IPD, Pertussis, and Mumps between January 1, 2023, and December 31, 2025, using the same inclusion criteria applied in the main study.

RESULTS

Between January 2008 and June 2020, 62,484 individuals underwent at least one transplantation. After excluding 7,121 individuals, 55,363 transplant recipients were included in this study (Fig. 1). Most transplants (64.0%, $n=35,449$) were SOTs, followed by allogeneic HCTs (19.6%, $n=10,834$) and autologous HCTs (16.4%, $n=9,080$). The mean age at transplantation was 46.6 ± 15.4 years, with 7.6% under 20 years of age. The male-to-female ratio

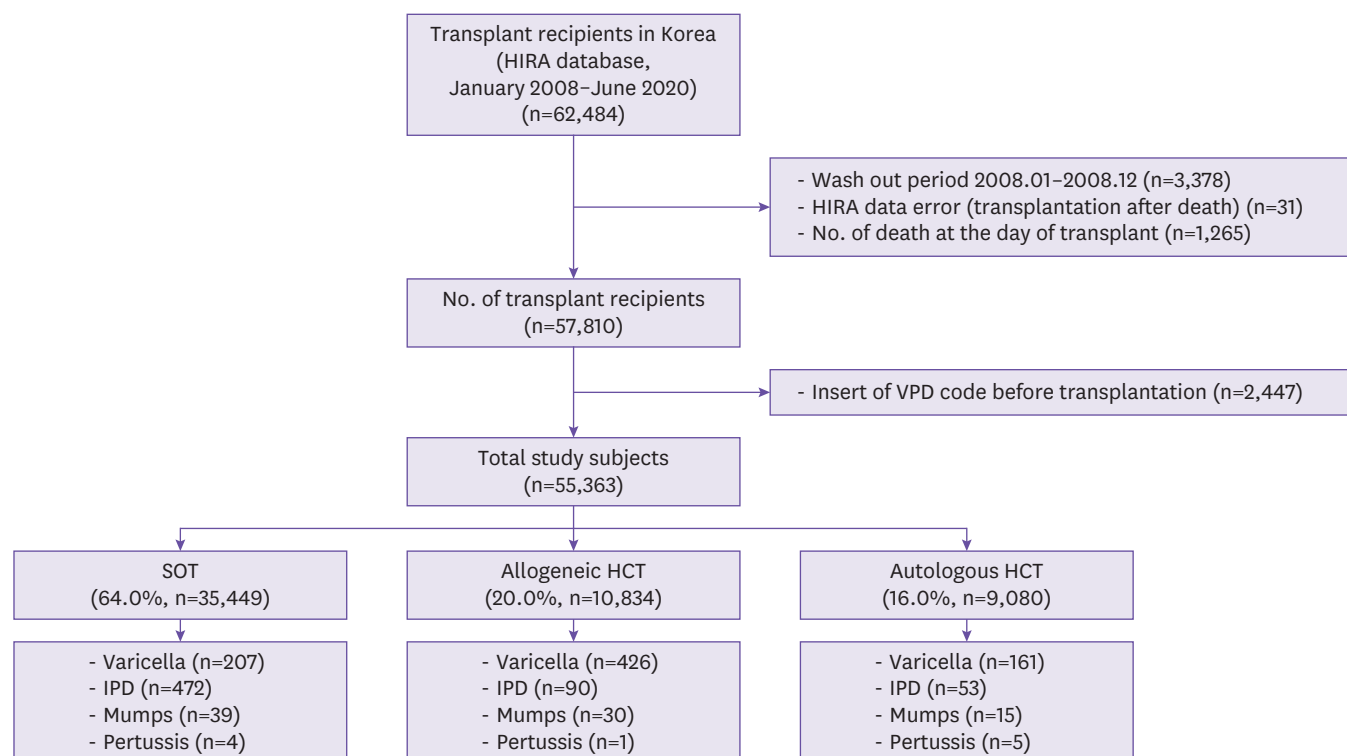


Figure 1. Flow chart of the study participants.

HIRA, Health Insurance Review and Assessment; VPD, vaccine-preventable disease; SOT, solid organ transplantation; HCT, hematopoietic stem cell transplantation; IPD, invasive pneumococcal disease.

Table 1. Characteristics of the study participants

Characteristic	All (N=55,363) n (%)	SOT (N=35,449) n (%)	Allogeneic HCT (N=10,834) n (%)	Autologous HCT (N=9,080) n (%)	P-value
Age at transplantation, mean±SD	46.6±15.4	48.9±13.0	38.6±18.1	47.7±17.0	<0.001
Follow-up period (years), mean±SD	5.3±3.5	5.8±3.4	4.3±3.7	4.5±3.4	<0.001
Age group					<0.001
0–9 years	2,069 (3.7)	572 (1.6)	930 (8.6)	567 (6.2)	
10–19 years	2,174 (3.9)	600 (1.7)	1,154 (10.7)	420 (4.6)	
20–59 years	40,736 (73.6)	27,421 (77.4)	7,535 (69.6)	5,780 (63.7)	
≥60 years	10,384 (18.8)	6,856 (19.3)	1,215 (11.2)	2,313 (25.5)	
Sex					<0.001
Male	34,105 (61.6)	22,713 (64.1)	6,069 (56.0)	5,323 (58.6)	
Female	21,258 (38.4)	12,736 (35.9)	4,765 (44.0)	3,757 (41.4)	
Type of transplantation					
Liver	13,108 (23.7)	13,108 (37.0)	-	-	
Kidney	20,222 (36.5)	20,222 (57.1)	-	-	
Heart	1,344 (2.4)	1,344 (3.8)	-	-	
Lung	599 (1.1)	599 (1.7)	-	-	
Others	176 (0.3)	176 (0.5)	-	-	
Cause of HCT					<0.001
AML	4,809 (8.7)	-	4,400 (40.6)	409 (4.5)	
ALL	2,697 (4.9)	-	2,614 (24.1)	83 (0.9)	
CML	364 (0.7)	-	348 (3.2)	16 (0.2)	
Lymphoma	4,292 (7.6)	-	566 (5.2)	3,664 (40.4)	
Multiple myeloma	4,132 (7.5)	-	78 (0.7)	4,054 (44.7)	
Severe aplastic anemia	7,856 (14.2)	-	4,631 (42.8)	3,225 (35.5)	
MDS	2,108 (2.6)	-	2,069 (19.1)	39 (0.4)	
Others	3,856 (7.0)	-	3,397 (31.4)	459 (5.1)	
Comorbidities					
Diabetes mellitus	22,431 (40.5)	16,992 (47.9)	2,640 (24.4)	2,799 (30.8)	<0.001
Hypertension	31,754 (57.4)	25,652 (72.4)	2,658 (24.5)	3,444 (37.9)	<0.001
Asthma	7,576 (13.7)	3,531 (10.0)	2,338 (21.6)	1,707 (18.8)	<0.001
COPD	3,134 (5.7)	1,281 (3.6)	1,048 (9.7)	805 (8.9)	<0.001
Liver cirrhosis	11,584 (20.9)	11,234 (31.7)	194 (1.8)	156 (1.7)	<0.001
Chronic kidney disease	21,216 (38.3)	20,601 (58.1)	94 (0.9)	521 (5.7)	<0.001
Post-gastrectomy	24 (<0.1)	16 (<0.1)	1 (<0.1)	7 (<0.1)	0.064
Solid tumor	12,345 (22.3)	7,954 (22.4)	905 (8.4)	3,486 (38.4)	<0.001
Hematologic malignancy	12,206 (22.1)	105 (0.3)	7,876 (72.7)	4,225 (46.5)	<0.001
Autoimmune disease	296 (0.5)	84 (0.2)	112 (1.0)	100 (1.1)	<0.001
Congenital malformations	1,276 (2.3)	1,103 (3.1)	95 (0.9)	78 (0.9)	
CCI score, mean±SD	5.5±2.9	5.7±2.7	4.1±2.4	6.5±3.3	<0.001

SOT, solid organ transplantation; HCT, hematopoietic stem cell transplantation; SD, standard deviation; AIDS, acquired immune deficiency syndrome; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index.

was 1.6:1. The mean follow-up period post-transplantation was 5.3±3.5 years. Additional characteristics of the study population are listed in **Table 1**.

1. Validation of diagnostic criteria

A total of 59 cases were analyzed after excluding *Bordetella parapertussis* cases. Our review revealed that 79.7% (47/59) of the cases identified by our inclusion criteria were clinically confirmed as actual cases. Specifically, IPD and Pertussis demonstrated 100% concordance with laboratory-confirmed cases. For varicella, 80.0% (32/40) were clinically confirmed; however, if five ambiguous cases (difficult to distinguish

between varicella and disseminated HZ) are included, the concordance rate rises to 92.5%. Conversely, Mumps showed a lower concordance rate of 50.0% (4/8) (**Supplementary Table 3**).

2. Incidence of VPDs in Transplant Recipients

Four VPDs—varicella, IPD, mumps, and pertussis—were included in the analysis. Among transplant recipients, 1,503 cases of these four VPDs were identified (794 varicella, 615 IPD, 84 mumps, and 10 pertussis) (**Fig. 1**). About half of the varicella (51.9%, 412/794) and IPD (48.3%, 297/615) cases occurred within 1 year post-transplantation, while cases of mumps (77%, 65/84) and

A

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total	100,000PY
Varicella (N)	70	72	82	74	46	62	73	61	39	62	147	6	794	119.5
IPD (N)	69	79	77	6	43	50	57	52	35	40	32	13	615	92.6
Mumps (N)	13	14	8	8	12	9	4	9	6	1	0	0	84	12.6
Pertussis (N)	1	1	1	0	0	2	2	1	1	1	0	0	10	1.5

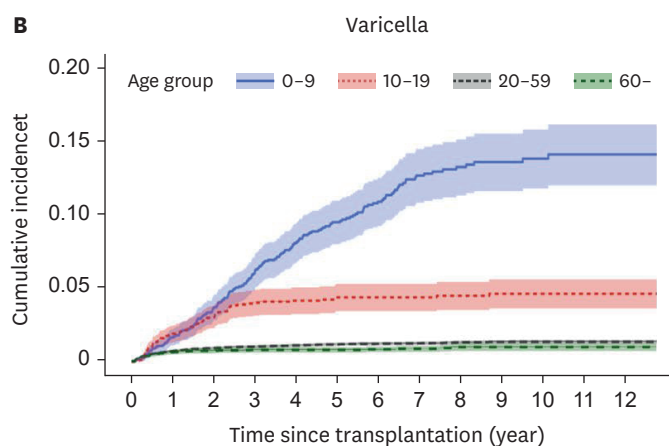
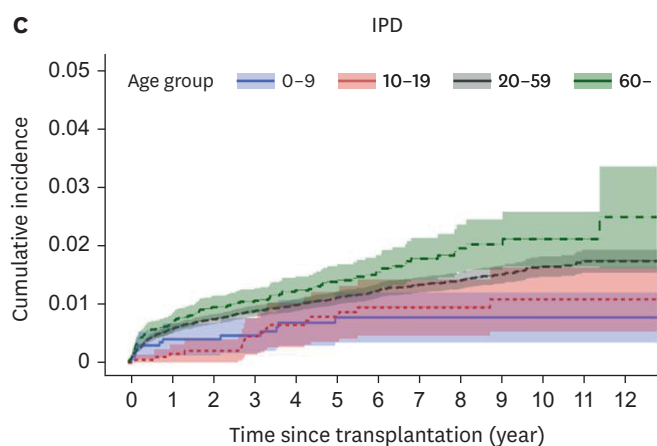
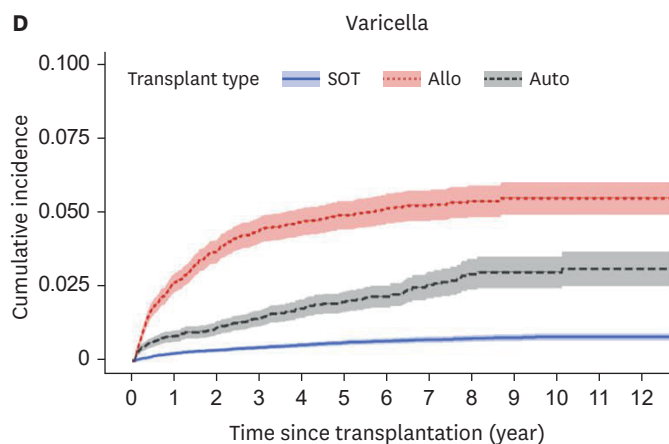
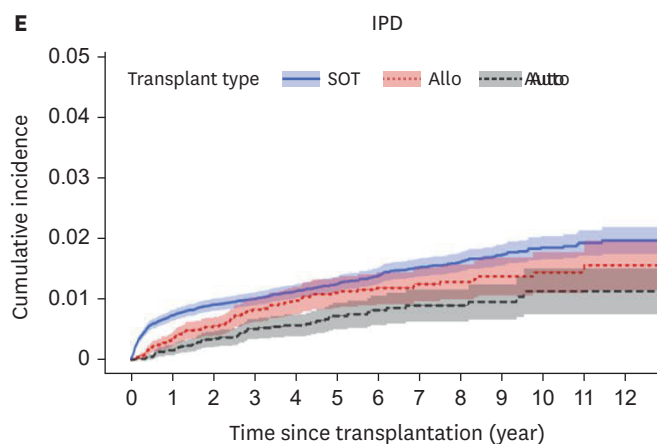
B**C****D****E**

Figure 2. Incidence of selected four vaccine-preventable diseases after transplantation, 2009–2020. (A) Annual number of cases of selected VPDs among transplant recipients, (B) Cumulative incidence of varicella by age group, (C) Cumulative incidence of IPD by age group, (D) Cumulative incidence of by transplantation type, (E) Cumulative incidence of by transplantation type.

VPDs, vaccine preventable diseases, IPD, invasive pneumococcal disease.

pertussis (90.0%, 9/10) were predominantly observed >1 year post-transplantation (Fig. 2A).

The 10-year CIR for varicella and IPD were similar at 1.9% (95% CI, 1.8–2.1) and 1.7% (95% CI, 1.5–1.8), respectively (Supplementary Fig. 1). However, when analyzed by age group, the CIR for varicella was highest in the youngest age group (0–9 years) at 14% and lowest in the 60+ age group at 5% ($P < 0.001$) (Fig. 2B). In contrast, the CIR for IPD was highest in the 60+ age group at 2.1% and lowest in the 0–9 age group at 0.8% ($P < 0.001$) (Fig. 2C). When analyzed by transplant type, the 10-year CIR of varicella

was highest in allogeneic HCT recipients at 5.4% (95% CI, 4.9–6.0), followed by those of autologous HCT (3.0%; 95% CI, 2.4–3.5) and SOT recipients (0.8%; 95% CI, 0.7–0.9) (Fig. 2D). In contrast, the 10-year CIR of IPD was highest in SOT recipients (1.8%; 95% CI, 1.7–2.0), followed by those of allogeneic HCT (1.4%; 95% CI, 1.1–1.8) and autologous HCT recipients (1.1%; 95% CI, 0.8–1.5) (Fig. 2E). The incidence rates of mumps and pertussis were low, and a subgroup analysis was not performed because of the limited number of cases. When calculated per 100,000 person-years (PY), the incidence rates of varicella, IPD, mumps, and pertussis were 120/100,000, 93/100,000,

13/100,000, and 1.5/100,000 PY, respectively (Fig. 2A). For varicella, the incidence rates were 328/100,000, 148/100,000, and 49/100,000 PY in allogeneic HCT, autologous HCT, and SOT recipients, respectively. For IPD, the rates were 69/100,000, 50/100,000, and 111/100,000 PY in allogeneic HCT, autologous HCT, and SOT recipients, respectively (data not shown).

3. Risk Factors for VPDs

In the multivariable analysis (Table 2), the risk of developing varicella in children and adolescents was significantly higher than that in adults aged 20–59 years (Hazard ratio [HR], 4.9; 95% CI, 4.1–5.4, $P<0.001$ in the 0–9 age group; HR, 1.9; 95% CI, 1.5–2.4, $P<0.001$ in the 10–19 age group). When stratified by transplant type, the risk of developing varicella was significantly higher in allogeneic HCT and autologous HCT recipients, with rates 6.2 and 2.8 times higher, respectively, compared to that of SOT recipients ($P<0.001$).

There was no significant difference in the risk of developing IPD among the different age groups; however, in a comparison according to the type of transplantation, the risk of IPD was significantly lower in autologous HCT patients compared to SOT (HR, 0.45; 95% CI 0.36–

0.64). CCI was significantly associated with an increased risk of IPD in the overall patient population (HR, 1.05; 95% CI, 1.02–1.08; $P=0.002$), and this association was also maintained in both SOT and allogeneic HCT recipient groups.

For mumps, the risk in children and adolescents was significantly higher, ranging from 19.4 to 27.9 times, compared to the reference group of adults aged 20–59 years ($P<0.001$). While there was no difference in risk by age group for pertussis, the incidence among autologous HCT recipients was significantly higher, by 5.2 times, compared to that of SOT recipients ($P=0.017$).

4. SIR of VPDs

Based on reported cases of varicella in the 2019 Annual Report, the SIR of varicella in transplant recipients was 0.56 (95% CI, 0.53–0.61). The SIR was significantly lower in children and adolescents compared to that of the general population (SIR, 0.18; 95% CI, 0.15–0.21 in the 0–9 age group; SIR, 0.31; 95% CI, 0.25–0.38 in the 10–19 age group). Conversely, the SIR of adult recipients aged 20 years or older was higher compared to that of the general population (SIR, 2.79; 95% CI, 2.53–3.06 in the 20–59 age group; SIR, 6.02; 95% CI, 4.89–7.33 in the >60 age group) (Fig. 3A).

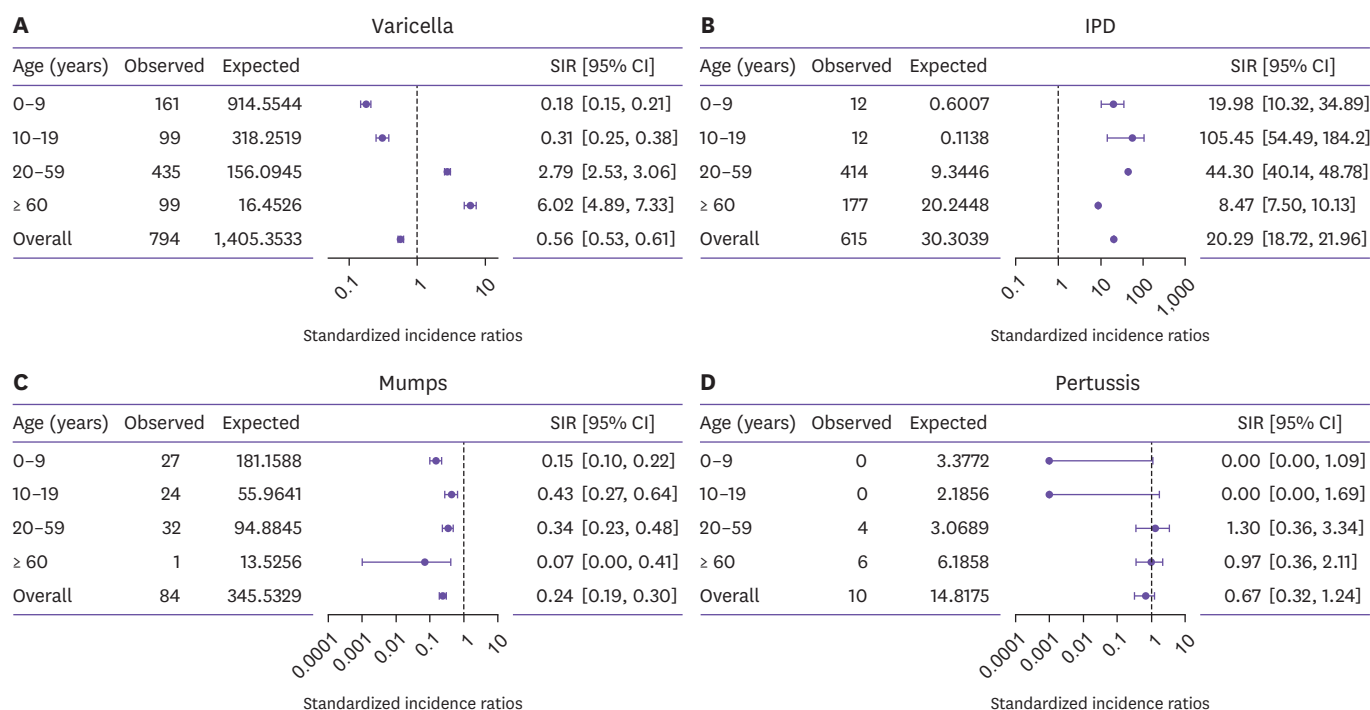


Figure 3. Standardized incidence ratio of major vaccine-preventable diseases compared to the 2019 general population data. The general population data were derived from the 2019 annual report of Infectious Diseases in Korea. SIR, standardized incidence ratio; CI, confidence interval; IPD, invasive pneumococcal disease.

Table 2. Multivariable analysis of risk factors for each VPD (varicella, invasive pneumococcal disease, mumps, and pertussis)^a

Variables	All		SOT		Allogeneic HCT		Autologous HCT	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Varicella								
Age group								
0-9 years	4.86 (4.05, 5.40)	<0.001	26.30 (18.42, 37.54)	<0.001	2.33 (1.78, 3.06)	<0.001	6.73 (4.70, 9.62)	<0.001
10-19 years	1.89 (1.48, 2.40)	<0.001	3.22 (1.62, 6.43)	0.001	1.75 (1.34, 2.29)	<0.001	0.93 (0.40, 2.13)	0.859
20-59 years	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
≥60 years	0.78 (0.61, 1.00)	0.050	0.72 (0.43, 1.22)	0.221	0.81 (0.56, 1.17)	0.258	0.88 (0.56, 1.38)	0.574
Sex								
Male	0.93 (0.81, 1.07)	0.286	0.87 (0.66, 1.15)	0.337	1.05 (0.86, 1.27)	0.654	0.95	0.766
Female	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Transplantation								
SOT	1 (Reference)							
Allogeneic HCT	6.22 (5.20, 7.44)	<0.001						
Autologous HCT	2.80 (2.26, 3.46)	<0.001						
CCI	1.04 (1.01, 1.06)	0.016	1.00 (0.94, 1.06)	0.926	1.09 (1.05, 1.13)	<0.001	1.03 (0.99, 1.08)	0.171
IPD								
Age group								
0-9 years	0.70 (0.40, 1.23)	0.212	1.24 (0.61, 2.52)	0.552	0.46 (0.17, 1.26)	0.129	0.28 (0.04, 2.02)	0.204
10-19 years	0.74 (0.45, 1.23)	0.239	1.48 (0.80, 2.67)	0.223	0.34 (0.13, 0.95)	0.039	0.33 (0.05, 2.40)	0.272
20-59 years	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
≥60 years	1.18 (0.96, 1.46)	0.123	1.12 (0.88, 1.42)	0.378	1.19 (0.64, 2.21)	0.591	1.64 (0.90, 3.00)	0.108
Sex								
Male	0.93 (0.79, 1.10)	0.404	0.89 (0.74, 1.07)	0.210	0.91 (0.60, 1.38)	0.665	1.71 (0.95, 3.08)	0.072
Female	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Transplantation								
SOT	1 (Reference)							
Allogeneic HCT	0.86 (0.68, 1.09)							
Autologous HCT	0.45 (0.36, 0.64)							
CCI	1.05 (1.02, 1.08)	0.002	1.06 (1.02, 1.10)	0.003	1.11 (1.03, 1.21)	0.010	0.99 (0.91, 1.08)	0.808
Mumps								
Age group								
0-9 years	27.86 (15.36, 50.55)	<0.001						
10-19 years	19.41 (10.57, 35.64)	<0.001						
20-59 years	1 (Reference)							
≥60 years	0.15 (0.02, 1.15)	0.064						
Sex								
Male	1.09 (0.71, 1.70)	0.691						
Female	1 (Reference)							
Transplantation								
SOT	1 (Reference)							
Allogeneic HCT	0.96 (0.57, 1.61)							
Autologous HCT	0.75 (0.39, 1.43)							
CCI	1.07 (0.98, 1.16)	0.121						
Pertussis								
Age group								
0-9 years	-							
10-19 years	-							
20-59 years	1 (Reference)							
≥60 years	1.97 (0.51, 7.60)	0.3326						
Sex								
Male	0.98 (0.28, 6.51)	0.978						
Female	1 (Reference)							
Transplantation								
SOT	1 (Reference)							
Allogeneic HCT	1.96 (0.21, 18.13)	0.554						
Autologous HCT	5.23 (1.34, 20.40)	0.017						
CCI	1.18 (0.98, 1.42)	0.082						

^aSubgroup analysis by transplant type was performed only for varicella and IPD owing to the limited number of cases of pertussis and mumps. In the multivariable analysis, we included the following variables: age, sex, transplantation type, and CCI score.

VPD, vaccine-preventable disease; SOT, solid organ transplantation; HCT, hematopoietic stem cell transplantation; HR, Hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; IPD, invasive pneumococcal disease.

For IPD, the SIR in transplant recipients of all ages was notably high at 20.3 (95% CI, 18.72–21.96). Specifically, transplant patients aged 10–19 years had the highest SIR at 105.5 (95% CI, 54.49–184.2), followed by those aged 20–59 (44.3; 95% CI, 40.14–48.78), 0–9 (19.98; 95% CI, 10.32–34.89), and >60 (8.47; 95% CI, 7.5–10.13) (**Fig. 3B**).

For mumps, the SIR was significantly lower at 0.24 (95% CI, 0.19–0.30) across all age groups, and in the case of pertussis, the SIR was 0.67 (95% CI, 0.32–1.24); however, the difference was not significant (**Fig. 3C, 3D**).

Conversely, based on data from the 2020 annual report, when intensive non-pharmaceutical interventions were implemented due to the COVID-19 pandemic in Korea, the SIR of all four VPDs increased compared to those of the 2019 annual report (**Supplementary Fig. 2A–2D**).

DISCUSSION

To the best of our knowledge, this is the largest population-based study investigating the incidence and risk factors of VPDs in transplant recipients. The spectrum of VPDs observed in transplant recipients broadly overlapped with that of the general population, suggesting continued exposure to community-acquired infections after transplantation. However, the relative distribution of specific VPDs differed between transplant recipients and the general population. In the general population in Korea, the incidence rates were highest for varicella, mumps, IPD, and pertussis, in that order. However, for transplant recipients, the order of the incidence rates was varicella, IPD, mumps, and pertussis.

The incidence of varicella among pediatric and adolescent transplant recipients aged 0–9 years and 10–19 years was significantly higher than that observed in adult recipients. In addition, the CIR was highest among allogeneic transplant recipients. These findings are consistent with those of previous studies [20]. A hospital-based study of pediatric solid-organ transplant recipients reported that, among 58 cases of varicella-zoster virus infection, 53% represented primary varicella. The median age at infection was 8 years, and the median interval from transplantation to infection was 1.6 years. Most varicella cases occurred within the first year after transplantation, and the cumulative incidence was highest in younger children [21]. Similarly, studies in adult transplant recipients have demonstrated

that primary varicella infection after transplantation is associated with greater disease severity compared with viral reactivation [22].

In our study, which encompassed all age groups, the risk of varicella was highest among pediatric transplant recipients. However, despite the higher absolute incidence, the SIR was lower among pediatric transplant recipients than in the general pediatric population. This finding likely reflects the exceptionally high background incidence of varicella in Korean children. Owing to the high incidence of varicella among children and adolescents who engage in social activities and group living, the incidence may still be relatively low among transplant recipients gradually reintegrating into the community. Therefore, the cumulative incidence of varicella in pediatric transplant recipients revealed a linear increase post-transplantation, plateauing approximately 8–9 years post-transplantation [23]. Additionally, following the implementation of stringent non-pharmacological interventions beginning in February 2020 due to the COVID-19 pandemic, the 2020 Annual Report further supported this finding by demonstrating a significant increase in the SIR for the 0–9-year age group, from 0.18 to 0.48.

In adults aged 60+, the incidence rate of varicella among transplant recipients was more than six times that in the general population. A recent study investigating the serology and infections related to measles, mumps, rubella, and varicella (MMRV) in SOT recipients during the first-year post-transplantation revealed that approximately 14% of transplant recipients were negative for antibodies against at least one of the MMRV viruses [24], emphasizing the importance of boosting active immunization.

The high incidence of IPD in transplant recipients was consistent with the results of previous studies [14–18]. However, in the Korean population, the incidence of IPD is not as high as that of varicella or mumps [13]. Possible explanations include: Universal pneumococcal vaccination for infants, young children, and older adults in the NIP may have reduced the risk of IPD in the general population [25–27]. However, except for pediatric HCT recipients, revaccination or administering a pneumococcal booster vaccination post-transplantation is uncommon in adult transplant recipients, as the cost is not covered by the government. Additionally, the risk of IPD can persist in transplant recipients until immune recovery and restoration of natural barriers post-transplantation,

allowing for colonization by pneumococcal strains and subsequent evasion, which can progress to IPD [14, 16]. Preceding or concurrent viral infections, particularly community-acquired respiratory viral infections such as respiratory syncytial virus, may increase the risk of subsequent IPD, providing another explanatory factor [28]. These factors suggest that the risk of IPD may be high not only during the early post-transplant period when immunity is insufficiently restored, but also in late post-transplant recipients exposed to community viral infections. Furthermore, when considering transplanted organs, SOT recipients showed significantly higher IPD rates than auto-HCT recipients and higher rates than allo-HCT recipients. Although the difference was not statistically significant, this increased risk in SOT recipients is likely due to their continuous exposure to risk because of long-term immunosuppressant use. These findings suggest that pneumococcal vaccination strategies for SOT recipients may warrant further consideration.

Interestingly, mumps was the second most common VPD after varicella in the general population. When considering the SIR, its incidence was lower in transplant patients than in the general population. Despite the two-dose MMR vaccination rate being >95% in South Korea, a significant 10-fold increase in the incidence of mumps was reported from 2001 to 2015, with most cases in school-age individuals, highlighting transmission in school settings as a crucial factor [29, 30]. Moreover, seropositivity did not reach a level sufficient to achieve herd immunity [31]. In our study, the proportion of school-age children (<20 years), the age group most commonly affected by mumps, accounted for less than 10% of the study population, which may have contributed to the observed lower SIR. This finding should not be interpreted as indicating a higher susceptibility to mumps infection in the general population. Rather, it likely reflects the more limited social activity among transplant recipients compared with the general population, resulting in fewer opportunities for exposure to infectious agents. This interpretation is further supported by reports demonstrating a reduction in mumps incidence during periods of social distancing implemented during the COVID-19 pandemic [32]. In this context, an increase in mumps prevalence in the general population may pose a potential risk to pediatric transplant recipients as they gradually reintegrate into social and school environments. In particular, because administration of the MMR vaccine is limited in solid organ transplant recipients [8], the risk of infection may be increased among those

with no or incomplete vaccination history. Therefore, ongoing consideration of MMR vaccination strategies in SOT recipients remains necessary.

This study has several limitations. First, due to the retrospective observational design of this study, not all potential confounding factors associated with the occurrence of VPDs could be fully adjusted for. Important clinical factors, including the intensity of immunosuppression, systemic corticosteroid therapy, asplenia, graft-versus-host disease, hypogammaglobulinemia, as well as individual immunosuppressive regimens and healthcare utilization patterns, were not available in the dataset. Therefore, the findings should be interpreted as associations rather than causal relationships.

Second, because this study was based on the HIRA database, individual vaccination histories could not be ascertained; therefore, we were unable to directly evaluate the impact of prior vaccination on the incidence of VPDs in transplant recipients. The absence of vaccination data may have led to underestimation or overestimation of infection risk, depending on baseline vaccine coverage in the study population. However, given that most vaccines included in the NIP have coverage rates exceeding 95%, substantial misclassification related to vaccination status—particularly in the pre-transplant period—is unlikely.

Third, because this study was conducted using administrative claims data, diagnoses were based on diagnostic codes rather than on clinical confirmation. As a result, some infection cases may have been missed or misclassified. In particular, infections with mild clinical manifestations that did not prompt medical visits, as well as limitations in the accuracy of diagnostic coding, may have led to either underestimation or overestimation of infection incidence. To address these limitations, we conducted a validation substudy to assess the validity of the diagnostic criteria used in this study, and a high concordance rate of 80–100% was observed for varicella, IPD, and pertussis. Conversely, Mumps showed a lower concordance rate of 50% (4/8), as half of the cases identified were diagnosed as acute parotitis with uncertain mumps etiology, reflecting the challenges of confirming mumps via PCR in routine clinical settings. Therefore, while our study may be subject to potential overestimation due to the operational definitions used, we estimate this overestimation to be within the range of 10–20%.

In addition, this study was a retrospective analysis based on National Health Insurance Service claims data, and the nature of such data limits the ability to directly assess the clinical severity or detailed course of individual infection episodes. Specifically, we were unable to determine whether VPDs were associated with severe complications, to evaluate detailed in-hospital clinical outcomes, or to ascertain whether these infections were the direct cause of death.

Finally, HZ was not included in the primary analysis, despite its clinical relevance in transplant recipients. This study relied on the national surveillance system to calculate SIRs; however, HZ is not included as a reportable disease, limiting the availability of reliable population-level incidence data for comparison with the general population. In addition, the primary objective of this study was to evaluate community-acquired infections following transplantation, whereas HZ represents reactivation of latent VZV rather than a newly acquired infection. Furthermore, the use of administrative claims data poses challenges in distinguishing primary varicella from disseminated HZ, introducing potential misclassification bias. For these reasons, a conservative approach was adopted by excluding HZ and focusing only on primary varicella infection. Nevertheless, HZ constitutes a substantial disease burden in immunocompromised populations, and with the recent availability of recombinant zoster vaccines, future studies incorporating HZ-specific outcomes are warranted to better capture the full spectrum of VZV-related disease burden in transplant recipients.

Nevertheless, our study has several strengths. First, to the best of our knowledge, this is the largest population-based study (>50,000 individuals) investigating the incidence and risk factors of VPDs such as varicella, IPD, mumps and pertussis in transplant recipients across all age groups post-transplantation. Second, by utilizing a national retrospective database, we could access the cumulative incidences of varicella and IPD, which are difficult to evaluate using a single- or multicenter study design. Third, our study can be used to assess the relative risk of major VPDs in transplant recipients compared with that of the general population by leveraging the characteristics of VPDs in Korea, where these diseases are mandated to be reported by clinicians upon diagnosis. While there are several strengths, a large-scale study incorporating factors we may not have considered, which could serve as risk factors for post-transplant infections, would be beneficial for future

vaccination planning in transplant recipients.

In conclusion, our study demonstrated that transplant recipients exhibit a higher risk of developing VPDs than does the general population. Although the incidence of VPDs varied across age groups and transplant types, these findings indicate that transplant recipients remain persistently vulnerable to specific infections. Therefore, timely administration of recommended vaccines, such as varicella and pneumococcal vaccines, along with strengthened and continuous infection surveillance after transplantation, should be emphasized in this population. Such targeted preventive strategies may help reduce the burden of VPDs and improve clinical outcomes among transplant recipients.

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Conflict of Interest

No conflict of interest.

Author Contributions

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Procedure codes for transplantation

Supplementary Table 2

Diagnostic criteria for 11 vaccine-preventable diseases in the annual report of infectious diseases in Korea and number of reported cases between 2016 and 2020

Supplementary Table 3

Validation study using medical records from Severance Hospital involving patients diagnosed with Varicella, IPD, Pertussis, and Mumps between January 1, 2023, and December 31, 2025

Supplementary Figure 1

Cumulative incidence rate of varicella and invasive pneumococcal disease (IPD).

Supplementary Figure 2

Standardized incidence ratio of major vaccine-preventable diseases (compared to general population data from the 2020 Annual Report of Infectious Diseases in Korea).

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