

Retrospective Study

Immunization status and hospitalization for vaccine-preventable and non-vaccine-preventable infections in liver-transplanted children

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Abstract**BACKGROUND**

Infections and associated morbidity and mortality may be more frequent in children who have undergone liver transplant than in healthy children. Immunization strategies to prevent vaccine-preventable infections (VPIs) can effectively minimize this infection burden. However, data on age-appropriate immunization and VPIs in children after liver transplant in Asia are limited.

AIM

To evaluate the immunization status, VPIs and non-VPIs requiring hospitalization in children who have undergone a liver transplant.

METHODS

The medical records of children who had a liver transplant between 2004 and 2018 at King Chulalongkorn Memorial Hospital (Bangkok, Thailand) were retrospectively reviewed. Immunization status was evaluated *via* their vaccination books. Hospitalization for infections that occurred up to 5 years after liver transplantation were evaluated, and divided into VPIs and non-VPIs. Hospitalizations for cytomegalovirus and Epstein-Barr virus were excluded. Severity of infection, length of hospital stay, ventilator support, intensive care unit requirement, and mortality were assessed.

RESULTS

informed consent to the study because the analysis used anonymous clinical data that were obtained after each the patient agreed to treatment by written consent.

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Seventy-seven children with a mean age of 3.29 ± 4.17 years were included in the study, of whom 41 (53.2%) were female. The mean follow-up duration was 3.68 ± 1.45 years. Forty-eight children (62.3%) had vaccination records. There was a significant difference in the proportion of children with incomplete vaccination according to Thailand's Expanded Program on Immunization (52.0%) and accelerated vaccine from Infectious Diseases Society of America (89.5%) ($P < 0.001$). Post-liver transplant, 47.9% of the children did not catch up with age-appropriate immunizations. There were 237 infections requiring hospitalization during the 5 years of follow-up. There were no significant differences in hospitalization for VPIs or non-VPIs in children with complete and incomplete immunizations. The risk of serious infection was high in the first year after receiving a liver transplant, and two children died. Respiratory and gastrointestinal systems were common sites of infection. The most common pathogens that caused VPIs were rotavirus, influenza virus, and varicella-zoster virus.

CONCLUSION

Incomplete immunization was common pre- and post-transplant, and nearly all children required hospitalization for non-VPIs or VPIs within 5 years post-transplant. Infection severity was high in the first year post-transplant.

Key Words: Children; Hospitalization; Immunization; Liver transplant; Thailand; Vaccine-preventable infection

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Core Tip: Incomplete age-appropriate immunization in children waiting for a liver transplant was expected, and nearly half of them had not caught up with age-appropriate vaccinations post-transplant. Though there was no significant difference in hospitalization from vaccine-preventable infections (VPIs) and non-VPIs in children with complete and incomplete immunizations. At least 13.1% required hospitalization within 5 years post-transplant, and > 10% were admitted to the intensive care unit and required respiratory support. The severity of infections was high during the first year post-transplant. Complete immunization and robust infection control should be prioritized in children both pre and post-liver transplant.

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INTRODUCTION

Infection after a liver transplant is a serious concern due to potential associated morbidity and mortality^[1-4], as well as the standard complications and severe symptoms that can be experienced by immunocompetent patients. Such infections can give rise to graft rejection, thus affecting short- or long-term graft survival^[4]. Accordingly, strategies to reduce overall post-transplant infection are warranted. Immunization is considered an effective, relatively noninvasive, and affordable way to reduce vaccine-preventable infections (VPIs)^[5] such as measles, varicella, influenza, and viral hepatitis A and B, among others. The Infectious Diseases Society of America (IDSA)^[6] and the American Society of Transplantation Infectious Disease Community of Practice^[7] encourage accelerated vaccination, particularly with regard to live vaccines in immunocompromised children awaiting for solid organ transplantation.

Children awaiting a liver transplant can be at a disproportionate risk of VPIs because they tend not to have undergone a complete series of age-appropriate immunizations, because their serious illness has taken medical priority over vaccination^[8]. Verma and Wade^[9] reported that in their experience at King's College



Hospital, only 20%-30% of children had undergone a complete series of age-appropriate immunizations prior to liver transplantation. Diana *et al*^[10] reported that less than half of a cohort of children who underwent liver transplant at the Children's Hospital of Geneva in Switzerland had undergone a complete series of age-appropriate vaccinations, with rates of 43% for diphtheria-tetanus-acellular pertussis-polio vaccine, 44% for measles-mumps-rubella (MMR) vaccine, 13% for hepatitis B vaccine, and 5% for hepatitis A vaccine at the time of liver transplantation. Feldman *et al*^[4,11] investigated morbidity, mortality, and costs associated with VPIs in children after solid organ transplants, and reported a significantly higher rate of VPIs in these children than in the general pediatric population.

Studies conducted in the United States and other western countries have highlighted the effects of VPIs in children after solid organ transplantation^[4,9-11], but published data on VPIs in children after liver transplantation in the East are scarce. To improve the quality of life of liver-transplanted children by minimizing the serious complications associated with post-liver transplant infections, strategies to avoid VPIs based on strong evidence should be initiated worldwide, including in Asia.

The aim of the present study was to evaluate immunization status in Thai children at the time of liver transplantation, and for up to 5 years post-liver transplantation. The prevalence and effects of VPIs and non-VPIs during hospitalization were also assessed.

MATERIALS AND METHODS

The current study was a retrospective review of all children who received a liver transplant at King Chulalongkorn Memorial Hospital in Thailand from January 2004 to August 2018. Demographic data, patient characteristics, and immunization records from vaccination books were collated. Hospitalization records pertaining to the liver transplant operation and admission due to infections for up to 5 years post-transplant were included. Hospitalizations for Epstein-Barr virus (EBV) and cytomegalovirus were excluded from the study. Infection etiology and source were investigated by the doctors in charge. Culture from specimens was available for all bacterial origins, and immunological and molecular techniques were available for the diagnosis of both viral and bacterial infections, including polymerase chain reaction panel analysis for respiratory tract infections and gastrointestinal infections, and antibody titers for hepatitis A/B/E, dengue, and measles.

Infections were divided into VPIs and non-VPIs. Length of hospital stay, severity of infections, and mortality from infections were collated and classified into three groups: Intensive care unit (ICU) requirement, ventilator support, and death. Complete immunization was defined as that conducted in accordance with the Expanded Program on Immunization (EPI) in Thailand (Table 1) and the accelerated vaccination recommendations described in the 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host^[6], which notes: "... children aged 6-12 mo can receive MMR and varicella vaccine and the second dose should be administered at 12 mo for MMR and ≥ 3 mo apart for varicella vaccine. However, the last MMR or varicella vaccine injection should not be within 4 wk of a liver transplant schedule."

Statistical analysis

Continuous and categorical data are presented as the mean \pm SD, medians and interquartile ranges, proportions, or percentages as appropriate. The Mann Whitney *U* test and unpaired *t*-test were used to compare continuous data, and Fisher's exact test and the χ^2 test were used to compare discrete data. $P < 0.05$ was considered statistically significant. Data analyses were performed using Statistical Package for the Social Sciences version 24.0.0 (SPSS, Inc.; Chicago, IL, United States). A biomedical statistician employed at the Department of Statistics Science, Kasetsart University (Bangkok, Thailand) reviewed the statistical analyses conducted in the study.

RESULTS

Patient characteristics and history of immunization

Seventy-seven children with a mean age of 3.29 ± 4.17 years were included in the study, of whom 41 (53.2%) were female. The indications for liver transplantation were biliary atresia ($n = 63$), indeterminate acute liver failure ($n = 3$), progressive familial

Table 1 The immunization schedule in Thailand and accelerated vaccines by the Infectious Disease Society of America

	Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	7 mo	9 mo	12 mo	18 mo	24 mo	4 yr	9 yr	11 yr	
Thai's EPI vaccines	BCG	1													
	HBV	1	(For positive maternal HBsAg)	2		3									
	DTP, OPV/IPV			1	2	3				4		5			
	MMR					Acc ¹		1	Acc ¹		2				
	JE							1			2				
	Influenza					1	2								
	Tdap														1
	HPV													Acc	1-2 ²
Optional vaccine in Thailand	Rota			1	2	(3)									
	PCV			1	2	3			4						
	Varicella					Acc ¹		Acc ¹	1	2					
	HAV								1	2					
	Dengue												1-3 ³		

¹Acc denotes accelerated vaccines from the 2013 Infectious Diseases Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host in which measles-mumps-rubella (MMR) at 6 and 12 mo of age and varicella at 6 mo of age and 3 mo apart from the first dose.

²Indicates 0 and 6 mo.

³Indicates 0, 6, 12 mo.

BCG: Bacillus Calmette-Guerin vaccine; DTP: Diphtheria-tetanus-pertussis; EPI: Expanded Program on Immunization; HAV: Hepatitis A vaccine; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B vaccine; HPV: Human papillomavirus vaccine; JE: Japanese encephalitis; OPV/IPV: Oral polio vaccine/inactivated polio vaccine; PCV: Pneumococcal conjugate vaccine; Tdap: Tetanus-diphtheria-acellular pertussis.

intrahepatic cholestasis ($n = 2$), Alagille syndrome ($n = 2$), cryptogenic cirrhosis ($n = 1$), citrin deficiency ($n = 1$), Budd-Chiari syndrome ($n = 1$), hepatoblastoma ($n = 1$), autoimmune hepatitis ($n = 1$), glycogen storage disease type IV ($n = 1$), and bile acid deficiency ($n = 1$). The mean follow-up time was 3.68 ± 1.45 years, and 32 children were followed up for a full 5 years after liver transplantation. Vaccinations were noted in the vaccination books of 48/77 children (62.3%). Substantial proportions of children did not have complete vaccinations in accordance with Thailand's EPI ($n = 25$, 52%) (Table 1) or accelerated vaccinations in accordance with the IDSA recommendations ($n = 43$, 89.5%) ($P < 0.001$). Post-liver transplant, 23 children (47.9%) could not catch up with the appropriate immunizations for age. All children were revaccinated with hepatitis B vaccine if hepatitis B surface antibody was < 10 mIU/mL. Other vaccines

they received after liver transplantation included those for influenza ($n = 12$), invasive pneumococcal disease ($n = 10$), Japanese encephalitis ($n = 6$), diphtheria/tetanus/pertussis-inactivated polio vaccine ($n = 6$), and hepatitis A ($n = 3$). A minority of children were not up-to-date with influenza vaccination ($n = 18$, 37.5%) and pneumococcal conjugate vaccine ($n = 22$, 45.8%) post-liver transplant compared with pre-liver transplant ($n = 30$, 62.5% for influenza and $n = 36$, 75% for pneumococcal conjugate vaccine) ($P < 0.001$; **Table 2**). With regard to live vaccines, three individuals were inadvertently vaccinated with MMR at their local hospitals without any serious side effects.

Infections during and after liver transplant

Infection severity and mortality were highest during the first year post-liver transplant. The respiratory and gastrointestinal systems were the most common sites of infection (**Table 3**). Two children died within 3 mo after liver transplantation, and both had underlying post-transplant lymphoproliferative disorder. One of these two children had mixed infection with bocavirus, mycoplasma, and parvovirus B19. The other exhibited EBV viremia that progressed to respiratory failure with an unidentified infectious origin. Of the 31 hospitalizations for VPIs recorded during the study period the median length of hospital stay was 6 d (range: 3-8 d), and in three cases ICU admission and ventilator support were required; two with influenza and one with *Streptococcus pneumoniae* infection. When the children were divided into complete and incomplete immunization groups based on Thailand's EPI, there were no significant differences in the numbers of hospitalizations for VPIs or non-VPIs (**Table 4**).

Pathogens causing hospitalization in children post-liver transplant

A total of 237 infections requiring hospitalization were recorded during the study period. The most commonly identified bacterial pathogens were *Escherichia coli* (13.1%), *Salmonella* sp. (8.1%), and *Klebsiella pneumoniae* (6.8%), and the most commonly identified viral pathogens were parainfluenza (5.9%), rotavirus (3.4%), and respiratory syncytial virus (3.4%). In cases of VPIs, the most common pathogens were rotavirus (3.4%), influenza virus (2.5%), and varicella-zoster virus (2.1%) (**Table 5 and 6**).

DISCUSSION

In this study, incomplete age-appropriate immunization before liver transplantation in children was common, particularly with regard to live vaccines that can be accelerated before liver transplantation. Post-liver transplant in nearly half of the children in the study did not catch up with all age-appropriate vaccines. At least 13.1% of the children in the study required hospitalization for VPIs during the 5 years post-liver transplant, and in these cases, the lengths of hospital stays were up to 1 wk. More than 10% of the children required admission to the ICU and respiratory support from VPIs, reflecting the burden of VPIs during the post-transplant period. With regard to non-VPIs, both bacterial and viral infections of the respiratory and gastrointestinal systems played major roles in hospitalizations with severe infections and mortality, especially during the first year post-transplant.

To the best of our knowledge, the current study is the first to investigate immunization status and infections requiring hospitalization in Asian children who underwent a liver transplant. Compared to previous studies in Europe^[9,10] and the United States^[4,11], in the present study, there was a higher rate of incomplete age-appropriate immunization before liver transplantation, particularly with respect to the accelerated MMR and varicella vaccination. However, the number of hospitalizations with VPIs (13.1%) was comparable to that in a study conducted in the United States by Feldman *et al*^[4,11] (11.3%). Moreover, the VPIs in that study were more severe and required longer hospital stays than those in the current study. Genetic risk factors may explain this phenomenon, as with the more contagious and severe coronavirus disease 2019 infections in Europe and the United States than in Thailand.

Prior to liver transplantation, physicians frequently do not offer patient immunization, particularly with respect to live vaccines^[8,12,13]. There is solid evidence of adequate immune responses to varicella and measles vaccinations in children aged < 1 year^[14-16]; hence, the policy to promote accelerated vaccination in children before immunosuppressant therapy was initiated^[6,7,17,18]. It is probable that this is not standard practice in healthy children. Moreover, children waiting for a liver transplant may have had complex and serious illnesses that needed to be given priority. Some physicians may not be familiar with the accelerated immunization program^[8,13], and

Table 2 Vaccination history in children at liver transplant and up to 5 years follow-up (n = 48)

Vaccines	Incomplete vaccination for age at transplantation		Incomplete vaccination for age after liver transplant, n (%)
	Thai EPI program, n (%)	Accelerated vaccine from IDSA, n (%)	
DTP-OPV/IPV	12 (25)	N/A	6 (12.5)
HBV	6 (12.5)		0
MMR	12 (25)	30 (62.5) ^b	27 (56.3) ^b
JE	16 (33.3)	N/A	10 (20.8)
Varicella	16 (33.3)	34 (70.8) ^b	34 (70.8) ^b
HAV	26 (54)		23 (47.9)
Influenza	30 (62.5)		18 (37.5) ^a
PCV	36 (75)		22 (45.8) ^b
Rota	37 (77)	N/A	37 (77)
All	25 (52)	43 (89.5) ^b	23 (47.9)
	(not included rota vaccine)		(not included live vaccine)

^a $P < 0.05$ vs Thai Expanded Program on Immunization (EPI).

^b $P < 0.001$ vs Thai EPI program.

DTP: Diphtheria-tetanus-pertussis; HAV: Hepatitis A vaccine; HBV: Hepatitis B vaccine; IDSA: Infectious Diseases Society of America; JE: Japanese encephalitis; MMR: Measles-mumps-rubella; N/A: Not applicable; OPV/IPV: Oral polio vaccine/inactivated polio vaccine; PCV: Pneumococcal conjugate vaccine.

therefore may decide to postpone vaccination. A specific protocol and concerted focus on educational interventions, or the development of specialized team care that is responsible for these issues is crucial to ensure that all candidates receive appropriate vaccinations to minimize complications associated with VPIs^[6]. One great benefit of pre-liver transplant vaccination is higher immunogenicity compared with revaccination post-liver transplant^[18]. Moreover, pretransplant vaccination of children will likely lead to herd immunity that will be beneficial for other transplant children in inpatient and outpatient clinics during their visits^[13].

In the present study, the rate of incomplete age-appropriate immunization after liver transplantation was high, and there was no significant difference between the pretransplant rate (52.0%) and the post-transplant rate (47.9%). In theory, children's vaccination schedules should be postponed for more than 2 mo after liver transplantation because of the possibility of an inadequate immune responses^[6]. The high level of immunosuppressants is another factor to consider. In the present study almost half of the children were not up-to-date with their age-appropriate immunizations during up to 5 years of follow-up. The reasons might be relatively low concern over children in a stable condition post-transplant, and a level of immunosuppression that is not low enough to warrant immunization. Notably, only 62.3% of the children's guardians brought vaccination books to visits to the doctor. As well as unawareness, financial problems would likely be a major concern for the children's guardians, especially with regard to vaccines that are not included in Thailand's EPI such as pneumococcal conjugate vaccine, influenza vaccine, hepatitis A vaccine, and varicella vaccine. Fortunately the infectious diseases unit in our department conducted a campaign to promote the administration of pneumococcal conjugate vaccine and influenza vaccine to all immunocompromised children every year at no charge. This afforded the children in the present study the opportunity to access these vaccines, and there was a significant increase in the proportion of children that received these vaccines post-transplant ($P < 0.001$). Long-term provision of these high-cost vaccines by the authorities would be a worthwhile venture. With respect to live vaccines, there has been controversy about whether they should be administered to children after liver transplantation^[17,19,20-23]. Thus, further reports and large cohort studies are required in order to clarify the safety of live vaccines in these vulnerable patients, before they are routinely vaccinated posttransplant.

In this study, the rate of hospitalization for VPIs up to 5 years post-transplant was similar to those reported in previous studies^[9-11], but significantly higher than that in

Table 3 Characteristics of hospitalization from vaccine-preventable infections and non-vaccine-preventable infections up to 5 years follow-up

Time	Type of infections				Organ specific infections, n (%)						The severity of infections, n (%)		
	VPIs		Non-VPIs		RS	GI	Blood	Renal	Skin	Others	ICU	Ventilator dependence	Death
	Times, n (%)	LOS (d) ¹	Times, n (%)	LOS (d) ¹									
During transplant	4 (5.2)	51 (24,79)	73 (94.8) ^b	35 (27,49)	25 (35.2)	24 (31.2)	20 (26)	6 (7.8)	2 (2.6)	0	All	All	0
< 3 mo	2 (6.9)	3 (3,3)	27 (93.1) ^b	12 (7,28) ^a	13 (44.8)	10 (34.5)	2 (6.9)	2 (6.9)	1 (3.4)	1 (3.4)	6 (20.7)	5 (17.2)	2 (6.9)
3-6 mo	5 (17.9)	8 (5,39)	23 (82.1) ^b	10 (4,15)	11 (39.3)	13 (46.4)	2 (7.1)	1 (3.6)	0	1 (3.6)	8 (28.6)	6 (21.4)	0
> 6-12 mo	3 (8.3)	5 (3,5)	33 (91.7) ^b	7 (6,17)	15 (41.7)	11 (30.6)	6 (16.7)	0	2 (5.6)	2 (5.6)	10 (27.8)	6 (8.3)	0
> 12-24 mo	6 (15)	5 (4,9)	34 (85) ^b	7.5 (5,10)	18 (45)	12 (30)	1 (2.5)	1 (2.5)	4 (10)	4 (10)	11 (27.5)	9 (22.5)	0
> 2-5 yr	11 (40.7)	6 (3,8)	16 (59.3)	5 (4,9)	7 (25.9)	10 (37)	1 (3.7)	0	6 (22.2)	3 (1.9)	5 (18.5)	1 (3.7)	0
Total	31 (13.1)	6 (3,8)	206 (86.9) ^b	8 (5,15)	89 (37.6)	80 (33.8)	32 (13.5)	10 (4.2)	15 (6.3)	11 (4.6)	40 (16.9)	27 (11.4)	2 (0.84)

^a $P < 0.05$ vs vaccine-preventable infection (VPI) group.

^b $P < 0.001$ vs VPI group.

¹Data are presented as median (interquartile range).

GI: Gastrointestinal; ICU: Intensive care unit; LOS: Length of stay; RS: Respiratory system.

the normal population^[9]. There was the mortality report of VPIs in children with immunocompromised hosts^[1,2,22,24,25], but in this study, there was no mortality from VPIs. The VPIs requiring hospitalization in the current study were due to rotavirus, influenza, varicella, dengue fever, measles, *Streptococcus pneumoniae*, hepatitis B/E, and *Vibrio cholera*. These data should emphasize the value of complete immunization and robust infection control to physicians.

Viral hepatitis is endemic in Thailand, but interestingly in the present study there were no reports of hospitalization for hepatitis A post-liver transplant, and only one case of hepatitis E infection that required hospitalization. Viral hepatitis can be symptomatic and severe in older children and adults, and older children and adults may ingest more contaminated food and water than young children. Consequently, serology testing and immunization may be valuable in these groups. There is a reported case in which *de novo* hepatitis B infection was diagnosed 3 years after a liver transplant despite the recipient having undergone complete hepatitis B immunization pre-transplant^[26]. This demonstrates that complete hepatitis B immunization pre-liver transplant does not guarantee post-transplant protection. That case prompted us to instigate a protocol for reimmunization and hepatitis B surface antibody monitoring every 3-6 mo to maintain a protective level of > 100 mIU/mL. *De novo* hepatitis B in the aforementioned boy who had hepatitis B surface antibody > 1000 mIU/mL pre

Table 4 Children with vaccination records who developed vaccine-preventable or non-vaccine-preventable diseases

Age-appropriate immunization	Thai's Expanded Program on Immunization				2013 Infectious Diseases Society of America			
	Infection and hospitalization, <i>n</i>			Total	Infection and hospitalization, <i>n</i>			Total
	None	VPIs and non-VPIs	Non-VPIs		None	VPIs and non-VPIs	Non-VPIs	
Complete immunization	5	5	12	22	9	9	25	43
Incomplete immunization	5	6	15	26	1	2	2	5
Total	10	11	27	48	10	11	27	48

VPIs: Vaccine-preventable infections.

transplant^[26] may reflect waning immunity post-liver transplant. As well as vaccination, research evaluating the humoral and cellular immunity evoked by each vaccine should be conducted to determine vaccination schedules and the antibody parameters required to prevent VPIs more effectively. In the present study, the overall infection rate was high in the first year post-transplant, hence vaccination should be initiated as soon as possible after liver transplanted children are sufficiently stable. Predictors of high immunogenic responsiveness to vaccination are needed to enable physicians to decide on optimal timepoints for reimmunization.

The current study had some limitations. It was a single-center study with a relatively small sample size. The true prevalence of VPIs may be lower than the frequency in the study, because the study only included children with severe enough illness to require hospitalization. Almost all children in the present study were referred from distant and rural areas, and it is possible that some of them subsequently attended more local hospitals due to infections. The main strength of the study was the reliable vaccination records obtained directly from the patients' vaccination books, which facilitated comparisons of vaccination status pre-transplant and post-transplant.

CONCLUSION

Incomplete immunization was common in children pre-liver transplant and post-liver transplant. Almost all of the children in the study required hospitalization due to VPIs or non-VPIs within 5 years post-liver transplant. The severity of infections was highest in the first year post-liver transplant.

Table 5 Pathogen causing hospitalization in children after liver transplantation

Time	The rank of the pathogen, n (%)			
	Bacteria	Total	Virus, fungus, and unidentified	Total
During transplant	<i>E. coli</i> (n = 19, 24.7), <i>K. pneumoniae</i> (n = 12, 15.6), <i>A. baumannii</i> (n = 11, 14.3), <i>Enterococcus/Staphylococcus</i> (n = 4, 5.2), <i>Salmonella</i> (n = 3, 3.9), <i>P. aeruginosa</i> (n = 2, 2.6), <i>B. cereus/Corynebacterium/S. pneumoniae/Elizabethkingia meningoseptica/Stenotrophomonas/Streptococcus mirabilis/C. difficile</i> (n = 1, 1.3)	62	Rotavirus/adenovirus/bocavirus (n = 2, 2.6), parainfluenza/fungus/varicella-zoster virus (n = 1, 1.3)	9 ^b
< 3 mo	<i>E. coli/K. pneumoniae/Enterococcus/Salmonella/Aeromonas</i> (n = 2, 6.9), <i>Corynebacterium/C. difficile/Plesiomonas</i> (n = 1, 3.4)	13	Parainfluenza (n = 3, 10.3), coronavirus (n = 2, 6.9), rotavirus/bocavirus/RSV/dengue/fungus/norovirus/rhinovirus/parvovirus B19 (n = 1, 3.4), unidentified (n = 6, 20.7)	19
3-6 mo	<i>Salmonella/E. coli</i> (n = 2, 7.1), <i>K. pneumoniae/Enterococcus/S. pneumoniae/Staphylococcus</i> (n = 1, 3.6)	8	RSV (n = 4, 14.3), influenza (n = 2, 7.1), rotavirus/parainfluenza/rhinovirus/measles/HHV6 (n = 1, 3.6), unidentified (n = 9, 32.1)	20
> 6-12 mo	<i>E. coli</i> (n = 4, 11.1), <i>Salmonella</i> (n = 3, 8.3), <i>A. baumannii/Enterococcus/mycoplasma/C. difficile</i> (n = 2, 5.6), <i>Stenotrophomonas/Staphylococcus/Aeromonas/Pseudomonas/Plesiomonas/P. jirovecii</i> (n = 1, 2.8)	21	Parainfluenza (n = 3, 8.3), norovirus/herpes simplex virus (n = 2, 5.6), fungus/RSV/rhinovirus/influenza/measles (n = 1, 2.8), unidentified (n = 3, 8.3)	15
> 12-24 mo	<i>Salmonella</i> (n = 8, 12.5), <i>E. coli</i> (n = 3, 7.5), <i>Aeromonas/Pseudomonas/mycoplasma/Plesiomonas</i> (n = 1, 2.5)	15	Parainfluenza (n = 6, 15), rotavirus (n = 2, 5), adenovirus/varicella-zoster virus/dengue/rhinovirus/influenza/measles/metapneumovirus/hepatitis E/coxakie AB (n = 1, 2.5) unidentified (n = 11, 27.5)	28
> 2-5 yr	<i>Salmonella/mycoplasma</i> (n = 2, 7.4), <i>E. coli/K. pneumoniae/Staphylococcus/Vibrio cholera/B. cereus</i> (n = 1, 3.7)	9	Varicella-zoster virus (n = 3, 11.1), rotavirus/RSV/dengue/influenza (n = 2, 7.4), fungus/norovirus/herpes simplex virus/hepatitis B (n = 1, 3.7), unidentified (n = 3, 11.1)	18
Overall	<i>E. coli</i> (n = 31, 13.1), <i>Salmonella</i> (n = 20, 8.1), <i>K. pneumoniae</i> (n = 16, 6.8), <i>A. baumannii</i> (n = 13, 5.5), <i>Enterococcus</i> (n = 9, 3.8), <i>Staphylococcus</i> (n = 8, 3.3), <i>mycoplasma</i> (n = 5, 2.1), <i>C. difficile</i> (n = 4, 1.7), <i>Plesiomonas Shigelloides/Aeromonas</i> (n = 3, 1.3), <i>Corynebacterium/S. pneumoniae/Stenotrophomonas/P. aeruginosa/Aeromonas</i> (n = 2, 0.8), <i>Bacillus/Elizabethkingia meningoseptica/Streptococcus mirabilis/P. jirovecii/Vibrio cholera/B. cereus</i> (n = 1, 0.4)	128	Parainfluenza (n = 14, 5.9), rotavirus/RSV (n = 8, 3.4), influenza (n = 6, 2.5), varicella-zoster virus (n = 5, 2.1), dengue/norovirus/fungus/rhinovirus (n = 4, 1.7), adenovirus/bocavirus/herpes simplex virus/measles (n = 3, 1.3), coronavirus (n=2, 0.8), HHV6/metapneumovirus/hepatitis E/coxakie AB/hepatitis B (n = 1, 0.4), unidentified (n = 32, 13.5)	109 ^b

^bP < 0.001; virus *vs* bacterial causes of infections at each time point. *A. baumannii*: *Acinetobacter baumannii*; *B. cereus*: *Bacillus cereus*; *C. difficile*: *Clostridium difficile*; *E. coli*: *Escherichia coli*; HHV6: Human herpes virus 6; *K. pneumoniae*: *Klebsiella pneumoniae*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. jirovecii*: *Pneumocystis jirovecii*; RSV: Respiratory syncytial virus; *S. pneumoniae*: *Streptococcus pneumoniae*.

Table 6 Vaccine-preventable infections causing hospitalization in children after liver transplantation

Time	During transplant	< 3 mo	3-6 mo	> 6-12 mo	> 12-24 mo	> 2-5 yr	Overall
Rota	2	1	1	0	2	2	8
Influenza	0	0	2	1	1	2	6
Varicella	1	0	0	0	1	3	5
Dengue	0	1	0	0	1	2	4
Measles	0	0	1	1	1	0	3
<i>Streptococcus pneumoniae</i>	1	0	1	0	0	0	2
Hepatitis B	0	0	0	0	0	1	1
Hepatitis E	0	0	0	0	1	0	1
<i>Vibrio cholera</i>	0	0	0	0	0	1	1

ARTICLE HIGHLIGHTS

Research background

Infection after liver transplantation is a serious concern due to potential morbidity and mortality, thus strategies to reduce overall post-transplant infection are warranted. Immunization is an effective and relatively noninvasive and affordable way to reduce vaccine-preventable infections (VPIs).

Research motivation

There is strong evidence that VPIs and non-VPIs post-transplant cause high fatality and increase graft rejection, but published data on VPIs and their effects in children post-liver transplant in Asia are scarce.

Research objectives

To investigate immunization status in children at the time of liver transplantation and up to 5 years thereafter. The prevalence and impact of VPIs and non-VPIs during hospitalization were also evaluated.

Research methods

The current retrospective study included 77 children who underwent liver transplantation and were followed up for up to 5 years thereafter. Demographic data, patient characteristics, immunization details derived from vaccination records, and hospitalizations for VPIs and non-VPIs were analyzed.

Research results

The mean follow-up duration after liver transplantation was 3.68 ± 1.45 years. Of the 77 children in the study, 48 (62.3%) had vaccination records in their vaccination books. There was a significant difference in the proportion of children with incomplete vaccination according to Thailand's Expanded Program on Immunization ($n = 25$, 52%) and accelerated vaccine from Infectious Diseases Society of America recommendations ($n = 43$, 89.5%) ($P < 0.001$). Post-liver transplant, almost half of the children in the study did not catch up with appropriate immunizations for age. There were 237 infections requiring hospitalization during up to 5 years of follow-up post-liver transplant at our hospital. The risks of VPIs and non-VPIs were highest during the first year after liver transplantation, and 2 children died. Respiratory and gastrointestinal systems were common sites of infection. The most commonly identified pathogens that caused VPIs were rotavirus, influenza virus, and varicella-zoster virus.

Research conclusions

Incomplete age-appropriate immunization in children pre-liver transplant and post-liver transplant were common. At least 13.1% of the children in the study required hospitalization for a VPI during a follow-up period of up to 5 years post-transplantation. There was high morbidity, especially during the first year after transplantation. Hence, complete immunization and robust infection control should be

considered in such children.

Research perspectives

The current study suggests that incomplete age-appropriate immunization is a major concern, because a large number of patients with VPIs requiring hospitalization were recorded. Interestingly, waning immunity post-liver transplant can evidently lead to VPIs, as evidenced by a case in which *de novo* hepatitis B infection developed 3 years postliver transplantation in a child who had a hepatitis B surface antibody titer of > 1000 mIU/mL pre-liver transplantation. As well as policies to increase pre- and post-transplant immunization rates, studies investigating humoral and cellular immunity induced by vaccination after liver transplantation are needed.

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