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COST EFFECTIVENESS OF PALIVIZUMAB PROPHYLAXIS FOR RESPIRATORY SYNCYTIAL VIRUS IN PRETERM INFANTS: A NATIONWIDE POPULATION-BASED COHORT STUDY IN TAIWAN

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ABSTRACT

Purpose. To determine the cost effectiveness of palivizumab through the hospitalization rate and duration due to respiratory syncytial virus (RSV) among preterm infants combined with chronic lung disease (CLD) or congenital heart disease (CHD) in Taiwan.

Methods. The target groups of this cohort study contained 17,665 (8,055 female and 9,610 male) preterm children from the Taiwan National Health Insurance Research Database in 2013. The eligible cases were preterm infants who were diagnosed with RSV infection. The hospitalization rate, duration of hospitalization, and medical expenditure of outpatient and inpatient services were estimated.

Results. The incidence of hospitalization caused by RSV was 30.2% (5,335/17,665), and the mean days of hospitalization was 12.86 ± 12.4 days. The hospitalization rate and duration of hospitalization for the palivizumab group were significantly lower than those of the nonpalivizumab group. Medical expenditure was significantly lower among preterm infants who were administered palivizumab. Significant cost effectiveness was observed among preterm children no matter whether diagnosed with CLD or CHD.

Conclusions. Palivizumab prophylaxis can effectively decrease both hospitalization rate and duration and therefore decreases the total medical expenditures incurred by RSV.

Introduction

Infants who are born prematurely have narrower respiratory tracts. Therefore, cases of respiratory syncytial virus (RSV) in preterm infants can be severe and even cause death [1]. RSV is the most prominent and common cause of respiratory tract infection among infants and young children worldwide [2]. Currently, in industrialized countries, a common belief is that RSV is more severe in older children [3], and this misconception has led to the RSV infection rate remaining high among young children. According to the World Health Organization, approximately 64 million cases of RSV infection occur each year worldwide, and approximately 160 million patients have died because of infection. In this study, the infection rate among children under 5 years was 60% [4].

Because the most common methods through which RSV is transmitted are droplet spread and person-to-person contact, the most effective method for preventing infection is avoiding pathogens. Clinical symptoms of RSV include a runny nose, cough, and mild fever. RSV is a prevalent respiratory virus that infects nearly all children aged under 2 years; 60%–70% are infected in their first year [5, 6]; however, infants born prematurely are at a higher risk of developing more severe RSV infections that often lead to acute bronchiolitis and pneumonia [7, 8]. However, no vaccine has yet been developed to prevent RSV; palivizumab is a passive preventative vaccine of RSV.

Palivizumab is a humanized anti-RSV IgG1 monoclonal antibody that binds to the RSV fusion protein [9]. Animal and human trials have proved that palivizumab can inhibit cell fusion and virus replication to achieve protection. However, until now, the vaccination rate of palivizumab remains low among children, so popularizing palivizumab vaccination to prevent RSV infection is essential.

The increasing health burden on children has become high profile, so government and academics are seeking to alleviate it. A study determined that palivizumab prophylaxis in preterm infants reduces the incidence of hospitalization caused by RSV [10]. Because the clinical benefit of palivizumab in preventing the hospitalization of preterm infants has been effectively established, using a placebo control group would be unethical. This prompted our study design of an observational study. We sought to determine the correlation between palivizumab vaccination and RSV cases to ascertain whether it can reduce the health burden.

Methods

Study design

The National Health Insurance (NHI) program has provided health care in Taiwan since 1995. This program has a coverage rate of more than 99% of the population of Taiwan. The Bureau of NHI provides the administrative data contained in the National Health Insurance Research Database (NHIRD) for research purposes. To ensure individual privacy, the Bureau of NHI devised a secret code for each subject and constructed this database. Subsequently, it randomized this information for research purposes. The International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM) is used to define diseases in the NHIRD. Because the National Health Research Institute has addressed the confidentiality assurance issue, all procedures in the present study were performed in accordance with the guidelines of our institutional ethics committee and adhered to the tenets of the Declaration of Helsinki. All patient information was anonymous. As the National Health Research Institute had addressed the confidentiality assurance issue, a full review of this study was by the Institution Review Board of Cheng-Hsin General Hospital (CHGH-IRB No: (459)103-36).

This was an observational cohort study to determine the effectiveness and economic benefits of the vaccination of palivizumab among preterm infants in Taiwan. Based on the NHIRD in 2013, the inclusion criteria used to select and evaluate patients are reported in Figure 1. We enrolled 17,665 cases in this study and further separated them by chronic lung disease (CLD) and congenital heart disease (CHD) incidence. We then classified

the cases into two groups depending on vaccination of palivizumab status and estimated the effectiveness and economic benefits of palivizumab vaccination.

In Taiwan, the RSV season generally occurs in spring and fall [11]. Although most patients recover in an average of 3 weeks, 1–2% patients develop severe complications and may require hospitalization [12]. The death and hospitalization rates are higher among preterm babies. Furthermore, infection during childhood might increase the risk of asthma in the future [13].

Determination of variables

The major group of preterm children is identified according to ICD9-code 765. Cases of CLD, CHD, and RSV are identified according to ICD0-code 7707, ICD-code 745–747, and ICD-code 466.xx, which refers to bronchitis caused by RSV, respectively [14]. Additionally, an initial dose of 15 mg/kg of palivizumab was administered to eligible study subjects [15]. Two to five injections of palivizumab were administered monthly. Therefore, the Taiwan Neonatology Medical Association suggested in 2015 that the first dose of palivizumab should be administered at the time of discharge; subsequently, further doses should be administered monthly, up to six times.

Medical expenditure

In this study, all medical expenses are given in New Taiwan dollars (NT$). According to the Premature Baby Foundation of Taiwan, each high-risk case requires an average of 11 doses of palivizumab. NT$266 million is the annual palivizumab expenditure, based on the current rate of premature births. However, if vaccinations can be successfully implemented and cover all premature babies, although expenses on palivizumab will increase, the expenditure for future hospitalization will be reduced by up to NT$454 million [14]. A substantial reduction in medical expenditures will also result [16].

Statistical analysis

Statistical analyses were performed using SAS version 9.4. The relationship to the effectiveness of palivizumab, hospitalization cause by RSV, and medical expenditure were estimated. The results are expressed as means ± standard deviations. A t-test was used on a continuous scale, and a chi-square test was used on a nominal scale. For the cost effectiveness of the palivizumab prophylaxis, the incremental cost-effectiveness ratio (ICER) is used, which is the comparison of the difference in cost between palivizumab prophylaxis and the control group, divided by the difference in the effectiveness. The level of significance was set at 0.05 for all statistical tests.

Results

As Table 1 shows, 17,665 children were enrolled in the study with 8,055 male (45.6%), and 9,610 female (54.4%) participants. Of these, 2,031 cases (11.5%) also had CLD and 424 cases (2.4%) also had CHD. The RSV cases were 8,002 (45.3%), which was consistent with the prevalence of RSV in Taiwan (40-55%). Furthermore, 2,155 cases (12.2%) had been inoculated with palivizumab, and 5,335 cases (30.2%) had been hospitalized with RSV.

Table 2 shows that among the 489 cases who were infected with RSV of the 2,155 cases who had been inoculated with palivizumab, a significant difference in infection rate between those inoculated using palivizumab and nonpalivizumab was observed (22.7% vs. 48.4%, $p < 0.001$). The palivizumab (+) case group with CLD (RSV (+) 17.4% vs. RSV (–) 56.9%, $p < 0.001$) and that with non-CLD (RSV (+) 24.3% vs. RSV (–) 47.5%, $p < 0.001$) exhibited a significant difference. The palivizumab (+) case group with CHD (RSV (+) 41.1% vs. RSV (–) 95.2%, $p < 0.001$) and that with non-CHD (RSV (+) 20.9% vs. RSV (–) 47.7%, $p < 0.001$) also exhibited a significant difference.

The rate and duration of hospitalization due to RSV were also estimated in this study. A significant difference in the hospitalization rate between the palivizumab and nonpalivizumab groups was observed (23.2% vs. 31.2%, $p = 0.023$). A significant difference was also observed among the palivizumab (+) case group with CLD (19.6% vs. 59.9%, $p < 0.001$), and the palivizumab (+) case group with CHD (11.8% vs. 52.4%, $p = 0.009$; Table 3). Additionally, the palivizumab group (+) was inferior to palivizumab cases (–) (2.42 ± 6.12 vs. 4.14 ± 9.35, $p < 0.001$) in terms of the average duration of hospitalization (Table 3). Regarding the medical expenses of outpatient clinics and hospitalization among preterm infants, Table 4 indicates that cases with palivizumab had higher expenses than did cases without palivizumab (NT$23,976.49 vs. NT$644.91, $p < 0.001$) in outpatient clinics, but hospitalization medical expenses were lower (NT$663,380.64 vs. NT$719,266.06, $p < 0.001$). We also determined that cases with palivizumab were more expensive, whether among the patients with CLD (NT$26,682.20 vs. NT$707.84, $p < 0.001$) or those with CHD (NT$22,986.51 vs. NT$583.42, $p < 0.001$). Among hospitalized patients, we determined the opposite outcome as compared with outpatient services. Lower expenses in cases of palivizumab were incurred, whether among the patients with CLD (NT$686,198.60 vs. NT$1,170,420.41 $p = 0.09$) or those with CHD (NT$762,080.41 vs. NT$1,127,560.80, $p < 0.001$)(Table 4). The main reason for the differences in medical expenditure for outpatient services was the cost of palivizumab.

Table 5 shows the ICER results for palivizumab: NT$90,784 in outpatient clinics and NT$698,568 in hospitalizations. These results indicated that although the expenditures for outpatient services increased among the palivizumab (+) group because of the high cost of palivizumab, the expenditures of inpatients services decreased significantly among the palivizumab (+) group.Discussion Clinical-epidemiological aspects of palivizumab prophylaxis for preterm infants against RSV The costs and benefits correlation of vaccination is debatable in many cases. Although clinical efficacy has been confirmed for many vaccines, some controversies surrounding prophylaxis by vaccination persist. RSV is the most common factor behind respiratory infections among infants. Because RSV can narrow the respiratory tract, it leads to a severe respiratory infection and develops into respiratory tract obstruction which can cause shock and even death. For high-risk patient groups including premature babies and CHD and CLD patients, RSV infection always develops complications, including bronchiolitis and pneumonia and leads to hospitalization and additional medical procedures; the death rate is high. Palivizumab is an IgG1 monoclonal antibody that can prevent RSV infection. The efficacy of RSV-associated hospitalization in premature infants was proven [17]. Although other recent studies have consistently confirmed that palivizumab effectively reduces the incidence of RSV in premature children [18, 19], few studies have identified the financial burden on healthcare caused by RSV. Because of different social and epidemiological factors, the eligibility criteria for receiving palivizumab may vary in different countries, especially for preterm infants [17].

Because of the high global incidence of RSV (40-55%), it imposes many medical burdens to save children's lives. Although the efficacy of palivizumab prophylaxis has been proven by many studies, its cost effectiveness varies between studies. In this study, we confirmed that palivizumab positively affects RSV prevention. The rate of infection of RSV with palivizumab (+) (22.7%) differed significantly from that with palivizumab (–) (48.7%). This outcome was confirmed by other studies from Japan [20], Korea [21], and other countries. By reviewing these studies, we ascertained that palivizumab is effective in preventing RSV-related infections among high-risk preterm infants [22].

However, these studies have only focused on the effectiveness of palivizumab for RSV prevention but did not analyze the cost effectiveness of palivizumab for RSV prevention. This study confirmed not only the effectiveness of RSV prevention but also the cost effectiveness of palivizumab by defining the total hospitalization period and total hospitalization costs. We determined that hospitalization expenses can be reduced by increasing outpatient expenses, that is, by increasing the use of palivizumab. Additionally, total medical expenditures in the short term may be increased because of the cost of palivizumab

vaccination, but in the long term the total medical expenditure can be almost halved. In the future, analyses of the utility and cost effectiveness of palivizumab for this population will become increasingly vital to reduce the costs related to RSV infections [22].
The following major issues were identified in this study: a) The palivizumab vaccination rate remains low in Taiwan: only 12.2% of preterm children received a palivizumab vaccination; meanwhile, 45.3% of preterm children were infected by RSV. Because the present study proved the cost effectiveness of palivizumab in Taiwan, increasing the vaccination rate will further reduce future medical expenditures. b) Insufficient studies have proved that palivizumab is effective against RSV; in industrialized countries, a common belief is that RSV is common and severe in older children [22]. Because of this misconception, parents have been unwilling to vaccinate their children, resulting in children with a high risk of developing RSV. c) In terms of medical expenditure, palivizumab has only recently been included in health insurance payments, and not all preterms are covered; therefore, more studies on the effectiveness and cost effectiveness of palivizumab must be undertaken—then we can provide more data to policy makers, taxpayers, and the public.

Perceived limitations

One major limitation involving this study population is that although our study only included newly diagnosed cases to avoid the potential effects of misclassification, some of them may not have been newly developed. Second, the evidence derived from a retrospective cohort study is generally lower in statistical quality than that from randomized trials because of potential biases linked to adjusting for confounding variables. Third, a meticulous study design and control measures for confounding factors were used, but bias resulting from unknown confounders may still have affected the results. Finally, all data in the NHIRD are anonymous, so relevant clinical variables, such as serum laboratory data, imaging results, and pathology findings, were unavailable regarding the study patient cases.

Conclusion

Infants have a greater risk of RSV infection, especially among preterm infants whose respiratory tract is narrower than those of others. This study determined that palivizumab is an effective intervention to prevent the complications of RSV infection among preterm infants. Furthermore, this study identified the benefits of administrating palivizumab to preterm infants for more favorable outcomes in both utility and costs. This paper provides taxpayers with the evidence to expand coverage to the high-risk preterm population.

Declarations

Ethics approval and consent to participate The study is in accordance with Helsinki Declaration. As the National Health Research Institute had addressed the confidentiality assurance issue, a full review of this study was waived by the Institution Review Board of Fu-Jen Catholic University.

The data supporting the conclusions of this article are included within the article.

Consent to publish
Not applicable
Competing interests
The authors have no proprietary interest in any aspect of this study.
Authors' contributions

Chi-Te Sun, Yu-Hsiang Tsao, Pei-Shin Cheng, and Tao-Hsin Tung conducted the study and drafted the manuscript. Zi-Hao Chao, Ming-Chih Chen, and Tao-Hsin Tung participated in the design of the study and performed statistical analyses. Chi-Te Sun, Yu-Hsiang Tsao, and Tao-Hsin Tung conceived the study, and participated in its design and coordination. All of the authors read and approved the final manuscript.

Availability of data and materials

All data underlying the findings are within the paper.

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List of abbreviations

CHD: congenital heart disease
CLD: chronic lung disease
ICER: incremental cost-effectiveness ratio
NHI: National Health Insurance
NHIRD: National Health Insurance Research Database
NTD: New Taiwan Dollars
RSV: respiratory syncytial virus

Table 1 Baseline characteristics among the study subjects (n=17,665)

Variables		N	%
Gender			
	male	8,055	45.6
	female	9,610	54.4
Chronic lung disease			
	yes	2,031	11.5
	no	15,634	88.5
Congenital heart disease			
	yes	424	2.40
	no	17,241	97.6
Respiratory syncytial virus			
	yes	8,002	45.3
	no	9,663	54.7
Palivizumab			
	yes	2,155	12.2
	no	15,510	87.8
Hospitalization			
	yes	5,335	30.2
	no	12,330	69.8

Table 2 The comparison of relationship between palivizumab and respiratory syncytial virus (RSV)

	Infection by RSV		non-infection by RSV		p-value
Variables	n	%	n	%	
All preterm infants (n=17,665)					<0.001
palivizumab(+) (n=2,155)	489	22.7	1,666	77.3	
palivizumab(-) (n=15,510)	7,507	48.4	8,003	51.6	
Preterm infants with CLD (n=2,031)					<0.001
palivizumab(+) (n=511)	89	17.4	422	82.6	
palivizumab(-) (n=1,520)	865	56.9	655	43.1	
Preterm infants without CLD (n=15,634)					<0.001
palivizumab(+) (n=1,644)	400	24.3	1,244	75.7	
palivizumab(-) (n=13,990)	6,645	47.5	7,345	52.5	

Preterm infants with CHD (n=424)					<0.001
palivizumab(+) (n=190)	78	41.1	112	58.9	
palivizumab(-) (n=234)	223	95.2	11	4.8	
Preterm infants without CHD (n=17,241)					<0.001
palivizumab(+) (n=1,965)	411	20.9	1,554	79.1	
palivizumab(-) (n=15,276)	7,287	47.7	7,989	52.3	

Table 3 the association between inoculation of palivizumab and the rate of hospitalized and length to stay of hospitalization

	Hospitalization %	p-value	Length to stay (days) mean±SD	p-value
All preterm infants (n=17,665)		0.023		<0.001
palivizumab(+) (n=2,155)	23.2		2.42±6.12	
palivizumab(-) (n=15,510)	31.2		4.14±9.35	
Preterm infants with CLD (n=2,031)		<0.001		<0.001
palivizumab(+) (n=511)	19.6		1.35±3.55	
palivizumab(-) (n=1,520)	59.9		7.37±12.87	
Preterm infants without CLD (n=15,634)		0.332		<0.001
palivizumab(+) (n=1,644)	24.3		2.76±6.69	
palivizumab(-) (n=13,990)	28.1		3.79±8.82	
Preterm infants with CHD (n=424)		0.009		<0.001
palivizumab(+) (n=190)	11.8		1.53±5.36	
palivizumab(-) (n=234)	52.4		4.90±6.36	
Preterm infants without CHD (n=17,241)		0.072		0.591
palivizumab(+) (n=1,965)	24.3		2.51±6.19	
palivizumab(-) (n=15,276)	30.9		4.13±9.39	

Table 4 The medical expenses of outpatient clinics and hospitalization among preterm infants

	Outpatient clinics (NTD)	p-value	Hospitalization (NTD)	p-value
All preterm infants (n=17,665)		<0.001		<0.001
palivizumab(+) (n=2,155)	23,976.49		663,380.64	
palivizumab(-) (n=15,510)	644.91		719,266.06	
Preterm infants with CLD (n=2,031)		<0.001		0.09
palivizumab(+) (n=511)	26,682.20		686,198.60	
palivizumab(-) (n=1,520)	707.84		1,170,420.41	
Preterm infants without CLD (n=15,634)		<0.001		<0.001
palivizumab(+) (n=1,644)	22,862.20		659,034.11	
palivizumab(-) (n=13,990)	641.73		664,960.32	
Preterm infants with CHD (n=424)		<0.001		0.001
palivizumab(+) (n=190)	22,986.51		762,080.41	
palivizumab(-) (n=234)	583.42		1,127,560.80	
Preterm infants without CHD (n=17,241)		0.056		<0.001
palivizumab(+) (n=1,965)	22,138.43		572,273.26	
palivizumab(-) (n=15,276)	646.59		572,462.53	

*Due to the low proportion of emergency (<1%) therefore do not discuss

Table 5 Cost-effectiveness analysis for palivizumab prophylaxis against respiratory syncytial virus

Outcomes	Cost	Effecttiveness	△Cost	△Effect	Incremental Cost-Effectiveness Ratio (Compared to control group)		
	palivizumab(+)	palivizumab(-)	palivizumab(+)	palivizumab(-)			
Outpatient clinics	NT$23,976	NT$645	0.227	0.484	NT$23,332	-0.257	(NT$90,784)
Hospitalization	NT$663,381	NT$719,266	0.232	0.312	(NT$55,885)	-0.08	NT$698,568

*Due to the low proportion of emergency (<1%) therefore do not discuss

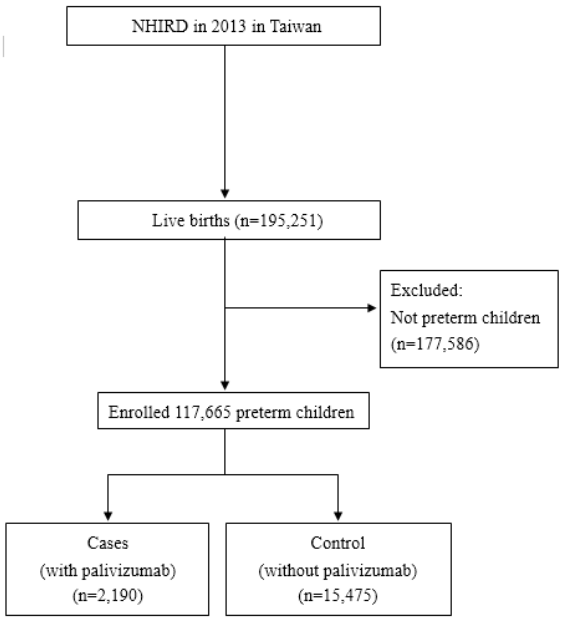

Figure 1 Flow chart of study subjects

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