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Original Article

Effects of influenza vaccine and sun exposure time against laboratory-confirmed influenza hospitalizations among young children during the 2012–13 to 2015–16 influenza seasons

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KEYWORDS
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Vaccine effectiveness;
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Sun exposure time

Abstract *Background:* Influenza is a major cause of acute respiratory infection burden worldwide, leading to many hospitalizations. An annual influenza vaccine is believed to be the best way to prevent influenza-related illnesses. We focused on the efficacies of other possible preventive measures such as increasing sun exposure time and dietary supplements to prevent these illnesses.

Methods: We conducted a matched-pair case–control study along with the Taiwan Pediatric Infectious Disease Alliance. We included influenza-related hospitalized patients with age ranging from 6 months to 5 years during the 2012–2013, 2013–2014, 2014–2015, and 2015–2016 influenza seasons. The controls were comparable to cases in age, sex, and residential area and had no influenza-related hospitalization records in the same season. We extracted data from vaccination histories and got the patients' guardians to complete questionnaires. Data were analyzed using conditional logistic regression.

Results: We enrolled 1514 children (421 influenza-infected cases and 1093 controls) in the study. We found seasonal influenza vaccination to be an independent protective factor against hospitalizations owing to influenza [$p < 0.01$; odds ratio (OR), 0.427; 95% confidence interval (CI), 0.306–0.594]. Children with mean sun exposure time of >7 h/week had a significantly lower risk of influenza-related hospitalizations than those with the mean sun exposure time of ≤7 h/week ($p < 0.05$; OR, 0.667; 95% CI, 0.491–0.906).

Conclusions: Seasonal influenza vaccination effectively prevents influenza-related hospitalizations in children aged ≤5 years. Besides, >7 h of sun exposure/week may also be associated with lower risk of influenza-related hospitalizations in children.

Introduction

Influenza is a major cause of acute respiratory infection worldwide, leading to a high number of hospitalizations, severe morbidity, and death in young children.[1–4] According to the Taiwan National Health Insurance Research Database, the influenza-related hospitalization rate is high in children aged younger than 7 years.[5] It is generally believed that an annual influenza vaccine is the best way to prevent influenza-related illnesses. In 2004, Taiwan Centers for Disease Control (CDC) launched a national vaccine program to provide free influenza vaccine for children aged 6–24 months. Later in 2009, CDC expanded the program to children aged <6 years, and this policy has remained unchanged to date. Many case–control studies have provided evidence regarding the efficacy of vaccines against influenza-related hospitalizations in children[6–8] and in adults.[9–11] However, very few studies have focused on the same issue among Taiwanese children.

Except for influenza vaccines, other factors may reduce the influenza-related hospitalization rate; for example, breastfeeding may have long-term protective effects against hospitalization for respiratory tract infections after infancy.[12,13] Other possible protective factors include high serum vitamin D levels and regular probiotic supplements.[14–21] Studies have shown that vitamin D supplementation during winter may prevent acute respiratory tract infections and reduce the incidence of influenza A virus infection.[14–17] In addition, daily dietary probiotic supplementation seems to decrease the incidence and duration of common cold and influenza infections as well as the severity of the symptoms associated with these diseases.[18–21] However, there is no consensus on the effect of probiotic to prevent influenza infection.

We conducted a 4-year, matched-pair case–control study to confirm the effectiveness of seasonal influenza vaccination against influenza-related hospitalizations in Taiwanese children and assessed the effectiveness of other measures that may reduce the hospitalization rate of children infected with influenza.

Material and methods

We conducted a matched-pair case–control study in collaboration with the Taiwan Pediatric Infectious Disease Alliance (TPIDA). TPIDA is a collaborative consortium established by nine pediatric infectious disease departments of tertiary medical centers, eight of which joined the study: the Mackay Memorial Hospital (Taipei City, Taiwan), the National Taiwan University Hospital (Taipei City, Taiwan), the Chang Gung Memorial Hospital at Linkou (Linkou, Taiwan), the China Medical University Hospital (Taichung City, Taiwan), the National Taiwan University Hospital Yun-Lin Branch (Douliou, Taiwan), the National Cheng Kung University Hospital (Tainan City, Taiwan), the Kaohsiung Chang Gung Memorial Hospital (Kaohsiung City, Taiwan), and the Buddhist Tzu Chi General Hospital (Hualien, Taiwan). We obtained informed consents from each participating patient's parents or guardians. The Institutional Review Boards of the aforementioned institutions approved the study protocols.

The burden of influenza is more severe in children aged <5 years than in older children and adults[1,2,22]; therefore, we decided to study patients hospitalized owing to influenza infections with ages ranging from 6 months to 5 years. The case group children included those who were admitted to one of the eight participating medical centers in Taiwan (TPIDA) owing to influenza infections [confirmed using rapid tests, polymerase chain reaction (PCR), or culture] during the 2012–2013, 2013–2014, 2014–2015, and 2015–2016 influenza seasons. We performed our study by matching the cases and controls by age (within ±3 months), sex, residential area (living in the same cities or counties), and time of seeking medical services (within ±1 month). When one case was included, the study nurse of each hospital would try to invite three matched controls to join the study as soon as possible within a period of 1 month. The controls were required to meet the following criteria to match the cases: 1. being of the same sex; 2. birthday matched to the case within ±3 months; 3. living in the same cities or counties; 4. seeking medical services from the same hospital: inpatients with diagnosis other than respiratory tract diseases, inpatients with respiratory tract infection due to pathogens other than influenza virus, or healthy children brought for routine vaccination; 5. having no history of influenza-related hospitalization before and 3 months after recruitment. We made follow-up phone calls to each control every month for 3 consecutive months after recruitment, or until the end of each influenza season (around mid-March) to ensure that there was no influenza-related hospitalization later on. Considering the various bed capacities of different hospitals, the ratios between case and control patients ranged from 1:1 to 1:3.

We collected the vaccination histories of both case and control patients from the registration data of each child's Children's Health Booklet. The Children's Health Booklet is issued by the Taiwan Ministry of Health and Welfare to every newborn's family and is a trustworthy source of every child's vaccination history. Full vaccination was defined as having received two vaccine doses administered ≥28 days apart in the current season or two doses administered ≥28 days apart in any previous season and one dose in the current season. Partial vaccination was defined as having received one dose in the current season and never being fully vaccinated in any previous season. Children were classified as being unvaccinated if they were not vaccinated in the current season. Other information was collected through a questionnaire; inquiries included number of family members living together, number of siblings, siblings' ages (in years), number of smokers at home, mother's education level, regular time of sun exposure (hours per week), time spent in the nursery (hours per day), number of children in the nursery, daily supplement history (multiple options: probiotics, multivitamins, vitamin C, calcium, enzyme, fish oil, cod liver oil, propolis, or others).

We analyzed the matched data using conditional logistic regression (backward elimination regression). Pearson chi-square test was used to confirm the quality of the matching result. Vaccine effectiveness (VE) was estimated as 1 minus the adjusted conditional odds ratio (OR). We estimated VE against influenza strains A and B combined. We analyzed all data using the Stata software (v11.0; Stata Corp, College Station, TX) and considered all p values < 0.05 as statistically significant.

Results

In total, 1514 children (421 influenza-infected cases and 1093 controls) participated in this study (Fig. 1). Table 1 shows demographics of study participants. Table 2 shows distribution of variables for cases and controls.

Using conditional logistic regression analysis, we found that receiving seasonal influenza vaccination was an independent protective factor against influenza-related hospitalizations [OR, 0.427; 95% confidence interval (CI), 0.306–0.594; Table 3]. We estimated VE against hospitalizations in children aged 6 months to 5 years to be 57.3% for the four seasons combined. VE was 58.1% (OR, 0.419; 95% CI, 0.297–0.591) for children who were fully vaccinated. VE was not significant for those who were partially vaccinated (OR, 0.639; 95% CI, 0.326–1.252; Table 4).

On further stratification of patients, it was found that VE for fully vaccinated children aged 24–60 months was 58.4% (OR, 0.416; 95% CI, 0.272–0.637) and that for children aged 6–23 months was 57.1% (OR, 0.429; 95% CI, 0.239–0.771; Table 4). Full vaccination was also significantly effective against influenza A (58.5%; OR, 0.415; 95% CI, 0.275–0.626) and influenza B (56.8%; OR, 0.432; 95% CI, 0.23–0.812) virus infections (Table 4). However, partial vaccination was not effective in any age group or against any influenza type (Table 4).

Moreover, children with a sun exposure time of >7 h/week exhibited a significantly lower risk of influenza-related hospitalizations than those with a sun exposure time of at least ≤7 h/week (OR, 0.667; 95% CI, 0.491–0.906). Children with a sun exposure time of ≥28 h/week may exhibit an even stronger protection (OR, 0.308; 95% CI, 0.106–0.898; Table 3).

Furthermore, we found that children regularly taking dietary probiotic supplements also exhibited a lower risk of influenza-related hospitalizations (OR, 0.66; 95% CI, 0.48–0.908; Table 3). However, our oversimplified questionnaire failed to identify the strains, dosage, and duration of the probiotics consumed, making the protective effect for this variable vague and uncertain.

We found no significant between-group differences regarding the hospitalization rates owing to influenza infections and other factors in the questionnaire including the number of family members, number of siblings, siblings' ages, number of smokers at home, the mother's education level, child nursery care times (h/day), number of children in child nursery care, breastfeeding status, or frequency of use of hi-tech products (h/day).

Discussion

From 2012–2013 to 2015–2016 influenza seasons, the influenza vaccine effectively reduced the risk of laboratory-confirmed influenza hospitalizations by 57.3% (OR, 0.427; 95% CI, 0.306–0.594) for children in Taiwan. Partial vaccination did not provide protection to any age group or against any influenza types. Our results agree with those of other case–control studies analyzing the effectiveness of influenza vaccines against influenza-related hospitalizations in children[6–8]; for example, Cowling et al. found a 61.7% efficacy of influenza vaccination for the

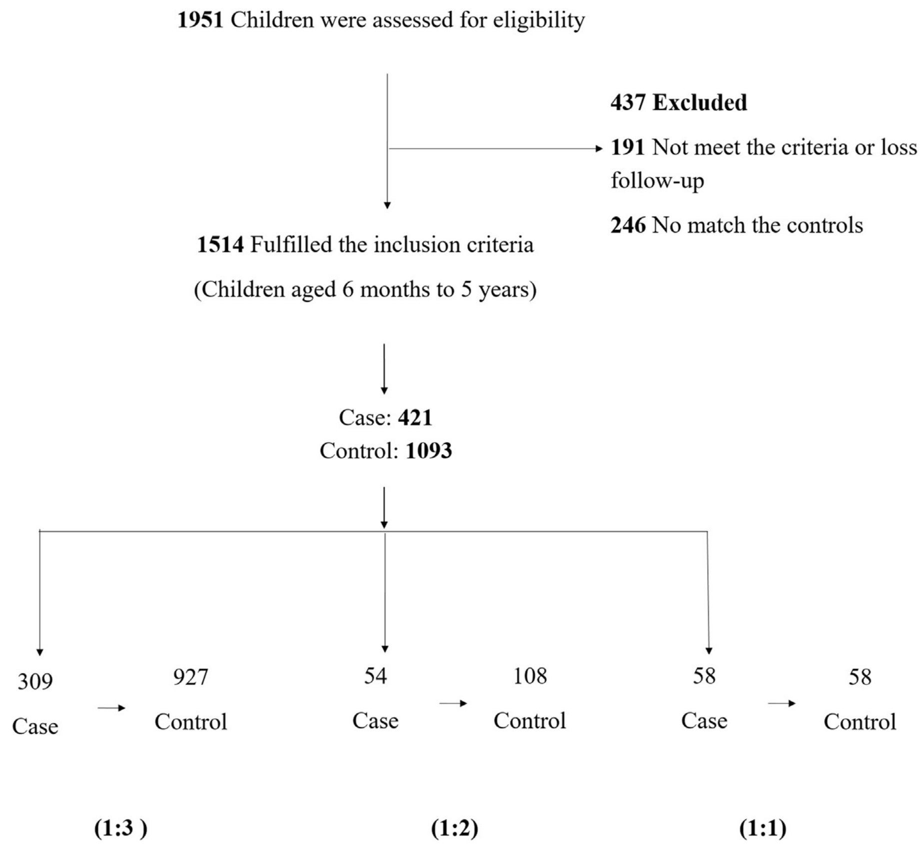

Figure 1. Flowchart of participant selection. The case group included the children aged 6 months to 5 years who were admitted to one of the eight participating medical centers in Taiwan (TPIDA) owing to influenza infections [confirmed using rapid tests, polymerase chain reaction (PCR), or culture]. The control group included healthy children or children with acute illness other than influenza. The ratio between case and control groups ranged from 1:1 to 1:3 among different hospitals.

prevention of hospitalizations in children aged 6 months–17 years in Hong Kong during 2009–2013.[6] In another study, Buchan et al. found a 60% VE for fully vaccinated children, 39% VE for partially vaccinated children, 67% VE for vaccinated children aged 24–59 months, and 48% VE for vaccinated children aged 6–23 months against hospitalizations during 2010–2014 in Ontario, Canada.[8] In Japan, during the 2013–2016 influenza seasons, the three-season adjusted VE for preventing hospitalizations was 52% for influenza A and 28% for influenza B virus infections.[7] According to these data, influenza vaccines can prevent at least half of the hospitalizations among children during influenza seasons in different countries. The Advisory Committee on Immunization Practices (ACIP) has recommended that children aged 6 months through 8 years who had no received influenza vaccine previously, should receive two doses of influenza vaccine to be fully protected for flu season.[23] We believe that our results would serve as another evidence to support this recommendation.

During the 4-year study period, the vaccine mismatch rates were low for influenza A virus during most years but not for influenza B virus in Taiwan. Circulating influenza A (H1N1) matched the vaccine strain in all four seasons, and influenza A (H3N2) matched the vaccine strain in the 2012–2013, 2013–2014, and 2015–2016 seasons, but a 58% mismatch was present in the 2014–2015 season. For influenza B virus, the mismatch rates were 13%, 81%, 55%, and

Table 1 Demographics of study participants.

	Cases (n = 421) No. (%)	Controls (n = 1093) No. (%)	*p*-value
Age(months)			0.841
6–12	65 (15.4)	167 (15.3)	
13–24	113 (26.8)	318 (29.1)	
25–36	104 (24.7)	271 (24.8)	
37–48	84 (20)	214 (19.6)	
49–60	55 (13.1)	123 (11.3)	
Sex			0.899
Male	218 (51.8)	562 (51.4)	
Female	203 (48.2)	531 (48.6)	
Year of enrollment			0.771
2012–2013	60 (14.3)	161 (14.7)	
2013–2014	175 (41.6)	476 (43.5)	
2014–2015	78 (18.5)	203 (18.6)	
2015–2016	108 (25.7)	253 (23.1)	
Residential area			0.396
Northern	155 (36.8)	395 (36.1)	
Central	15 (3.6)	23 (2.1)	
Southern	211 (50.1)	574 (52.5)	
Eastern	40 (9.5)	101 (9.2)	

p-value were analyzed by Pearson chi-square test.

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Table 2 Distribution of variables for cases and controls.

Variables	Cases (n = 421) No. (%)	Controls (n = 1093) No. (%)
Number of family members		
≥6	131 (31.1)	346 (31.7)
4–5	178 (42.3)	506 (46.3)
≤3	112 (26.6)	239 (21.9)
N/A		2 (0.2)
Number of siblings		
5–6	2 (0.5)	4 (0.4)
3–4	7 (1.7)	28 (2.6)
0–2	412 (97.9)	1061 (97.1)
Siblings' age(years)		
≥10	36 (8.6)	92 (8.4)
5–10	63 (15)	192 (17.6)
≤5	182 (43.2)	459 (42)
N/A	140 (33.3)	350 (32)
Someone smoking at home		
Yes	206 (48.9)	485 (44.4)
No	215 (51.1)	607 (55.5)
N/A		1 (0.1)
Mother's education level		
Master and above	35 (8.3)	124 (11.3)
University	177 (42)	477 (43.6)
College	63 (15)	171 (15.6)
High school	122 (29)	255 (23.3)
Junior high school and below	24 (5.7)	61 (5.6)
N/A		5 (0.5)
Children with mean sun exposure time(h/week)		
≥28	10 (2.4)	27 (2.5)
7–28	258 (61.3)	741 (67.8)
≤7	153 (36.3)	324 (29.6)
N/A		1 (0.1)
Child nursery care time(h/day)		
≥6	186 (44.2)	427 (39.1)
1–6	9 (2.1)	12 (1.1)
0	226 (53.7)	651 (59.6)
N/A		3 (0.3)
Number of children in child nursery care		
≥13	102 (24.2)	254 (23.2)
4–12	51 (12.1)	101 (9.2)
≤3	263 (62.5)	732 (67)
N/A	5 (1.2)	6 (0.5)
Supplement		
Supplement without probiotic	41 (9.7)	131 (12)
Supplement contain probiotic	48 (11.4)	141 (12.9)
Probiotic only	91 (21.6)	287 (26.3)
None	240 (57)	526 (48.1)
Unknown	1 (0.2)	8 (0.7)
Breastfeeding		
Yes	342 (81.2)	913 (83.5)
No	29 (6.9)	141 (12.9)
N/A	50 (11.9)	39 (3.6)
Child using hi-tech products time(h/day)		
≥4	12 (2.9)	49 (4.5)
1–4	186 (44.2)	480 (43.9)
≤1	223 (53)	561 (51.3)
N/A		3 (0.3)
Receiving seasonal influenza vaccination		
Yes	60 (14.3)	288 (26.3)
No	361 (85.7)	805 (73.7)

Abbreviations: N/A, Not available.

64% during the 2012–2013, 2013–2014, 2014–2015, and 2015–2016 seasons, respectively.[24] Although the number of mismatch years was more for influenza B virus than for influenza A virus, VEs for both viruses were similar. In a study by McLean et al., the researchers found that the inactivated influenza vaccine provided a higher degree of residual protection against the influenza B virus than against influenza A virus among children aged 2–17 years during the 2013–2014, 2014–2015, and 2015–2016 seasons.[25] This may explain why VE for influenza B virus did not reduce considerably during the 4 study years combined despite the mismatch issue.

The efficacy or effectiveness of influenza vaccines against influenza-like illnesses in children aged <7 years varies from −7% to 77% across different years and regions worldwide.[26,27] In Taiwan, Su et al. analyzed VE in a total of 4494 children aged 6–59 months, for whom laboratory results and vaccination status were available for five winter seasons, and found a VE of 62% (95% CI, 48–83%) in the seasons from 2004 to 2005 to 2008–2009 among Taiwanese children.[28] Our study further confirmed the protection conferred by the influenza vaccine against laboratory-confirmed influenza infections and related hospitalizations among children aged 6–60 months in Taiwan despite the variations in vaccine mismatch rates across different years.

Interestingly, children with mean sun exposure time of >7 h/week had a significantly less risk of influenza-related hospitalizations than those with shorter sun exposure times. Although we did not obtain the basic vitamin D levels of all the cases and controls, we believe that the sun exposure time probably correlated with serum vitamin D levels, and the finding may be interpreted as the protective effect of vitamin D against influenza-related hospitalizations in children. Higher serum vitamin D levels are thought to upregulate innate immunity and may reduce the incidence of influenza infection.[14] Vitamin D increases the synthesis of the antimicrobial peptide cathelicidin in the respiratory epithelium, which has been shown to reduce disease severity and influenza virus replication.[16] Observational and clinical trial data have suggested an association between low serum 25-hydroxyvitamin D levels and increased respiratory tract infection rates.[29,30] Although vitamin D deficiency is defined as a 25(OH)D level of <20 ng/mL (50 nmol/L),[31–33] a 25(OH)D level of ≥38 ng/mL can significantly reduce the incidence of acute viral respiratory tract infections.[34]

In a population-based study of Taiwanese children aged 5–18 years, the mean serum 25(OH)D level of participants was only 20.4 ng/mL (SD, 7.1 ng/mL) and vitamin D deficiency [defined as serum 25(OH)D levels < 20 ng/mL] was

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Table 3 Result of conditional logistic regression analysis.

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Number of family members						
≥6	0.86	0.631–1.172	0.339	0.751	0.503–1.123	0.163
4–5	0.778	0.581–1.043	0.093	0.696	0.485–1.000	0.05
≤3	–	–	–	–	–	–
Number of siblings						
5–6	1.203	0.213–6.812	0.834	0.451	0.046–4.410	0.494
3–4	0.692	0.296–1.62	0.396	0.706	0.265–1.885	0.488
0–2	–	–	–	–	–	–
Siblings' age(years)						
≥10	1.072	0.706–1.627	0.744	1.098	0.663–1.820	0.715
5–10	0.824	0.593–1.145	0.249	0.884	0.603–1.295	0.526
≤5	0.971	0.763–1.234	0.808	1.153	0.848–1.568	0.363
Someone smoking at home						
Yes	1.169	0.93–1.471	0.181	1.226	0.923–1.625	0.156
Mother's education level						
Master and above	0.72	0.388–1.336	0.297	0.707	0.338–1.477	0.356
University	0.911	0.547–1.517	0.72	1.04	0.568–1.906	0.899
College	0.947	0.538–1.666	0.849	1.07	0.559–2.046	0.838
High school	1.227	0.729–2.066	0.441	1.302	0.722–2.350	0.38
Junior high school and below	–	–	–	–	–	–
Children with mean sun exposure time(h/week)						
≥28	0.461	0.181–1.175	0.105	0.308	0.106–0.898	0.031
7–28	0.638	0.486–0.837	<0.01	0.667	0.491–0.906	0.01
≤7	–	–	–	–	–	–
Child nursery care time(h/day)						
≥6	1.223	0.936–1.599	0.141	1.131	0.707–1.809	0.608
1–6	2.052	0.849–4.961	0.11	2.179	0.721–6.590	0.168
0	–	–	–	–	–	–
Number of children in child nursery care						
≥13	1.006	0.712–1.423	0.972	1.066	0.621–1.830	0.815
4–12	1.399	0.95–2.06	0.089	1.291	0.723–2.307	0.388
≤3	–	–	–	–	–	–
Supplement						
Supplement without probiotic	0.639	0.428–0.953	0.028	0.655	0.424–1.013	0.057
Supplement contain probiotic	0.692	0.477–1.004	0.05	0.604	0.398–0.915	0.017
Probiotic only	0.655	0.491–0.873	<0.01	0.66	0.48–0.908	0.011
None	–	–	–	–	–	–
Breastfeeding						
Yes	0.85	0.605–1.193	0.346	0.792	0.543–1.155	0.226
Child using hi-tech products time(h/day)						
≥4	0.535	0.269–1.062	0.074	0.501	0.247–1.017	0.056
1–4	0.91	0.702–1.18	0.477	0.908	0.694–1.189	0.484
≤1	–	–	–	–	–	–
Receiving seasonal influenza vaccination						
Yes	0.442	0.325–0.601	<0.01	0.427	0.306–0.594	<0.01

Risk for influenza-related hospitalization was significantly lower in children who had received seasonal influenza vaccination, taken probiotic supplement regularly, and exposed to more than 7 h of sun a week.

present in 51.0% of surveyed individuals.[35] Because the whole island is located in a tropical/subtropical region, there should be no reason for Taiwanese children to have a lack of sun exposure. Interestingly, we found that children living in the northern Taiwan have greater sun exposure time than those living in the south (Supplementary Table). Therefore, lack of outdoor spaces in urban areas and insufficient outdoor activity time might be the major factors contributing to low serum vitamin D levels in Taiwanese children. This scenario was observed in our study, in which up to 31.5% of children had an insufficient sun exposure time of ≤7 h/week. However, without testing serum vitamin D levels, we could not provide any direct laboratory evidence to prove our hypothesis.

Finally, we found that daily dietary probiotic supplementation may reduce the risk for influenza-related

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Table 4 Vaccination status in case/control group with conditional logistic regression analysis, sub-grouping aged 24–60 months, aged 6–23 months, influenza A, and influenza B.

Vaccination status	Odds ratio	95% CI	*p*-value
Fully			
All	0.419	0.297–0.591	<0.01
Aged 6–23 months	0.429	0.239–0.771	<0.01
Aged 24–60 months	0.416	0.272–0.637	<0.01
Influenza A	0.415	0.275–0.626	<0.01
Influenza B	0.432	0.23–0.812	<0.01
Partially			
All	0.639	0.326–1.252	0.192
Aged 6–23 months	0.695	0.266–1.815	0.457
Aged 24–60 months	0.591	0.23–1.518	0.275
Influenza A	0.556	0.236–1.309	0.179
Influenza B	0.823	0.271–2.501	0.731
Unvaccinated	–	–	–

Full vaccination groups showed significant difference between case and control in both age groups against both influenza A and B. Partial vaccination did not show significant difference between case and control groups.

hospitalizations (OR, 0.66; 95% CI, 0.48–0.908). This finding is not novel because few studies have reported similar results. In a double-blind, placebo-controlled study conducted by Leyer et al., 6-month daily dietary probiotic supplementation was found to be a safe and effective way to reduce the incidence and duration of fever, rhinorrhea, and coughing episodes; furthermore, this supplementation reduced the frequency of antibiotic prescription and the number of missed school days attributable to influenza-related illness among children aged 3–5 years.[18] A systematic review and meta-analysis of randomized controlled trials also showed that consumption of probiotics significantly decreased the number of individuals having at least one respiratory tract infection episode (17 randomized controlled trials; 4513 children; relative risk 0.89, 95% CI, 0.82–0.96; $p = 0.004$).[36] Children taking probiotic supplements had fewer respiratory tract infection days per person than those taking placebo (six randomized controlled trials, 2067 children; mean difference (MD), −0.16; 95% CI,−0.29–0.02; $p = 0.03$) and had fewer absences from daycare/school (eight randomized controlled trials, 1499 children; MD, −0.94; 95% CI,−1.72 to −0.15; $p = 0.02$).[36]

We are aware of the limitations of our study. First, we did not monitor serum vitamin D levels in study participants, and the average serum vitamin D level in children with sun exposure durations of >7 h/week is unknown. Moreover, the observed protection conferred by increased sun exposure time may not necessarily be related to increased vitamin D production but to other factors such as increased outdoor activity time.[37] The true underlying mechanism remains to be further studied. Second, we obtained no data on the strains and dosage of probiotic supplements in our study because the questionnaire designed by us did not distinguish category items of probiotic supplements. Various effective probiotics are available; these include *Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium lactis*, etc., and their effective dosages range from 10^7 to 10^{10} colony-forming units daily.[20] One may also argue the fact that only families with high socioeconomic status can afford the expensive price of probiotic products, which is a confounding factor for the reduction of influenza-related hospitalization rates.[38] This might be true, although we could not find a correlation between dietary probiotic consumption and any other variable investigated in our study.

In conclusion, seasonal influenza vaccination is effective in preventing influenza-related hospitalizations in Taiwanese children aged ≤5 years. Besides, >7 h of sun exposure/week may also be associated with lower risk of influenza-related hospitalizations in these children.

Declaration of Competing Interest

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.09.010.