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ORIGINAL ARTICLE

Is influenza vaccination associated with nephrotic syndrome relapse in children? A multicenter prospective study

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Abstract

Background Prospective research of children receiving heterogeneous vaccines has shown that immunization is not associated with pediatric idiopathic nephrotic syndrome (NS) relapses. However, prospective data concentrating only on influenza (flu) virus vaccines are not available.

Methods This multicenter prospective study was conducted in children with NS who received inactivated flu vaccines from June 2017 to July 2018. The day of flu vaccination was defined as day 0, and the period between prevaccination and postvaccination days was defined as $-X$ to $+Y$ (period from day -180 to 0 as the precontrolled period). The primary outcome was the NS relapse rate from day 0 to + 30 as a direct association with vaccination compared with those in the precontrolled period. Exacerbation was defined as children experiencing more NS relapses after vaccination compared with those in the precontrolled period, or children starting any new immunosuppressants due to NS relapse after vaccination.

Results Sixty-three children were included. Relapse rates were not significantly different between the precontrolled period and 0 to + 30 periods (0.38 vs. 0.19 times/person-year, $p = 0.95$). Although the exacerbation rate during the 0 to + 180 period in children without NS relapse in the precontrolled period was very low (4/54 [7.4 %]), children with at least one NS relapse in the precontrolled period showed a remarkable increase in the rate (4/9 [44.4%]; $p = 0.01$).

Conclusions Flu vaccination did not significantly precipitate the direct relapse of NS in children. However, it might increase the disease activity in children with at least one NS relapse within a half year before vaccination.

Keywords Adverse event · Exacerbation · Idiopathic nephrotic syndrome · Influenza virus vaccination · Relapse

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Introduction

Children with idiopathic nephrotic syndrome (NS) are in an immunocompromised state and require prolonged steroid therapy and immunosuppressive agents to prevent NS relapse [1, 2]. This immune suppression contributes to the potential high risk for upper respiratory viral infections and influenza (flu) virus. Guidelines suggest that these children should receive inactivated vaccines to reduce the risk of serious infections, and the use of live attenuated vaccines is not recommended [3].

Several reports have indicated that immunizations may precipitate or induce relapses of NS as an immunogenic stimulus [4–9]. T-cell–mediated podocyte injury has been hypothesized as the pathology underlying the elicitation of the immune response by vaccination [10]. Relapse of NS associated with a monovalent whole-virion inactivated flu virus vaccine during a pandemic influenza season has been described [11, 12]. Because there were no available data focusing on the relative risk of NS relapse related to the flu vaccine, we first conducted a retrospective study targeting vaccinated children with NS in a single institution [13]. In comparing the NS relapse rate between the prevaccination and postvaccination periods, we found that the flu vaccine was not associated with a higher risk of NS relapse. We subsequently conducted a nationwide retrospective cohort study including 306 children with idiopathic NS to investigate both vaccinated and unvaccinated patients at a number of facilities [14]. The results of the multivariate analysis showed that children who received flu vaccination had significantly fewer flu infections and NS relapses than those who did not receive the flu vaccination. Moreover, children receiving flu vaccination had a significantly lower risk of NS relapse during the postvaccination period (risk ratio: 0.31, 95% confidence interval: 0.17–0.56) than during the prevaccination period.

Recently, a prospective study was published that evaluated the association between NS relapse and plural vaccination not limited to the flu vaccine. The authors of that research reported that the administration of vaccines developed by purified proteins was not associated with a higher risk of NS relapse in children with steroid-dependent NS (SDNS) [15]. However, the limitations of that research were the relatively small sample size, as only 19 vaccinated children were included, and that the vaccinated group was composed of a heterogeneous population receiving flu, diphtheria, tetanus, and acellular pertussis vaccine combined with inactivated polio virus vaccine.

Here, we report a multicenter prospective study of children with NS who received inactivated subunit-antigen flu vaccination and evaluate the occurrence of NS relapses related to flu vaccinations.

Materials and methods

Patients

We conducted a multicenter prospective study of patients with NS who received inactivated subunit-antigen flu vaccines from June 2017 to July 2018 at the following six hospitals: Takatsuki General Hospital, Kakogawa Central City Hospital, Kobe University Hospital, Kita-Harima Medical Center, Himeji Red Cross Hospital, and National Center for Child Health and Development. Patients were eligible if they were newly diagnosed with idiopathic NS between the ages of 6 months and 15 years old and if their last relapse was steroid-sensitive NS (SSNS), regardless of history of steroid-resistant NS (SRNS). Children with congenital NS or NS secondary to nephritis were excluded.

We prospectively collected the following data: sex, age at first manifestation of NS, age at first inactivated subunit-antigen flu vaccination, history of SRNS, last NS type (frequently relapsing NS (FRNS)/SDNS or others), last creatinine (Cr) estimated glomerular filtration rate before administration of first vaccination, duration between onset of NS and flu vaccination, duration between last relapse of NS and flu vaccination (excluded children who have never had any relapse from onset of NS), total number of NS relapses during the period between onset of NS and flu vaccination, use of immunosuppressants at the day − 180 preceding flu vaccination (cyclosporine, mycophenolate mofetil, mizoribine, cyclophosphamide, tacrolimus, and rituximab (RTX)), use of immunosuppressants at first vaccination, use of RTX at first vaccination, use of prednisolone (PSL) at flu vaccination, total number of NS relapses during study period, total number of flu vaccinations, and total number of flu infections. We requested the participant to fill out a questionnaire that included the date of side effects within 1 week of flu vaccination (fever, local redness, swelling, pain, and feeling of heat) and fever, symptoms of various infections, and other events.

Definitions

The definitions of the general condition in pediatric NS used in the present study were in accordance with the clinical guidelines issued by the Japanese Society for Pediatric Nephrology [16, 17]. Idiopathic NS in children was defined as hypoalbuminemia (serum albumin levels ≤ 2.5 g/dL) and severe proteinuria (≥ 40 mg/h/m^2 in pooled nighttime urine or an early morning urine protein Cr ratio > 2.0 g/g Cr). Complete remission was defined as a urine protein creatinine ratio < 0.2 g/g Cr or $\leq -$ protein on dipstick testing of early morning urine for 3 consecutive days. SSNS was defined as complete remission in less than 4 weeks after

initiation of daily PSL therapy. Relapse of NS was defined as ≥ 3 + protein on dipstick testing of early morning urine for 3 consecutive days. FRNS was defined as two or more relapses within 6 months of the initial response or more than four relapses within any 12-month period. SDNS was defined as two consecutive relapses during PSL tapering or < 14 days after discontinuation of PSL therapy. SRNS was defined as the absence of complete remission after ≥ 4 weeks of daily PSL therapy. In our institutions, all patients with NS administer urine protein check on dipstick testing of every first-morning urine at home. In addition, if the results of their dipstick testing meet the criteria of NS relapse, they are instructed to contact their institution.

The day of administration of inactivated subunit-antigen flu vaccination was defined as day 0. The periods within 1 month following and 6 months preceding flu vaccination were designated + 30 to − 180. Based on the background that the side effects of inactivated vaccines generally occur within 1 month of administration, we defined the period between 0 to + 30 as the direct association period involving vaccination. To define the period − 180 to 0 as the prevaccination period (precontrolled period), we examine the NS relapse rates during the period 0 to + 180.

Children older than 13 years generally receive a flu vaccination once per year, and those younger than 13 years receive a flu vaccination twice per year. In children who received two vaccinations in the same year, we defined "first flu vaccine" as only their first vaccination of the two. The rate of NS relapse was defined as the number of relapses one person experienced within 1 year. The duration of RTX therapy was defined as the period from the day of RTX administration to the day of B-cell recovery (CD19 + B-cell count of ≥ 1% of total lymphocytes). Exacerbation of NS was defined following two patterns. The first pattern consisted of children with greater numbers of NS relapses during the period 0 to + 180 than the number of NS relapses occurring during the precontrolled period. The other pattern was children starting any new immunosuppressants because they experienced a relapse in NS during the period 0 to + 180.

Study design

The primary outcome was the rate of NS relapse occurring within the direct association period involving vaccination during the period 0 to + 30 compared with the rate during the precontrolled period in all patients. We examined and subdivided this outcome into each group as follows: (1) in patients receiving oral glucocorticoids at the time of flu vaccination or not, (2) in patients with at least one NS relapse during the precontrolled period (unstable group) or those without NS relapse during the precontrolled period (stable group), (3) in patients receiving immunosuppressants at the time of flu vaccination or not, and (4) in patients with side effects within 1 week of flu vaccination or not. Secondary outcomes were the rate of NS relapse during the period 0 to + 180 compared with the rate during the precontrolled period, the rate of patients infected with the flu virus, and the rate of patients with severe flu virus infection.

In addition, we evaluated the clinical characteristics and percentage of children with an NS exacerbation and compared the results between patients in the unstable group and those in the stable group.

Regimens

Our NS treatment strategy is based on the modified protocol of the International Study of Kidney Diseases in Children, as shown in the Japanese pediatric idiopathic NS guideline [1, 17–19]. The initial 8-week treatment protocol was 60 mg/m^2/day PSL (maximum daily dosage 60 mg) for 4 weeks, followed by 40 mg/m^2/day (maximum daily dosage 40 mg) on alternate days for 4 weeks. Our policy was to administer inactivated subunit-antigen flu vaccine to consenting children with NS, except during a relapse of NS and during any period of PSL therapy of ≥ 2 mg/kg/day.

Statistical analysis

We performed all analyses using JMP version 11.0 (SAS institute Japan Ltd., Tokyo, Japan). The Wilcoxon rank-sum test was used to evaluate the association between categorical values and continuous values, and Fisher's exact test was used for two categorical values. All data were expressed as median value + interquartile range or number (percentage). The NS relapse rate was calculated using the person-year method. A p value of < 0.05 was considered statistically significant.

The calculated sample size was 40 children. Because we assumed that the median number of events was greater than two times per year in each patient, we required approximately 80 events (NS relapse) in our analysis. Our institutions included both children diagnosed as FRNS/SDNS and those diagnosed as non-FRNS/SDNS. Children with FRNS or SDNS experience two or more NS relapses within 6 months. If the ratio of the FRNS/SDNS and non-FRNS/SDNS groups was 1:1, the estimated median number of events was two times per year in each patient cumulatively. In each of our institutions, the number of patients with NS for < 15 years ranges from 5 to 80 (median: 15–20 children with NS/institution). If approximately half of the children with NS in our institutions receive the flu vaccine, the estimated number in six institutions would be 45–60 (7.5–10 children × 6 institutions = 45–60). Moreover, we assumed that 10–20 children would be omitted because of not gaining consent. Hence, to satisfy these assumptions, we calculated the sample size as 40 children.

Results

Clinical characteristics

In the present study, we included 79 children who received the flu vaccination. We excluded eight children who were infected with the flu virus before receiving the flu vaccine during the study period, and eight children with a record that was inadequate for analysis. Thus, we included a total of 63 children (24 boys and 39 girls) in this study (Fig. 1). Table 1 summarizes the patients' characteristics. The median age at first manifestation of NS and age at flu vaccination were 3.4 (2.3–7.5) and 10.8 (7.7–14.3) years, respectively. Only one patient (1.6%) was under 1 year old, and 11 children (17.4%) were teenage at the first manifestation of NS. The remaining 51 children (81.0%) were between 1 and 10 years old at the first manifestation of NS. Eight children (12.7%) had a history of SRNS. The duration between the last relapse of NS and flu vaccination in the unstable group was significantly shorter than those in the stable group (0.1 vs. 1.3 years; $p = 0.002$). The proportion of children who changed immunosuppressants during the precontrolled period in the unstable group was slightly higher than those in the stable group but without reaching significance. The numbers of children with adverse events within 1 week of flu vaccination were 22 (34.9%). During the period after flu vaccination from day 0 to + 180, there were 16 flu infections and 16 children with flu infections. No patients experienced a severe infection of the flu virus. In 16 children with flu infection in this study, there were two NS relapses associated directly with flu infection. Among them, the first patient showed no NS relapse during the precontrolled period. However, the patient relapsed a day after the flu infection from day 0 to + 180 (more than 1 month after flu vaccination). The second patient with a relapse of NS during the precontrolled period showed two NS relapses from day 0 to + 180. In this case, one relapse occurred 4 days after flu infection (more than 1 month after flu vaccination). Therefore, NS relapses within 4 days after flu infection might be associated directly with infection. We considered these events as confounders and excluded them from the analysis.

The total number of NS relapses during the whole study period was 30 in 13 children. In comparison between the children with at least one relapse and those with no relapse, there was no significant difference in terms of NS (history of SRNS, last NS type of FRNS, or SDNS), age at first flu vaccination, age at the first manifestation of NS, history of flu vaccination, and type of immunosuppressants (cyclosporine, mycophenolate mofetil, mizoribine, cyclophosphamide, tacrolimus, and RTX). There were 12 NS relapses and 9 children who experienced NS relapse before flu vaccination during the study period. We evaluated and compared the patients' clinical characteristics between the unstable group ($n = 9$) and the stable group ($n = 54$; Table 1). A significantly higher proportion of children was receiving glucocorticoids during the time of flu vaccination in the unstable group as compared with the stable group. There were no other significant differences between the two groups in other clinical characteristics, including background, receiving immunosuppressants, total number of flu-infected children, or total number of children experiencing a side effect within 1 week of flu vaccination.

We observed 37 episodes in 23 children, which included symptoms of infectious diseases (for example, fever, coughing, and diarrhea) outside of flu infection during the study period. Of these, 15 episodes of infections occurred during the precontrolled period, and the remaining 22 occurred during the period between day 0 and + 180. Further, there

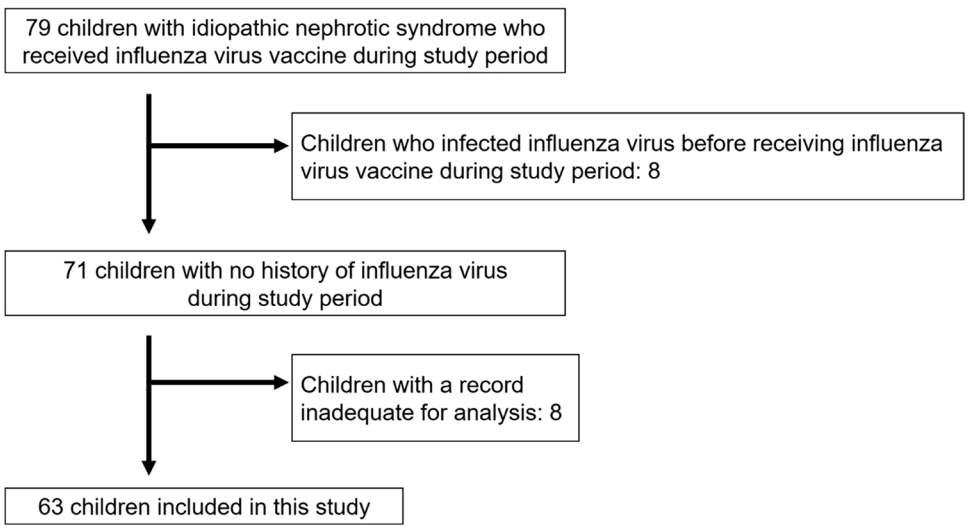

Fig. 1 Patient flow chart. Of 79 children who received the flu vaccination, a total of 63 children were included in this study

Table 1 Comparison of patient clinical characteristics between the unstable group and the stable group

	All ($n=63$)	NS relapse during the period between day –180 and 0		p value
		Unstable group ($n=9$)	Stable group ($n=54$)	
Background				
Age at first manifestation of NS (years)	3.4 (2.3–7.5)	2.9 (1.9–7.5)	3.5 (2.3–7.8)	0.43
Age group of NS, n (%) under than 1 year old between 1 and 10 years old over than 10 years old	1 (1.6) 51 (81.0) 11 (17.4)	0 (0.0) 9 (100) 0 (0.0)	1 (1.8) 42 (77.8) 11 (20.4)	
Age at first flu vaccination (years)	10.8 (7.7–14.3)	9.8 (8.0–13.1)	11.0 (7.4–14.9)	0.34
Boy:girl, *n* (%)	39:24 (61.9:38.1)	7:2 (77.8:22.2)	32:22 (59.3:40.7)	0.46
Past history of flu vaccination, *n* (%)*	44 (81.5)	7 (87.5)	37 (80.4)	1.0
Past history of steroid-resistant NS, *n* (%)	8 (12.7)	1 (11.1)	7 (13.0)	1.0
Frequent relapsing or steroid-dependent NS as last NS type, *n* (%)	21 (33.3)	2 (22.2)	19 (35.2)	0.71
The last Cr-eGFR before administration of first vaccination (ml/min/1.73 m^2)†	120.1 ± 18.7	113.2 ± 6.6	121.8 ± 3.2	0.25
Duration between onset of NS and flu vaccination (years)	5.4 (3.4–8.7)	5.3 (4.7–7.9)	5.7 (3.0–9.1)	0.73
Duration between last relapse of NS and flu vaccination (years)	0.8 (0.5–2.4)	0.1 (0.1–0.3)	1.3 (0.6–0.2.8)	0.002
Total number of NS relapse during the period between onset of NS and flu vaccination	8 (4–11)	10 (6.5–10.5)	7 (3–11)	0.77
The state of being on immunosuppressants at the day –180 before flu vaccinations	40 (63.5)	6 (66.7)	34 (63.0)	1.0
The change of immunosuppressants during the period between day –180 and 0	5 (7.9)	2 (22.2)	3 (5.6)	0.16
The state of being on glucocorticoid at flu vaccinations	6 (9.5)	5 (55.6)	1 (1.9)	0.0001
The state of being on immunosuppressants at flu vaccinations	42 (66.7)	7 (77.8)	35 (64.8)	0.71
being on cyclosporine	18 (28.6)	5 (55.6)	13 (24.1)	0.10
being on mycophenolate mofetil	18 (28.6)	2 (22.2)	16 (29.6)	1.0
being on mizoribine	8 (12.7)	0 (0.0)	8 (14.8)	0.59
being on tacrolimus	2 (3.2)	1 (11.1)	1 (1.9)	0.27
being on rituximab	2 (3.2)	1 (11.1)	1 (1.9)	0.27
Total number of flu infected patient, *n* (%)	16 (25.4)	3 (33.3)	13 (24.1)	0.68
Total number of flu infection, (times/person-year)	0.51 ± 0.88	0.67 ± 0.29	0.48 ± 0.12	0.56
Total number of patients who have the local side effects within a week of flu vaccination, *n* (%)	22 (34.9)	3 (33.3)	19 (35.2)	1.0
Local redness	14 (22.2)	2 (22.2)	12 (22.2)	1.0
Local swelling	15 (23.8)	2 (22.2)	13 (24.1)	0.71
Local pain	13 (20.6)	1 (11.1)	2 (22.2)	0.67
Local feeling of heat or fever	13 (20.6)	2 (22.2)	11 (20.4)	1.0

NS nephrotic syndrome, *Flu* influenza virus, *Cr-eGFR* creatinine-estimated glomerular filtration rate

*Evaluated 54 children with data for past history of influenza vaccination

†Evaluated 41 children with data of the last Cr-eGFR before administration of first vaccination

were two NS relapses associated directly with infections other than flu infection. Among these, the first patient had a relapse 2 days after acute enterocolitis during the precontrolled period (more than 1 month before flu vaccination). In the second patient, a relapse occurred 3 days after upper respiratory tract infection during the precontrolled period (more than 1 month before flu vaccination). Although we considered that NS relapses 2 or 3 days after the appearance of any infectious symptoms might be associated directly with infection, relapse after flu vaccination was not seriously affected by these those occurring during the precontrolled period (more than 1 month before flu vaccination). We observed eight vaccinations in six children who received any of the following vaccines: Varicella vaccine, Mumps vaccine, Measles–Rubella mixed vaccine, and Pneumococcal vaccine, before flu vaccination during the precontrolled period,

and five times in four children who received vaccinations other than flu vaccine (Varicella vaccine, Diphtheria-Tetanus mixed vaccine, Japanese encephalitis vaccine, Mixed Measles, and Rubella vaccine) after flu vaccination during the period from day 0 to + 180. Moreover, none of the above 10 children experienced NS relapse after 13 heterogeneous vaccinations during the study period. Therefore, we considered that other vaccines did not affect either flu vaccinations or NS relapse in these 10 children. The remaining 53 children received no other vaccines during the study period.

Comparison of the NS relapse rate between the precontrolled period and the period after flu vaccination from day 0 to + 30 as a direct association with vaccination

During the period after flu vaccination from day 0 to + 180, there were 18 occurrences of NS relapse and 11 children experiencing NS relapse. Figure 2 shows that among all 63 patients, the relapse rate was not significantly different between the precontrolled period and the period 0 to + 30 (0.38 vs. 0.19 times/person-year, $p = 0.95$) as the primary outcome. The additional analysis subdivided the primary outcome into each group as follows. The number of patients receiving glucocorticoids at the time of flu vaccination was too small ($n = 6$) to allow a comparison of the relapse rate between the prevaccination and postvaccination periods in this group. In patients not receiving glucocorticoids at the time of flu vaccination ($n = 57$), the relapse rate was 0 times/person-year during days 0 to + 30 ($p = 0.94$) as compared

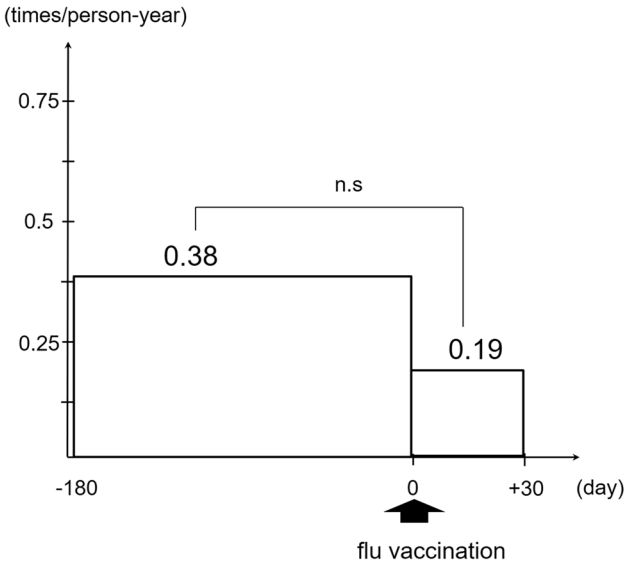

Fig. 2 Comparison of the relapse rate between the precontrolled period and the 0 to + 30 period in all 63 children. *ns* not significant

with 0.14 times/person-year during the precontrolled period (Supplementary Figure 1). Among the patients in the unstable group ($n = 9$) and in the stable group ($n = 54$), there was no significant difference in the relapse rate in each period during the precontrolled period between patients who were receiving immunosuppressants at the time of flu vaccination ($n = 42$) or not ($n = 21$) and in patients with adverse events within 1 week of flu vaccination ($n = 22$) or not ($n = 41$) as compared with those in each group during the 0 to + 30 period. The difference in the relapse rate in each period during the precontrolled period was not significant (Supplementary Figures 2–4).

Comparison of exacerbation rates during the precontrolled period between the unstable and stable groups

As shown in Fig. 3a, the rate of children with an exacerbation of NS during the period 0 to + 180 in the unstable group (4/9 [44.4%]) was significantly higher than that in the stable group (4/54 [7.4%]; $p = 0.01$). The details of the four children in the unstable group were as follows: two children with a relapse of NS during the precontrolled period experienced three relapses during the period 0 to + 180 following initiating mizoribine therapy, and two children with two relapses of NS during the precontrolled period experienced two relapses during the period 0 to + 180 following initiating cyclosporine therapy. The details of the four children in the stable group were as follows: three patients without a relapse of NS during the precontrolled period experienced a relapse during the period 0 to + 180, and one patient without a relapse during the precontrolled period experienced two NS relapses during the period 0 to + 180. We performed an analysis of the comparison of the relapse rate between the precontrolled period and the day 0 to + 180 period in all 63 children (Fig. 3b) and subdivided results into the unstable and stable groups (Fig. 3c in 9 children in the unstable group and Fig. 3d in 54 children in the stable group). As shown in Fig. 3b–d), the relapse rates from day 0 to + 180 did not increase compared with those during the precontrolled period both in all children and in subdivided groups.

Discussion

In this current prospective cohort study, we indicate that flu vaccination does not significantly precipitate the direct relapse of NS in children. However, it might increase the disease activity in children with at least one NS relapse within a half year before vaccination. Children who did not have an NS relapse during the precontrolled period also experienced no relapse during the postvaccination 0

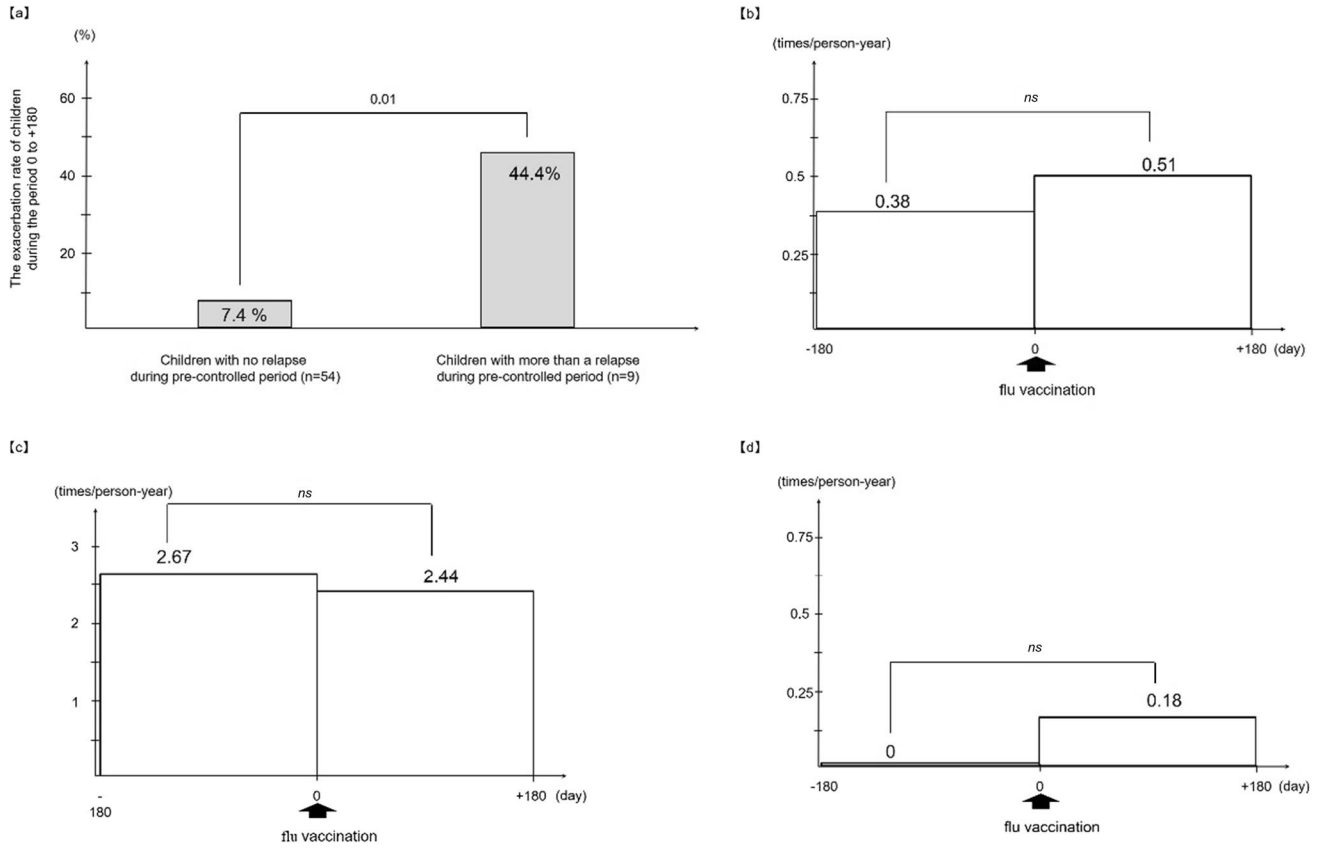

Fig. 3 Comparison of the rates of children with exacerbation of nephrotic syndrome during the 0 to + 180 period between the unstable group and the stable group (**a**). Comparison of the relapse rate between the precontrolled period and the 0 to + 180 period (**b-d**). **a** The rates of children with an exacerbation of nephrotic syndrome during the 0 to + 180 period in the unstable group (4/9 [44.4%]) was significantly higher than those in the stable group (4/54 [7.4%]; $p = 0.01$): **b** in 63 children, *ns* not significant, **c** in 9 children in the unstable group, *ns* not significant, **d** in 54 children in the stable group, *ns* not significant

to + 30 period. In addition, the percentage of patients with an exacerbation of NS relapse during the 0 to + 180 period was significantly higher in the unstable group than in the stable group, although the relapse rate from day 0 to + 180 did not increase compared with those during the precontrolled period in the unstable group. To the best of our knowledge, this is the first prospective study to evaluate the relationship between NS relapses and only flu vaccination (i.e., without other vaccinations).

In this prospective study, we compared relapse rates during the postvaccination 0 to + 30 period with those during the precontrolled period and found no significant difference between the two periods. The immunogenic pathogenesis by which vaccination itself can ignite NS relapse was speculated to be T-cell activation [10]; however, the in-depth mechanism has not been elucidated. Recently, two studies have reported a minimal change disease following the Coronavirus 2019 vaccination [20, 21], and the authors speculate that the mechanism was T-cell–mediated podocyte injury in the immunologic response to the vaccine. A review of reports with minimal change disease after vaccination described a range between 4 days and 4 months from the time of vaccine receipt to the onset of clinical symptoms [22]. From another point of view, adverse events associated with various vaccines can be observed within 1 month from vaccine administration [6, 23]. From these background studies, we set the period within 1 month after receiving flu vaccination as having a direct association with flu vaccination. Our results suggest that, because the NS relapse rates were not significantly different between the precontrolled period and the 0 to + 30 period, children with NS can receive the inactivated flu vaccine without fear of potential NS relapses as a directly associated adverse effect. In our study, no child without NS relapse in the 6 months prior to flu vaccination experienced a relapse in NS within 1 month after receiving the flu vaccine. This finding might be useful for determining the timing of flu vaccine administration in children with NS, as it provides information regarding the substantial risk of NS relapse due to vaccination.

In general, any vaccination can have several adverse effects. One such effect is an allergic reaction characterized by fever, local redness, swelling, pain, and feeling of heat

resulting from an immunologic response [24]. Although the infection by upper respiratory viruses and presentation of clinical symptoms such as general fever in children with NS can elicit a relapse in NS [25], there have been no reports on the association between the allergic reaction of immunization as a side effect and the relapse of NS. In the present study, we found that among patients who experienced a side effect within 1 week of flu vaccination, the relapse rate during the postvaccination 0 to + 30 period was not significantly different from that during the precontrolled period. Even if an allergic reaction to vaccines is caused by an immunologic mechanism, there might be no association between the allergic immune response and NS relapse.

In this study, there was a possibility that the administration of flu vaccines might have exacerbated the relapse of NS in children who had experienced more than one NS relapse within 6 months before immunization. Macdonald et al. prospectively evaluated upper respiratory infections in 32 children with NS and found an association with the exacerbation of NS [25]. They defined an unstable state of NS as an initial diagnosis of NS or relapse in the year before the study, and the stable state of NS as no relapses in the year before the study. Fifteen of 19 patients (79%) with unstable NS experienced an exacerbation of NS compared with only 4 of 13 patients (31%) with stable NS ($p < 0.001$). In our previous report on children with NS, taking glucocorticoids at the time of flu vaccination was a significant risk factor for NS relapse [14]. We argue that children receiving steroids at the time of flu vaccination indicates it occurred soon after the last NS relapse. Their results might indicate that the immunologic latent state in children with NS was unstable during the period immediately after the initial diagnosis of NS or the last relapse, and immunologic stimulation involving vaccinations might exacerbate the immunologic state after the relapse of NS. Our prospective evaluation showed that an exacerbation of NS relapse may depend on the most recent timing of relapse according to the rates of children with an exacerbation of NS; however, the relapse rate from day 0 to + 180 did not increase compared with those during the precontrolled period in the unstable group. Despite the fact that there was a gap as described above, we speculated that the direct relapse rate of NS was more important than the exacerbation rate 30 days after vaccination, and the exacerbation rate as the rate of children with an exacerbation of NS was more important than the relapse rate of NS from day 0 to + 180 after vaccination.

This study has several limitations. The first is the relatively small number of NS relapses that occurred during the study period after the patients received the flu vaccine. However, we believe that this problem is acceptable, as our sample size of children with NS was the largest among all prospective studies evaluating the relationship between various vaccinations and NS relapse, and pediatric idiopathic NS is a rare disease. The second limitation is that the study population in the present study included only children receiving flu vaccines, and we could not compare the relative rate of NS relapse in vaccinated children with those in nonvaccinated children. A further study is required in which the primary outcome is the relative rate of NS relapse as compared between vaccinated and nonvaccinated patients. Third, we noted several potential confounders of NS relapse, including various infections and vaccinations, outside of flu infection and flu vaccination. We cannot exclude these confounders completely because the study period was between − 180 days before flu vaccination and + 30 days after flu vaccination, which covered fall to winter when several infections become prevalent. Moreover, we extracted the precise interval between each infectious event and various vaccinations and the timing of NS relapse. We considered that NS relapses within 1 month (particularly within 1 week) after infectious events or several vaccinations might be associated directly with these events. We evaluated these factors and their association with NS relapse. However, we observed no NS relapse within 1 month after infectious events or vaccinations, excepting flu infection and flu vaccination, from day + 0 to + 180. We have interpreted these confounders by evaluating our study results. Fourth, the statement on significantly increased relapse rates between the unstable and stable groups is not supported convincingly as the group sizes are very different (9 vs. 54). Finally, a selection bias might have been present, as a high proportion of patients with severe disease is frequently referred to our institutions.

In conclusion, our prospective study indicates that flu vaccination did not significantly precipitate the direct relapse of NS in children. However, it might increase the disease activity in children with at least one NS relapse within a half year before vaccination.

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Author contribution S.I. prepared the manuscript. T.H., J.F., T.Y., N.M., N.K., and K.K. collected the clinical data. M.S., M.O., K.Is., K.Ii., and K.N. revised the article. All the authors have read and approved the final manuscript.

Data Availability Data from this study can be obtained from the corresponding authors at reasonable request.

Declarations

Ethics approval All procedures performed in this study involving human participants were in accordance with the ethical standards set by the Ethics Board at Kakogawa Central City Hospital in which the study was conducted (approval number 29–12) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Before enrollment, written informed consent was obtained from all patients and their parents for this study in accordance with guidelines.

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