Clinical and Experimental Nephrology (2020) 24:1069–1076
https://doi.org/10.1007/s10157-020-01930-8

ORIGINAL ARTICLE

Influenza virus vaccination in children with nephrotic syndrome: insignificant risk of relapse

Shingo Ishimori[1,2] · Koichi Kamei[1] · Takashi Ando[3] · Takahisa Yoshikawa[1] · Yuji Kano[1] · Hiroko Nagata[1] · Ken Saida[1] · Mai Sato[1] · Masao Ogura[1] · Shuichi Ito[4] · Kenji Ishikura[1,5]

Received: 28 September 2019 / Accepted: 8 July 2020 / Published online: 27 July 2020

Abstract

Background Immunization with various vaccines is considered desirable for children with idiopathic nephrotic syndrome (NS) because of their high risk of severe infections. Vaccinations may precipitate relapses of NS, but there is no available data regarding inactivated influenza (flu) virus vaccines.

Methods We retrospectively reviewed the medical records of children with NS who had received flu vaccines between 2002 and 2015. The day of flu vaccination was defined as day 0, and the period between the pre-vaccination and the post-vaccination days was defined as − X to + Y. The risk ratios and their 95% confidence intervals for NS relapse rate were estimated by generalized estimating equation (GEE) Poisson regression.

Results A total of 104 pediatric patients received 208 flu vaccines. The mean age at onset of NS was at 4.85 ± 3.87 years old. There were 261 NS relapses between days − 180 and + 180. Compared with the relapse rate in the − 180 to 0 interval (1.19 times/person-year), those in 0 to + 30 (1.23), + 31 to + 60 (1.58), + 61 to + 90 (1.41), + 91 to + 120 (1.41), and + 121 to + 180 (1.32) days groups were slightly increased, but without significance. Multivariate analysis using GEE Poisson regression also showed no significant increase in relapse rate in each day group compared with days − 180 to 0. Risk ratios for NS relapse were significantly higher in children who were treated with steroids at the first vaccination.

Conclusions Our results suggest that flu vaccines should not be avoided in children with NS based on the potential for NS relapses.

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

Introduction

More than half of children with idiopathic nephrotic syndrome (NS) develop frequent relapses or steroid dependence. These children require various immunosuppressants to prevent relapses of NS. Children with NS are therefore exposed to the risk of recurrent infections and are at high risk of severe infections because of their relatively immunocompromised state. These infections also have the potential to precipitate NS relapses.

Notably, upper respiratory viral infections are common and may precipitate or induce relapses of NS [1]. Several reports have described relapse of NS related to influenza (flu) virus in a season of pandemic influenza [2, 3]. Guidelines recommend that these children should have flu vaccinations to reduce the risk of having serious infections [4]. However, relapse of NS can reportedly occur after various vaccinations [5–10]. Although inactivated flu vaccinations

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10157-020-01930-8) contains supplementary material, which is available to authorized users.

✉ Kenji Ishikura
kenzo@ii.e-mansion.com

1 Division of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan

2 Department of Pediatrics, Takatsuki General Hospital, Osaka, Japan

3 International University of Health and Welfare Hospital, Tochigi, Japan

4 Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokosuka, Japan

5 Department of Pediatrics, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 2520375, Japan

could also precipitate relapses of NS [11, 12], no data are available on the relative risk of NS relapse related to flu vaccines.

We report a retrospective cohort study of children with NS who received inactivated subunit-antigen flu vaccination in our hospital, with a focus on relapses of NS related to flu vaccinations.

Materials and methods

Patients

We examined data from children who were enrolled in the NS database of the National Center for Child Health and Development in Tokyo, Japan. Children were eligible for this study if they were newly diagnosed with idiopathic NS between the ages of 6 months and 15 years and if their last relapse was steroid-sensitive NS (SSNS), regardless of history of steroid-resistant NS (SRNS). Excluded were children with NS secondary to nephritis and those with congenital NS. This study was conducted in accordance with the Declaration of Helsinki and with the ethical guidelines for Medical and Health Research Involving Human Subjects created by the Ministry of Health, Labor and Welfare in Japan. In accordance with these guidelines, informed consent was not obtained from patients or their parents for this study. The National Center for Child Health and Development Ethics Review Board approved this study (approval number: 1097).

Definitions

In the present study, the definitions of general conditions in pediatric NS were made according to clinical guidelines issued by the Japanese Society for Pediatric Nephrology [13, 14]. 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 creatinine (Cr) ratio > 2.0 g/g Cr). Complete remission was defined as a urine protein creatinine ratio < 0.2 g/g Cr or ≤ − protein on dipstick testing of early morning urine for three consecutive days. SSNS was defined as complete remission in < 4 weeks after starting daily prednisolone (PSL) therapy. The relapse of NS was defined as ≥ 3 + protein on dipstick testing of early morning urine for three consecutive days. Frequently relapsing NS (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. Steroid-dependent NS (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.

The day of inactivated subunit-antigen flu vaccination was defined as day 0, and the period from the pre-vaccination to the post-vaccination days as − X to + Y, respectively. 'Day 0′ is not necessarily the timing when patients had an influenza vaccine for the first time since they developed NS. In our study, we included children who received several times of vaccinations. The NS relapse rate was defined as the number of relapses one person had within one year. The duration of rituximab (RTX) therapy was defined as the period from the day of rituximab administration to the day of B cell recovery (CD19 + B cell count of ≥ 1% of total lymphocytes).

Study design

We reviewed the following data: sex, age at onset of NS, age at first inactivated subunit-antigen flu vaccination, observation period, the total number of NS relapses, the total number of flu vaccinations, the total number of flu infections, use of RTX at first vaccination, and use of PSL at flu vaccinations. We also reviewed types of NS (SRNS, FRNS, SDNS); we reviewed renal histopathology (minimal change, focal segmental glomerulosclerosis, diffuse mesangial hypercellularity, or no history of renal biopsy) and also use of immunosuppressants at first vaccination (cyclosporine, mycophenolate mofetil, mizoribine, cyclophosphamide, tacrolimus).

We compared NS relapse rates between days − 180 and 0 (the day of flu vaccination) with relapse rates from days 0 to + 30, + 31 to + 60, + 61 to + 90, + 91 to + 120, and + 121 to + 180. Based on the background that the side effects of an inactivated vaccine generally occur within a month of its administration, we subdivided into the relapse rate in the post-vaccination period from days 0 to + 30. In addition, to compare with NS relapse rates between days − 180 and 0 as the controlled pre-vaccination period, it was decided to examine NS relapse rates between days 0 and + 180 during the post-vaccination period.

Vaccines

Our policy was to administer inactivated subunit-antigen flu vaccine to consenting children with NS, except during any period of PSL therapy of ≥ 2 mg/kg/day. The other exception was if the patient was in a relapse of NS. In Japan, children younger than 13 years generally have a flu vaccination twice per year and those older than 13 have a flu vaccination once 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 details of antigen strains in inactivated flu vaccines between 2002 and 2015 are shown in the Supplementary Table.

Statistical analysis

The relapse rate of NS was calculated by the person-year method. The risk ratio between pre- and post-vaccination was calculated with 95% confidence intervals (CIs) on the basis of the person-year method. Risk ratios and their 95% CIs for the NS relapse rate were also estimated by generalized estimating equation (GEE) Poisson regression. This regression was adjusted for parameters, including treatment with various immunosuppressants or no treatment, treatment with RTX or no treatment, treatment with PSL or no treatment, and flu infection in the same flu epidemic season or no flu infection. All statistical analyses were performed using The SAS software package for Windows, release 9.4 (SAS Institute Inc. Cary, NC). A p value < 0.05 was considered statistically significant.

Results

Clinical characteristics

Available for assessment were 304 children with NS who were newly diagnosed between 2002 and 2015. Of these, 104 children (73 boys) received flu vaccines. The clinical characteristics of these children are shown in Table 1. The total number of flu vaccinations was 208. Vaccination details are as follows: 49 children received one vaccination, 25 received two vaccinations, 18 received three vaccinations, seven received four vaccinations, four received five vaccinations, and one received seven vaccinations. No patients experienced fever or symptoms of an allergic reaction that required any treatment after flu vaccination, even though the quantity of the flu vaccine in Japan since 2011 was changed. One boy received an inactivated subunit-antigen flu vaccine; he was taking oral anti-allergic medicines because he had suffered from local swelling of the arm following a flu vaccination before the onset of NS. A greater proportion of patients were taking immunosuppressants at the time of flu vaccination (91.8%) of the 26 children with a history of SRNS than of the other 78 children who did not have a history of SRNS. Only those with complete remission at the time of flu vaccination were included. The use of immunosuppressants, however, was similar among the children with and without a history of SRNS (data not shown). We could not evaluate the infection rate of children with NS because there were no data from children who received no flu vaccines but did not contract the flu.

Table 1 Clinical characteristics of the patients

	$n = 104$
Boy : Girl	73 : 31
Age at onset of NS (years)	4.85 ± 3.87
Age at first flu vaccination (years)	7.76 ± 5.10
Observation period (years)	2.64 ± 2.20
Renal histopathology	
MC	62 (59.6%)
FSGS	10 (9.6 %)
DMH	7 (6.7 %)
No history of renal biopsy	25 (24.0%)
Past history of NS type	
SRNS	26 (25.2%)
FRNS/SDNS	87 (83.7%)
From day −180 ~ +180	
Total number of NS relapses (times)	261
Total number of flu vaccinations (times)	208
Immunosuppressants at flu vaccination	
No	43 (20.7%)
Yes	165 (79.3%)
CsA	104 (50.0%)
MMF	40 (19.2%)
MZR	31 (14.9%)
CPM	5 (2.4%)
Tac	2 (1.0%)
RTX	6 (2.9%)
PSL	49 (23.6%)

SRNS Steroid resistance nephrotic syndrome, *FRNS* Frequent relapsing nephrotic syndrome, *SDNS* Steroid dependence nephrotic syndrome, *MC* Minimal change, *FSGS* Focal segmental glomerulosclerosis, *DMH* Diffuse mesangial hypercellularity, *CsA* Cyclosporine, *MMF* Mycophenolate Mofetil, *MZR* Mizoribine, *CPM* Cyclophosphamide, *Tac* Tacrolimus, *RTX* Rituximab, *PSL*; prednisolone

Comparison of the relapse rate between the pre- and post-vaccination periods, and the risk ratio for nephrotic syndrome relapse in the post-vaccination vs. pre-vaccination periods

Compared with the relapse rate during the −180 to 0 interval (1.19 times/person-year), the relapse rate was 1.23 during 0 to +30 (risk ratio: 1.04, 95% CI 0.82–1.89, $p = 0.88$), 1.58 during +31 to +60 (risk ratio: 1.33, 95% CI 1.08–2.30, $p = 0.18$), 1.41 during +61 to +90 (risk ratio: 1.19, 95% CI 0.94–2.10, $p = 0.45$), 1.41 during +91 to +120 (risk ratio: 1.19, 95% CI 0.94–2.10, $p = 0.45$), and 1.32 during +121 to +180 (risk ratio: 1.11, 95% CI 0.98–1.76, $p = 0.54$) (Fig. 1). Multivariate analysis showed that being administered PSL (at first vaccination) was a significant independent risk factor associated with NS relapses in all periods (Table 2). In 49 children with PSL, the difference in the relapse rate in each post-vaccination period was

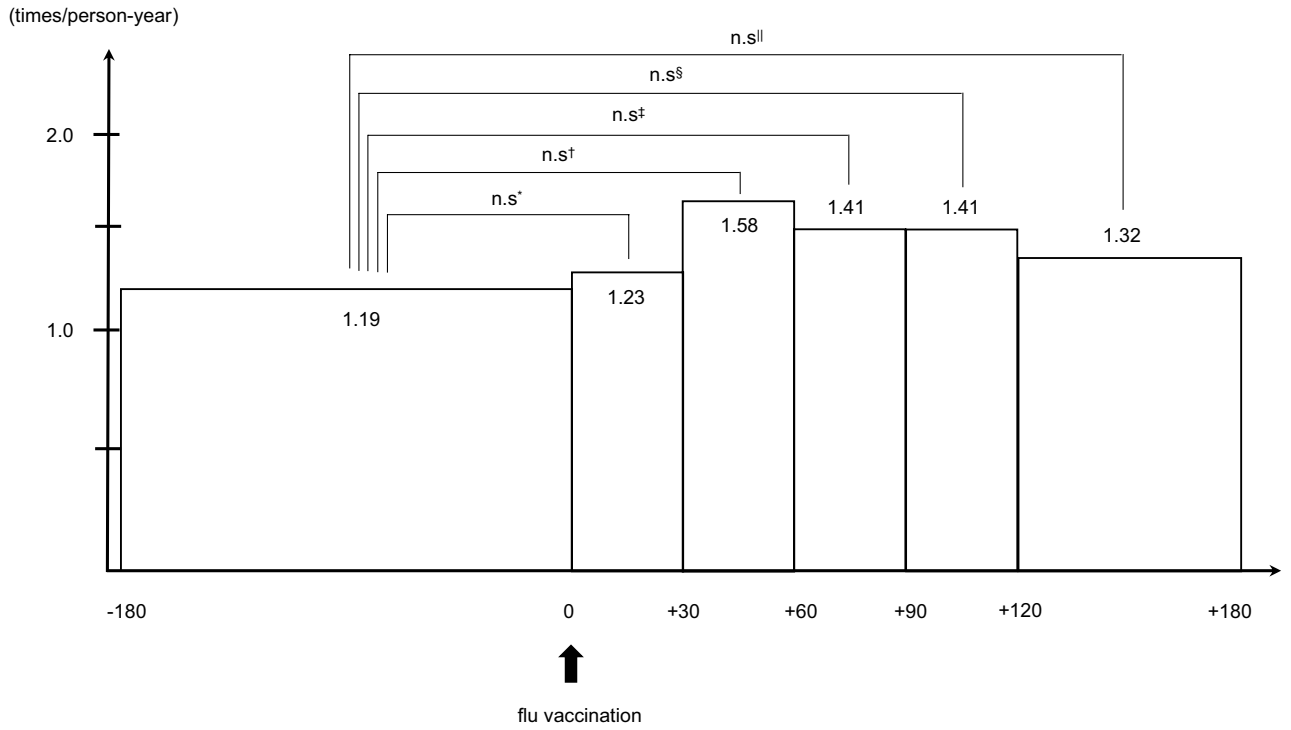

Fig. 1 Comparison of relapse rates between the pre-vaccination period from days −180 to 0 and the post-vaccination period (univariate analysis). *in the post-vaccination period from days 0 to + 30 (risk ratio: 1.04, 95% confidence intervals: 0.82–1.89, $p = 0.88$). †in the post-vaccination period from days + 31 to + 60 (risk ratio: 1.33, 95% confidence intervals: 1.08–2.30, $p = 0.18$). ‡in the post-vaccination period from days + 61 to 90 (risk ratio: 1.19, 95% confidence intervals: 0.94–2.10, $p = 0.45$). §in the post-vaccination period from days + 91 to + 120 (risk ratio: 1.19, 95% confidence intervals: 0.94–2.10, $p = 0.45$). ‖in the post-vaccination period from days + 121 to 180 (risk ratio: 1.11, 95% confidence intervals: 0.98–1.76, $p = 0.54$). *n.s* not significant

Table 2 Risk ratio for NS relapse (Generalized estimating equation Poisson regression)

	for NS relapses	
	Risk ratio	95% Confidence interval
The post-vaccination period (days 0 to + 30)	1.02	0.64–1.62
The post-vaccination period (days + 31 to + 60)	1.3	0.86–1.98
The post-vaccination period (days + 61 to + 90)	1.16	0.74–1.80
The post-vaccination period (days + 91 to + 120)	1.14	0.73–1.77
The post-vaccination period (days + 121 to + 180)	1.09	0.77–1.54
On Immunosuppressants (reference: no immunosuppressants)	0.86	0.62–1.20
On RTX (reference: no RTX)	1.11	0.50–2.49
On PSL (reference: no PSL)	3.01	2.18–4.17
Flu infection (reference: no infection)	2.38	0.81–6.99

NS Nephrotic syndrome, *RTX* Rituximab, *PSL* prednisolone

not significantly different compared with the relapse rate in the pre-vaccination period from days −180 to 0 (data not shown). Moreover, these results did not change when we repeated the analysis with exclusion of data from children with a history of SRNS (data not shown). We examined data regarding times of flu vaccination. The mean age at vaccination in the group that was limited to a vaccine twice (83 times) was significantly younger compared with the group that was limited to a vaccine once (125 times) (10.5 ± 5.5 vs 7.3 ± 3.8 years, $p < 0.0001$). In the once vaccination group, the relapse rate in the post-vaccination period from days 0 to + 30 was significantly higher than that in the

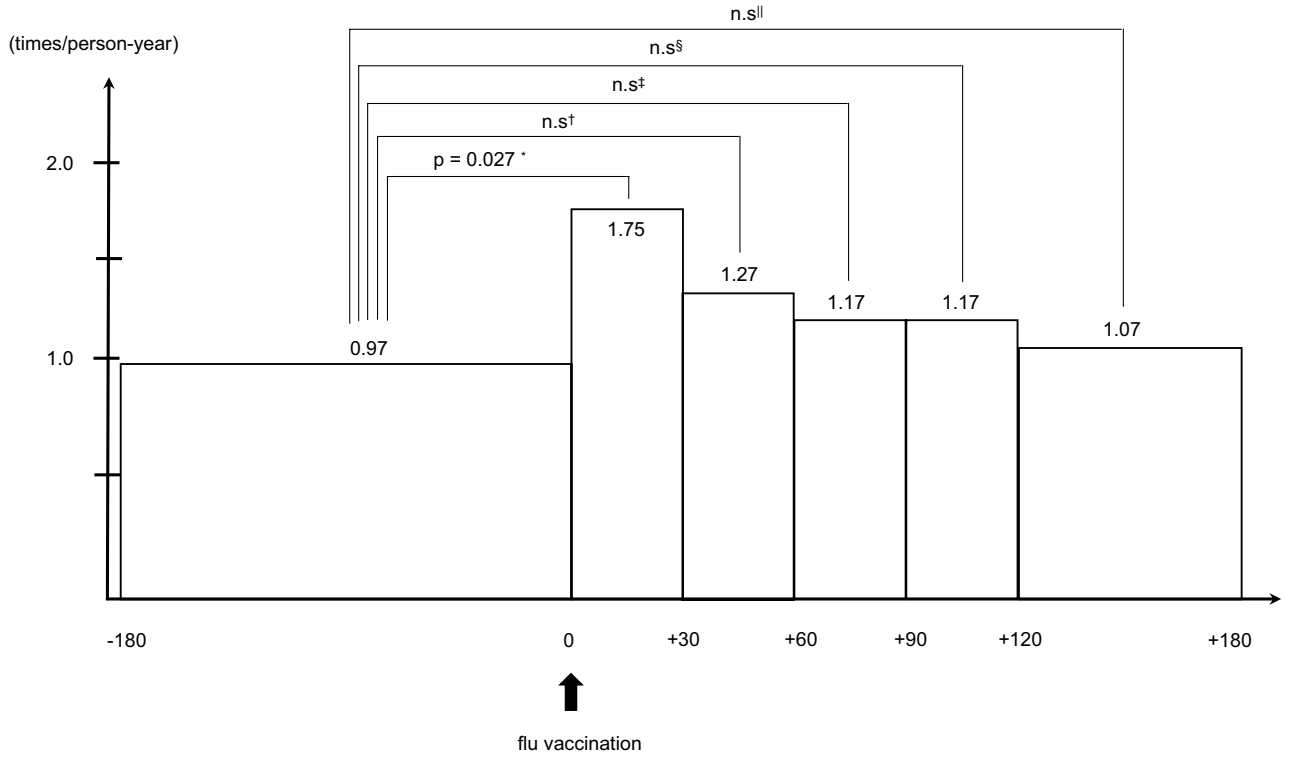

Fig. 2 Comparison of relapse rates between the pre-vaccination period from days −180 to 0 and the post-vaccination period in children who received a flu vaccination (univariate analysis). *in the post-vaccination period from days 0 to + 30 (risk ratio: 1.82, 95% confidence interval: 1.07–3.08, relapse rate: 1.75, $p = 0.027$). †in the post-vaccination period from days + 31 to + 60 (risk ratio: 1.31, 95% confidence interval: 0.72–2.39, relapse rate: 1.27, $p = 0.38$). ‡in the post-vaccination period from days + 61 to 90 (risk ratio: 1.21, 95% confidence interval: 0.65– 2.25, relapse rate: 1.17, $p = 0.55$). §in the post-vaccination period from days + 91 to + 120 (risk ratio: 1.21, 95% confidence interval: 0.65–2.25, relapse rate: 1.17, $p = 0.55$). ‖in the post-vaccination period from days + 121 to 180 (risk ratio: 1.11, 95% confidence interval: 0.68–1.81, relapse rate: 1.07, $p = 0.68$). *n.s* not significant

pre-vaccination period. Compared with the relapse rate in the pre-vaccination period from days − 180 to 0, the difference in relapse rate in each post-vaccination period, except for from days 0 to + 30, was not significant (Fig. 2). However, in the twice vaccination group, the relapse rate in the post-vaccination period from days 0 to + 30 was significantly lower than that in the pre-vaccination period. Compared with the relapse rate in the pre-vaccination period from days − 180 to 0, the difference in relapse rate in each post-vaccination period, except for from days 0 to + 30, was not significant (Fig. 3). However, the event of NS relapse from days 0 to + 30 in the twice vaccination group only occurred three times in three children.

Discussion

In our retrospective cohort study, we showed that inactivated subunit-antigen flu vaccination caused a slight, but nonsignificant increase in the risk of NS relapse (1.2 to 1.3–1.5 times in one person within a year) in children. Because the relapse rate in the post-vaccination period from days 0 to + 30 in the once vaccination group was significantly higher than that in the pre-vaccination period, we consider that flu vaccination might be prone to precipitating relapse of NS in older children who have flu vaccine once a year. Furthermore, inactivated subunit-antigen flu vaccination in children with NS did not precipitate SRNS or other severe adverse events. Our results suggest that these children can be immunized without a significantly increased risk of NS relapse. To the best of our knowledge, this is the first published study of NS relapses and other adverse effects related to flu vaccination.

In the present study, the relative risk of NS relapses was not significantly increased in the post- flu vaccination period compared with the pre-vaccination period. A small study of NS relapses in 19 children [12], which used inactivated split-virion influenza vaccine same as Japan, reported one relapse episode three months after flu vaccination and three episodes of relapse six months after regarding the rate of NS relapse due to flu vaccination.

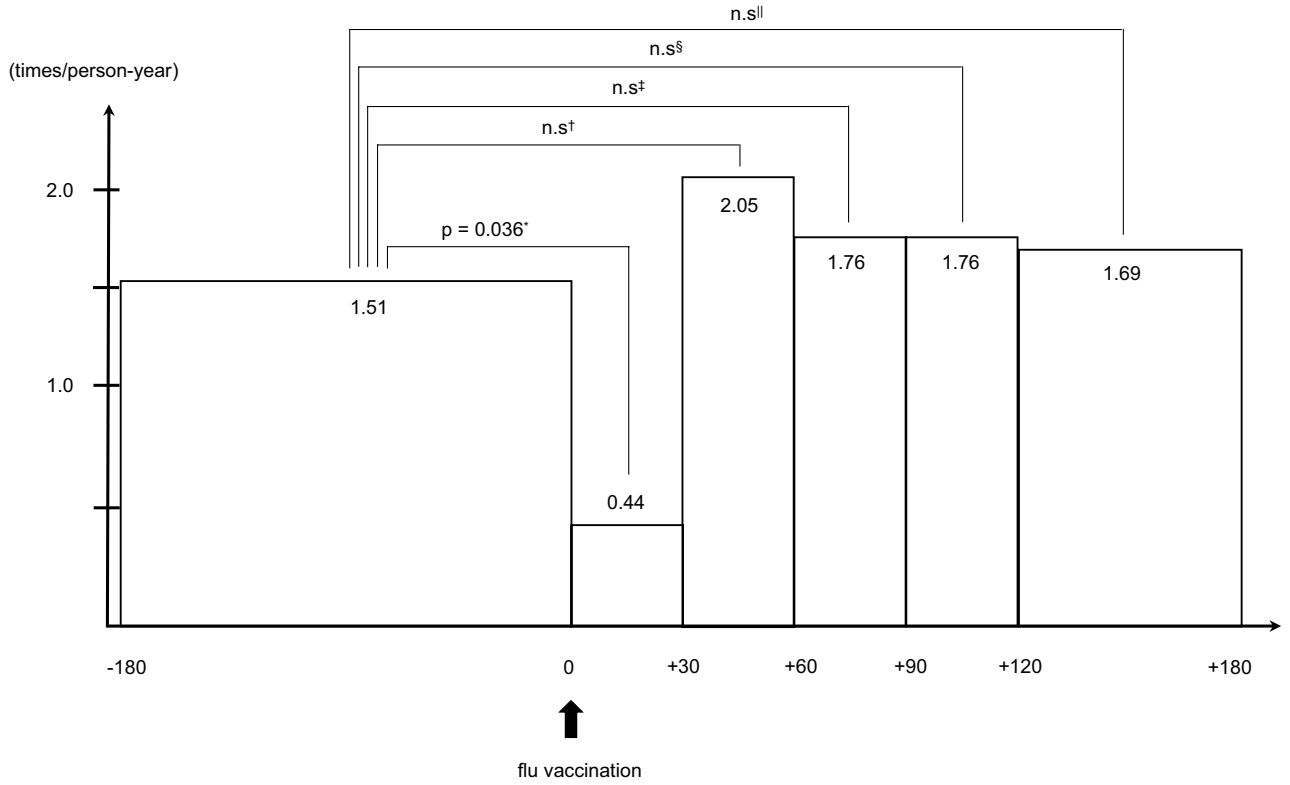

Fig. 3 Comparison of relapse rates between the pre-vaccination period from days −180 to 0 and the post-vaccination period in children who received two vaccinations in the same year (univariate analysis). *in the post-vaccination period from days 0 to + 30 (risk ratio: 0.29, 95% confidence interval: 0.09–0.93, relapse rate: 0.44, $p = 0.036$). †in the post-vaccination period from days + 31 to + 60 (risk ratio: 1.35, 95% confidence interval: 0.76–2.42, relapse rate: 2.05, $p = 0.31$). ‡in the post-vaccination period from days + 61 to 90 (risk ratio: 1.16, 95% confidence interval: 0.63–2.16, relapse rate: 1.76, $p = 0.64$). §in the post-vaccination period from days + 91 to + 120 (risk ratio: 1.16, 95% confidence interval: 0.63–2.16, relapse rate: 1.76, $p = 0.64$). ‖in the post-vaccination period from days + 121 to 180 (risk ratio: 1.11, 95% confidence interval: 0.69–1.80, relapse rate: 1.69, $p = 0.66$). *n.s* not significant

Fernandes et al. [11] reported a woman with NS had relapsed after monovalent whole-virion inactivated influenza vaccination [11]. If we investigate the NS relapse associated with those different types of flu vaccines, we may get different results from the present study. NS relapses following the administration of other vaccines have also been reported. Abeyagunawardena et al. [8] showed an increased risk of NS relapse following meningococcal C conjugate vaccine administration [8]. It was suggested that the decision to administer the meningococcal C conjugate vaccine should be carefully considered in children with SSNS. Yildiz et al. [9] suggested that patients with SSNS in hepatitis B virus (HBV) endemic regions should receive HBV vaccines because of the risk of HBV infections. They also suggested that HBV vaccines might trigger NS relapses in some pediatric patients with NS [9]. To date, however, no reports have evaluated the details of relapses, such as the risk ratio of NS relapses, related to flu vaccination.

In the current study, inactivated subunit-antigen flu vaccination in children with NS was not associated with severe adverse events. While an allergic reaction is a serious concern for immunized patients, none of the children in our study had these symptoms. Although approximately one-quarter of the children in this study had a history of SRNS, NS relapses were all steroid-sensitive between approximately days − 180 and + 180. This suggests that no children who experienced relapses of NS became steroid-resistant after receiving an inactivated subunit-antigen flu vaccine. In another study, NS relapses after receiving varicella-zoster vaccines were all steroid-sensitive [7].

An immunogenic stimulus may trigger NS relapse in children. The major pathogenesis of NS relapses related to various infections or vaccinations may involve activation of T cells in an acute process [2, 8]. However, the precise mechanism of this pathogenesis has not been biologically demonstrated. In the present study, we found a significantly high risk of NS relapse in children who were treated with steroids at the first vaccination. Flu vaccination in children

taking steroids may occur soon after the last relapse of NS. If they are taking steroids when they have their flu vaccination, they may be susceptible to further NS relapse during this period. Therefore, this result may be not because of the steroids, but due to it been soon after the relapse.

Flu infections have the potential to become severe [15], but the administration of flu vaccines is effective in reducing the prevalence of flu infections and the risk of severe flu infections. Notably, inactive immunizations are effective against pediatric patients with NS, even when they are being treated with glucocorticoids or other immunosuppressive drugs [16]. Poyrazoglu et al. [12] showed that pediatric patients with NS had adequate antibody responses to flu vaccination at 6 months post-vaccination compared with healthy controls [12]. Although the present study was not intended to evaluate the efficacy of flu vaccination in preventing severe flu infections, none of the children in our study suffered from any severe infections.

There are several limitations to the present study. It was a retrospective chart review in a single center and comprised of a limited number of patients. A randomized, controlled trial is ideal for evaluating risk ratios for NS relapses regarding flu virus vaccines. A study is required, with the primary outcome of the relative rate of NS relapse in children with flu vaccination compared with those without flu vaccination. However, the feasibility of this type of randomized, controlled trial is low owing to the difficulty in establishing the side effects of vaccinations as a primary endpoint. A second limitation of this study is that selection bias may have resulted from the fact that our hospital is a tertiary institution, and a high proportion of severe patients were referred to this hospital. Therefore, we need to be careful if applying our results to all children who do not have FRNS or SDNS at a general hospital. A further limitation is that the 180 days of pre- and post- flu vaccination occurred from approximately fall to winter, when several infectious diseases become prevalent, and these infections could have resulted in NS relapses. In our study, we did not have data concerning other infections. A final limitation is that we did not examine the efficacy of the flu vaccinations because there was no data of children who received no flu vaccines but did not contract the flu.

In conclusion, inactivated subunit-antigen flu virus vaccination in children with NS produces a slightly increased, but nonsignificant, risk of relapse. Our results suggest that flu vaccines should not be avoided in children with NS for fear of potential NS relapses and other adverse events. Flu vaccination in children taking steroids may occur soon after the last relapse of NS. Therefore, providing flu vaccination soon after the last relapse of NS might risk further relapse. At the same time, pediatric nephrologists should consider a minimal increase in relapse due to vaccination against the substantial risk of flu infection and its consequences.

Acknowledgements The authors thank Benjamin Phillis at the Clinical Study Support Center, Wakayama Medical University, for proofreading and editing the manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest Shuichi lto has received honoraria from Alexion Pharma and Sano-fi Gebzyme. Kenji lshikura has received research grant from Novartis pharma K.K. Shuichi lto has received research grant from Astellas pharma.

Human rights All procedures performed in this study involving human participants were in accordance with the ethical standards set by the Ethics Board at National Center for Child Health and Development in which the study was conducted (approval number 1097) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants For this type of retrospective study, registration of clinical trials and informed consent were not needed.

References

1. MacDonald NE, Wolfish N, McLaine P, Phipps P, Rossier E. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. J Pediatr. 1986;108:378–82.
2. Kim SR, Lee SB, Kim IY, Lee DW, Rhee H, Seong EY, Song SH, Kwak IS. Relapse of minimal change disease following infection with the 2009 pandemic influenza (H1N1) virus. Clin Exp Nephrol. 2012;16:329–32.
3. Ferrara P, Gatto A, Vitelli O, Liberatore P, Del Bufalo F, Bottaro G. Nephrotic syndrome following H1N1 influenza in a 3-year –old boy. Iran J Pediatr. 2012;22:265–8.
4. KDIGO clinical practice guideline for glomerulonephritis. Chapter 3: Steroid-sensitive nephritic syndrome in children. Kidney Int. 2012; Suppl2: 163- 71.
5. Szajner-Milart I, Zajaczkowska M, Zinkiewicz Z, Borzecka H, Majewski M. Efficacy of vaccination against viral hepatitis type B in children with the nephrotic syndrome. Ann Univ Mariae Curie Sklodowska Med. 2003;58:402–8.
6. Furth SL, Arbus GS, Hogg R, Tarver J, Chan C, Fivush BA. Varicella vaccination in children with nephrotic syndrome: a report of the Southwest Pediatric Nephrology Study Group. J Pediatr. 2003;142:145–8.
7. Alpay H, Yildiz N, Onar A, Temizer H, Ozcay S. Varicella vaccination in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2002;17:181–3.
8. Abeyagunawardena AS, Goldblatt D, Andrews N, Trompeter RS. Risk of relapse after meningococcal C conjugate vaccine in nephrotic syndrome. Lancet. 2003;362:449–50.
9. Yildiz N, Sever L, Kasapcopur O, Cullu F, Arisoy N, Caliskan S. Hepatitis B virus vaccination in children with steroid sensitive nephrotic syndrome: immunogenicity and safety? Vaccine. 2013;31:3309–12.
10. Liakou CD, Askiti V, Mitsioni A, Stefanidis CJ, Theodoridou MC, Spoulou VI. Safety and immunogenicity of booster immunization with 7-valent pneumococcal conjugate vaccine in children with idiopathic nephrotic syndrome. Vaccine. 2014;32:1394–7.

11. Fernandes P, Jorge S, Lopes JA. Relapse of nephrotic syndrome following the use of 2009 pandemic influenza A (H1N1) vaccine. Am J Kidney Dis. 2010;56:185–6.
12. Poyrazoglu HM, Dusunsel R, Gunduz Z, Patiroglu T, Koklu S. Antibody response to influenza. A vaccination in children with nephrotic syndrome. Ped Nephrol. 2004;19:57–60.
13. Ishikura K, Matsumoto S, Sako M, Tsuruga K, Nakanishi K, Kamei K, Saito H, Fujinaga S, Hamasaki Y, Chikamoto H, Ohtsuka Y, Komatsu Y, Ohta T, Nagai T, Kaito H, Kondo S, Ikezumi Y, Tanaka S, Kaku Y, Iijima K. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. Clin Exp Nephrol. 2015;19:6–33.
14. Kaku Y, Ohtsuka Y, Komatsu Y, Ohta T, Nagai T, Kaito H, Kondo S, Ikezumi Y, Tanaka S, Matsumoto S, Sako M, Tsuruga K, Nakanishi K, Kamei K, Saito H, Fujinaga S, Hamasaki Y, Chikamoto H, Ishikura K, Iijima K. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: general therapy. Clin Exp Nephrol. 2015;19:34–533.
15. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and control of influenza with vaccines: recommendation of the advisory committee on immunization practices, United States, 2015–16 influenza season. Morb Mortal Wkly Rep. 2015;64:818–25.
16. Steele RW. Current status of vaccines and immune globulins for children with renal disease. Pediatr Nephrol. 1994;8:7–10.