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Association of influenza vaccination or influenza virus infection history with subsequent infection risk among children: The Japan Environment and Children's Study (JECS)

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ABSTRACT

We measured the association between history of influenza vaccination by age 2 years and influenza virus (IFV) infection at ages 3 and 4 years by relative risk reduction. We also examined the association between history of IFV infection by age 2 years and recurrent IFV infection at age 3 years. This study included 73,666 children from a large Japanese birth cohort. Among children vaccinated never, once or twice when aged under 2 years, 16.0%, 10.8% and 11.3%, respectively, had been infected with IFV by age 3 years, and 19.2%, 14.5% and 16.0%, respectively, by age 4 years. Compared with no history of influenza vaccination, vaccination at ages 1 and/or 2 years reduced the risk of IFV infection at age 3 by 30%–32% and at age 4 by 17%–24%. The relative risk of recurrent IFV infection at ages 3 and 4 years increased in proportion to the number of prior infections by age 2. One-season-prior influenza vaccination history reduced the IFV infection risk at age 3 years by 25%–42%. Influenza vaccination most effectively protected children at age 3 who lacked older sibling(s) and did not attend nursery school. One-season-prior IFV infection increased the relative risk of recurrent infection at age 3 years (1.72–3.33). In conclusion, influenza vaccination-induced protection may partly extend to the next season. Owing to the relative risk reduction by influenza vaccination and the increased relative risk of IFV infection from prior-season infection, annual influenza vaccination is recommended.

1. Introduction

According to the World Health Organization, an estimated 290,000–650,000 deaths annually are attributable to seasonal influenza-associated respiratory diseases (Lee et al., 2018). Seasonal influenza epidemics also increase the incidence of respiratory diseases and related hospitalisations in children (Yokomichi et al., 2019; Bennet et al., 2016). Vaccination is an effective infection countermeasure

Abbreviations: IFV, Influenza virus; JECS, Japan environment and Children's study; RR, Relative risk; 95% CI, 95% confidence interval.

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(Krammer and Palese, 2015; Lipsitch and Eyal, 2017). However, evidence indicates that despite its efficacy to some extent to adults, the effectiveness of influenza vaccination in children may be limited (Banzhoff and Stoddard, 2012; Osterholm et al., 2012).

Although the short-term effectiveness of influenza vaccine has been studied (Nichol, 2008; Treanor et al., 2012), limited research has been conducted on its long-term effectiveness against preventing infection in children (McLean et al., 2014; Beyer et al., 1999). Most studies have focused on preventing acute respiratory infection or hospitalisation, while the effectiveness of preventing influenza virus (IFV) infection is less understood. Influenza vaccination in the prior season has been reported to be of some effectiveness against the current epidemic virus strain (McLean et al., 2014). If previous influenza vaccination is confirmed as effective for preventing current-season IFV infection, this information might encourage caregivers and clinicians to receive the influenza vaccine annually. Therefore, the long-term effectiveness of influenza vaccination needs to be assessed.

Infection with IFV can also confer immunity and may effectively prevent subsequent infection in the next influenza season (Iwasaki and Pillai, 2014), and therefore some people may consider influenza vaccination unnecessary if their child was previously infected by IFV. Others may interpret this occurrence as indicative of being in an environment with a high chance of IFV infection (Vissing et al., 2018). Therefore, assessment is also needed on whether a history of previous IFV infection (s) is associated with a decreased or increased risk of subsequent IFV infection.

Here, we examined the long-term effectiveness of influenza vaccination and the recurrent IFV infection risk of prior IFV infection using data from a large birth cohort.

2. Methods

2.1. Enrolment

The Japan Environmental Children's Study (JECS) project is described in detail in a separate article (Kawamoto et al., 2014). Briefly, this cohort followed 100,300 children born during the years 2011–2014 in 15 regions across Japan. We used the JECS 'jecs-ta-20190930-qsn' and 'jecs-qa-20210401-qsn' datasets. The project aimed to collect evidence on the relationship between child health and the family environment to inform policymaking. Here, we analysed data from all enrolled children aged 1–4 years with a reported history of influenza vaccination or IFV infection during 2012–2019.

2.2. Vaccination and infection

The JECS Programme Office mailed questionnaires to caregivers when their children were 6 months, 1 year, 1.5 years, 2 years, 3 years and 4 years old. The JECS questionnaire included questions about the child's immunisation history at the ages of 1 and 2 years. This question was not present in the questionnaire administered at the age of 3 years. In the questionnaires, the caregiver was asked 'Has the child ever received an influenza vaccine?' In Japan, the vaccination history of infants and preschool children is recorded in the Maternal and Child Health Handbook provided by the local government (Yokomichi et al., 2020). In cases where it was difficult for caregivers to recall the child's influenza vaccination history, input was taken from the above-mentioned handbook records. The questionnaire also asked about history of IFV infection at the ages of 1, 1.5, 2, 3 and 4 years. The recorded IFV infection history was based on parental recall of paediatrician diagnoses.

The Japanese Society of Paediatrics recommends the influenza vaccination schedule for childcare providers and clinicians (Japan Pediatric Society, 2020). In Japan, influenza vaccination is voluntary and is not part of the routine childhood immunisation schedule. However, it is recommended that children aged 6 months–12 years receive two doses of influenza vaccine per season (October–December) (Japan Pediatric Society, 2020). Inactivated influenza vaccines are manufactured by Daiichi Sankyo Company, Limited; KM Biologics Company, Limited; Biken Company, Limited; and Denka Seiken Company, Limited. In Japan, the trivalent vaccine was manufactured until the 2015/16 season, when it was switched to the quadrivalent vaccine. Therefore, a subset of the children was considered to have received the quadrivalent vaccine.

2.3. Statistical analysis

Descriptive statistics were calculated for the numbers of children with a reported history of influenza vaccination. We calculated relative risks (RRs) and 95% confidence intervals (CIs) of IFV infection by number of reported influenza vaccinations until age 2 years. Relative risk was calculated as a simple division of risk by risk, and its 95% CI was calculated through logarithmic transformation (Morris and Gardner, 1988). From the RRs, we calculated the RR reductions (percentage for 1 minus RR) for IFV infection at ages 3 and 4 years. The primary outcome of this study was RR reduction for IFV infection at age 4 years by the number of vaccination(s) received by age 2 years. Influenza vaccination history was queried in the 1-year and 2-year questionnaires. Because older sibling(s) might import IFV from outside the home (Endo et al., 2019), and attending nursery school might increase the probability of IFV infection, we calculated the RR of IFV infection stratified by children who had older sibling(s) and children who went to nursery school at age 1 year. To compare the IFV infection risks at ages 3 and 4 years posed by previous IFV infection, we also calculated the RR of IFV infection stratified by previous IFV infection number.

We assessed the RR reduction at age 3 years from reported influenza vaccination at ages 1 and 2 years by calculating the RR of IFV infection in those with reported influenza vaccination history at age 1 year and/or 2 years as compared with a reported history of no influenza vaccination at the corresponding ages. We also calculated the RR of IFV infection in those with a history of IFV infection at age(s) 1 year and/or 2 years as compared with no history of IFV infection at either age. Missing values resulting from participant drop-out were not included in the main analyses. Because the missing data might bias the main results, we analysed data with multiple imputations 20 times. With the imputed data, we re-calculated the RR reduction by vaccination and RR by prior infection. All statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). All reported p-values were two-sided, and values of $p < 0.05$ were considered statistically significant.

2.4. Ethics approval

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions. The study was conducted in accordance with the ethical guidelines and regulations outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

3. Results

Out of the 100,300 children in the study cohort, 90,476 (90.2%) and 86,065 (85.8%) had a history of influenza vaccination at ages 1 year and 2 years, respectively, and 82,411 (82.2%) and 78,137 (77.9%) reported a history of IFV infection at ages 3 and 4 years, respectively. In total, 73,666 children had complete information on influenza vaccination at ages 1 year and 2 years and IFV infection at ages 3 and 4 years. Table 1 lists the numbers and percentages of children with reported influenza vaccination; 42% (30,668/73,666), 42% (30,798/73,666), and 17% (12,200/73,666) of 2-year-old children had reportedly received zero, one and two influenza vaccinations, respectively.

Table 1
Reported influenza vaccination history by age 2 years ($n = 73,666$).

Vaccination	Number (percentage)
Reported history of influenza vaccination at 1 year of age	13,264 (18%)
Reported history of influenza vaccination at 2 years of age	41,934 (57%)
History of no influenza vaccination by age 2 years	30,668 (42%)
History of one influenza vaccination by age 2 years	30,798 (42%)
History of two influenza vaccinations by age 2 years	12,200 (17%)

Table 2 reports the RR reduction for IFV infection at ages 3 and 4 years, stratified by the reported number of received influenza vaccinations. As compared with reportedly having received no influenza vaccination, having a reported history of one and two influenza vaccinations provided RR reductions of 32% (95% CI: 30%–35%; *p*-value for Fisher's exact test < 0.0001) and 30% (25%–33%; $p < 0.0001$), respectively, at age 3 years, and of 24% (21%–27%; $p < 0.0001$) and 17% (13%–20%; $p < 0.0001$), respectively, at age 4 years. Similar levels of RR reduction were observed for the subsets of children with older sibling(s) and of those who attended nursery school at age 1 year.

Table 3 shows RR of IFV infection at ages 3 and 4 years, stratified by the number of previous IFV infections. At both 3 and 4 years, the IFV infection risk increased as the number of previous IFV infections increased. This phenomenon was preserved in the subsets of children with older sibling(s) and of children who went to nursery school at age 1 year.

Table 4 presents the RR reduction in IFV infection at age 3 years by reported influenza vaccination history before age 3. Compared with a reported history of no influenza vaccination at either 1 or 2 years, the RR reduction in IFV infection at age 3 for reported influenza vaccination histories of none at 1 year but one at 2 years and for one each at ages 1 and 2 years were 33% (95% CI: 30%–35%; $p < 0.0001$) and 30% (25%–33%; $p < 0.0001$), respectively. However, the RR reduction for a reported influenza vaccination history of one at 1 year but none at 2 years was smaller (23%; 10%–35%; $p = 0.0008$). The greatest RR reduction in IFV infection (39%–55%) for the reported influenza vaccination histories was observed in the subset of children who did not have older sibling(s) and did not go to nursery school. In the subsets of children who had older sibling(s) and/or went to nursery school, a reported history of influenza vaccination at age 2 years yielded a RR reduction in IFV infection of 25%–35% at age 3.

Table 5 displays the RR of IFV infection at age 3 years according to the history of previous IFV infection(s). Compared with a history of no IFV infection by age 1 or 2 years, the RR for IFV infection at 3 years posed by IFV infection at 2 years was 2.52–2.61, which was greater than the RR for IFV infection of 1.32 posed by a history of IFV infection at 1 year but no history of IFV infection at 2 years. Similar phenomena were observed in the subsets of children who had older sibling(s) and/or went to nursery school at age 1 year.

Supplementary Table 1 lists the number of missing values for the explanatory and response variables of the main results. Supplementary Table 2 shows the RR reduction for IFV infection at ages 3 and 4 years, by the reported number of received influenza vaccinations, in the imputed data. Supplementary Table 3 shows the RR of IFV infection at ages 3 and 4 years, by the number of previous IFV infections, in the imputed data. The results in the imputed data were similar to those of the main results (Tables 2 and 3). Supplementary Table 4 presents the annual influenza vaccine strains and prevalent IFV strains (National

Table 2
Number of influenza vaccinations received at ages 1 or 2 years old, and the relative risk reduction in subsequent influenza virus (IFV) infection at ages 3 and 4 years.

Reported influenza vaccination history	IFV infection history at age 3 years	RR reduction, (95% CI)	IFV infection history at age 4 years	RR reduction, (95% CI)
All				
None	4893/33,668 (16.0%)	Reference	5879/30,668 (19.2%)	Reference
Once	3319/30,798 (10.8%)	32% (30%–35%)	4461/30,798 (14.5%)	24% (21%–27%)
Twice	1372/12,200 (11.3%)	30% (25%–33%)	1950/12,200 (16.0%)	17% (13%–20%)
Subset with an older sibling				
None	3258/17,598 (18.5%)	Reference	3650/17,598 (20.7%)	Reference
Once	2092/16,636 (12.6%)	32% (29%–35%)	2647/16,636 (15.9%)	23% (20%–27%)
Twice	912/6802 (13.4%)	28% (22%–32%)	1218/6802 (17.9%)	14% (8%–19%)
Subset attending nursery school				
None	3312/23,389 (14.2%)	Reference	4141/23,389 (17.7%)	Reference
Once	2079/22,204 (9.4%)	34% (30%–37%)	2904/22,204 (13.1%)	26% (23%–29%)
Twice	928/8998 (10.3%)	27% (22%–32%)	1356/8998 (15.1%)	15% (10%–20%)

RR, relative risk; CI, confidence interval.

Table 3
Influenza virus (IFV) infection history and relative risk of subsequent IFV infection.

IFV infection history	IFV infection at age 3 years	Relative risk (95% CI)	IFV infection at age 4 years	Relative risk (95% CI)
All				
None	6637/60,881 (10.9%)	Reference	7207/54,244 (13.3%)	Reference
Once	2058/9161 (22.5%)	2.06 (1.97–2.15)	3436/13,740 (25.0%)	1.88 (1.82–1.95)
Twice	673/2611 (25.9%)	2.36 (2.21–2.53)	1124/3996 (28.1%)	2.12 (2.01–2.23)
Three times	133/430 (30.9%)	2.84 (2.46–3.27)	346/970 (35.7%)	2.68 (2.46–2.93)
Four times	–	–	65/133 (48.9%)	3.68 (3.09–4.38)
Subset with an older sibling				
None	4157/32,251 (12.9%)	Reference	4092/28,094 (14.6%)	Reference
Once	443/6291 (22.9%)	1.78 (1.69–1.88)	2249/9005 (25.0%)	1.71 (1.64–1.79)
Twice	499/1841 (27.1%)	2.10 (1.94–2.28)	785/2785 (28.2%)	1.94 (1.81–2.07)
Three times	106/331 (32.0%)	2.48 (2.12–2.91)	266/724 (36.7%)	2.52 (2.28–2.79)
Four times	–	–	50/106 (47.2%)	3.24 (2.64–3.97)
Subset attending nursery school				
None	4594/46,616 (9.9%)	Reference	5237/42022 (12.5%)	Reference
Once	1206/5771 (20.9%)	2.12 (2.00–2.25)	2224/9159 (24.3%)	1.95 (1.86–2.04)
Twice	400/1588 (25.2%)	2.56 (2.34–2.79)	634/2394 (26.5%)	2.13 (1.98–2.28)
Three times	79/259 (30.5%)	3.10 (2.57–3.73)	204/580 (35.2%)	2.82 (2.52–3.16)
Four times	–	–	40/79 (50.6%)	4.06 (3.26–5.06)

CI, confidence interval.

Table 4
Relative risk reduction in IFV infection at age 3 years by reported history of influenza vaccination by age 1 or 2 years and older sibling(s) and/or nursery school attendance.

Reported influenza vaccination history	RR reduction of IFV infection, (95% CI)
All	
Vaccine (−) at 1 y and vaccine (−) at 2 y	Reference
Vaccine (+) at 1 y and vaccine (−) at 2 y	23% (10%–35%)
Vaccine (−) at 1 y and vaccine (+) at 2 y	33% (30%–35%)
Vaccine (+) at 1 y and vaccine (+) at 2 y	30% (25%–33%)
Sibling (−) and nursery school (−)	
Vaccine (−) at 1 y and vaccine (−) at 2 y	Reference
Vaccine (+) at 1 y and vaccine (−) at 2 y	55% (19%–75%)
Vaccine (−) at 1 y and vaccine (+) at 2 y	39% (31%–45%)
Vaccine (+) at 1 y and vaccine (+) at 2 y	42% (31%–51%)
Sibling (+) and nursery school (−)	
Vaccine (−) at 1 y and vaccine (−) at 2 y	Reference
Vaccine (+) at 1 y and vaccine (−) at 2 y	13% (−14%–34%)
Vaccine (−) at 1 y and vaccine (+) at 2 y	30% (23%–35%)
Vaccine (+) at 1 y and vaccine (+) at 2 y	33% (25%–40%)
Sibling (−) and nursery school (+)	
Vaccine (−) at 1 y and vaccine (−) at 2 y	Reference
Vaccine (+) at 1 y and vaccine (−) at 2 y	14% (−21%–39%)
Vaccine (−) at 1 y and vaccine (+) at 2 y	31% (25%–37%)
Vaccine (+) at 1 y and vaccine (+) at 2 y	30% (21%–38%)
Sibling (+) and nursery school (+)	
Vaccine (−) at 1 y and vaccine (−) at 2 y	Reference
Vaccine (+) at 1 y and vaccine (−) at 2 y	31% (10%–48%)
Vaccine (−) at 1 y and vaccine (+) at 2 y	35% (30%–39%)
Vaccine (+) at 1 y and vaccine (+) at 2 y	25% (19%–31%)

Vaccine (−), reported history of no influenza vaccination by the indicated age.
Vaccine (+), reported history of receiving an influenza vaccination by the indicated age.
Sibling (−), no older siblings.
Sibling (+), at least one older sibling.
Nursery school (−), no nursery school attendance at age 1 year.
Nursery school (+), nursery school attendance at age 1 year.
RR, relative risk; IFV, influenza virus; CI, confidence interval.

Table 5
IFV infection history at ages 1 and 2 years, and relative risk of subsequent IFV infection at age 3 years.

IFV infection history	RR of IFV infection at 3 y (95% CI)
All	
Infection (−) at 1 y and infection (−) at 2 y	Reference
Infection (+) at 1 y and infection (−) at 2 y	1.32 (1.21–1.44)
Infection (−) at 1 y and infection (+) at 2 y	2.61 (2.49–2.73)
Infection (+) at 1 y and infection (+) at 2 y	2.52 (2.26–2.82)
Sibling (−) and nursery school (−)	
Infection (−) at 1 y and infection (−) at 2 y	Reference
Infection (+) at 1 y and infection (−) at 2 y	1.22 (0.90–1.65)
Infection (−) at 1 y and infection (+) at 2 y	2.40 (2.11–2.73)
Infection (+) at 1 y and infection (+) at 2 y	2.51 (1.82–3.47)
Sibling (+) and nursery school (−)	
Infection (−) at 1 y and infection (−) at 2 y	Reference
Infection (+) at 1 y and infection (−) at 2 y	1.16 (0.99–1.35)
Infection (−) at 1 y and infection (+) at 2 y	1.93 (1.76–2.12)
Infection (+) at 1 y and infection (+) at 2 y	1.72 (1.41–2.11)
Sibling (−) and nursery school (+)	
Infection (−) at 1 y and infection (−) at 2 y	Reference
Infection (+) at 1 y and infection (−) at 2 y	1.10 (0.83–1.47)
Infection (−) at 1 y and infection (+) at 2 y	3.33 (3.00–3.70)
Infection (+) at 1 y and infection (+) at 2 y	2.74 (1.85–4.04)
Sibling (+) and nursery school (+)	
Infection (−) at 1 y and infection (−) at 2 y	Reference
Infection (+) at 1 y and infection (−) at 2 y	1.21 (1.07–1.38)
Infection (−) at 1 y and infection (+) at 2 y	2.41 (2.24–2.59)
Infection (+) at 1 y and infection (+) at 2 y	2.43 (2.08–2.84)

Infection (−), history of no IFV infection by the indicated age.
Infection (+), history of at least one IFV infection by the indicated age.
Sibling (−), no older siblings.
Sibling (+), at least one older sibling.
Nursery school (−), no nursery school attendance at age 1 year.
Nursery school (+), nursery school attendance at age 1 year.
RR, relative risk; IFV, influenza virus; CI, confidence interval.

Institute of Infectious Diseases, Japan, n.d). The vaccine strains sufficiently match the IFV strains that were prevalent during the corresponding season.

4. Discussion

The results suggest that a reported history of influenza vaccination before age 3 years reduced the risk of subsequent IFV infection by 30%–32% at 3 years of age and by 17%–24% at 4 years of age (Table 2). Stratified analyses of children who had older sibling(s) and those who attended nursery school at age 1 year support these results. The recurrent IFV infection risk increased in proportion to the number of prior IFV infections (Table 3). Children who did not have older sibling(s) or attend nursery school were the most protected by influenza vaccination (Table 4). Overall, the influenza vaccination effectiveness at age 3 years was higher when the influenza vaccine was administered at age 2 years than when the influenza vaccine was administered at 1 year. For children in any strata of IFV infection risk, a previous IFV infection experience suggests a high risk of IFV infection during the next influenza season (Table 5). Thus, these data suggest that if children were infected by IFV during the previous season, they would benefit from influenza vaccination in the current season.

Our results on the effectiveness of previous-season influenza vaccination are consistent with earlier reports. A combination of data from several cohorts indicates that influenza vaccination in the elderly population provides a 27% RR reduction in hospitalisation from pneumonia or influenza (Nichol et al., 2007). Another study suggested that prior-season influenza vaccination may be effective against the current influenza epidemic, but depends on the current IFV strain (Belongia et al., 2017). Other research found that prior influenza vaccination improved the influenza vaccine immunogenicity in children under 3 years of age (Ito et al., 2018).

Our data suggest that previous-season influenza vaccination tended to be more effective at preventing current-season IFV infection compared with two-season-prior influenza vaccination. This may be because influenza vaccine effectiveness in infants appears to be limited (Maeda et al., 2004; Maeda et al., 2002; Allison et al., 2006), and influenza vaccine immunogenicity increases with age in infants (Levy and Wynn, 2014). This assumption is supported by our previous study, which revealed increased influenza vaccine effectiveness with increasing age (Yokomichi et al., 2021). Therefore, children should be vaccinated against influenza annually from infancy.

Few studies have measured the effectiveness of influenza vaccination by risk strata. One previous study reported a 28% effectiveness of previous-season influenza vaccination in 3-year-olds who have an older sibling(s) and attend nursery school, whereas in children who neither have older sibling(s) nor attend nursery school, it was 33% (Yokomichi et al., 2021). Day-care and school may be ideal environments for being infected with influenza (Gaglani, 2014). A 2014 Japanese cohort study estimated that influenza vaccination effectiveness is 34% and 25% (not significantly different) among day-care-attending children aged 3 years and 4 years, respectively (Mori et al., 2014). Our data (27%–34% at age 3 and 15%–26% at age 4; Table 2) are in line with those values for long-term influenza vaccination effectiveness among nursery school children.

Having sibling(s) increases the risk of hospitalisation from influenza (Hardelid et al., 2017). Our stratification analysis revealed that influenza vaccination would be most effective in children who do not have older sibling(s) or attend nursery school (Table 4). This refutes the assumption of some caregivers that their child who is at low risk of IFV infection because the child lacks siblings and does not attend day-care does not need to receive an influenza vaccine. The reason for this surprising phenomenon is unknown. The present results support vaccinating children who are presumptively at low risk of IFV infection.

This study has several strengths. First, the number of participants in the birth cohort was large. Second, in most municipalities of Japan, the cost of medical care for preschool children by a consulting physician is less expensive than for adults. Therefore, because most children with influenza and a high fever would consult a physician, the detection bias for influenza should be small. Third, in a large population, the histories of influenza vaccination at 1–2 years of age and histories of IFV infection at 1–4 years of age were measured. Fourth, we measured the long-term effectiveness of influenza vaccination prior to the drop in rates of IFV infection and influenza vaccination due to the coronavirus disease 2019 (COVID-19) pandemic.

This study also has several limitations. First, we could not directly investigate the IFV infection and influenza vaccination histories of the participant families, who could have transmitted IFV to the study children. Second, the questionnaire for vaccination history given at age 2 years asked about the child's history of influenza vaccination but not the timing of the vaccination; therefore, a reported history of influenza vaccination at 2 years of age could refer to vaccination performed at any time before the child's second birthday (i.e. not just within the previous 1 year; the child could have been vaccinated before turning 1 year old). Third, although the Japan Paediatric Society recommends that children aged 6 months–12 years receive an influenza vaccine twice per season, whether the individual children were vaccinated once or twice per season is unknown (Japan Pediatric Society, 2020). Fourth, we could not investigate the history of receiving the vaccine at 3 years old. In other words, the effect of the latest vaccination prior to the determination of infection history at age 4 years was not considered for the RR reduction of infection at age 4 years. Fifth, recall bias, in which caregivers misreport the influenza vaccination and IFV infection histories of their children, may exist.

This study has important clinical implications. First, the analysis provides real-world data for caregivers and clinicians regarding the long-term effectiveness of influenza vaccines. Second, our data showing that previous-season influenza vaccination is more effective against current-season influenza compared with two-season-ago vaccination (Table 4) suggest that children with previous influenza vaccination should still receive an influenza vaccine in the current season to protect themselves. Third, children who were infected with influenza in the previous season should still receive influenza vaccination because our data indicate that they are at higher risk of reinfection compared with children who were not infected in the previous influenza season (Table 5). This finding is also supported by our previous study (Yokomichi et al., 2021), which showed that children who had been infected by IFV two seasons ago would also be protected by influenza vaccination in the prior season. Fourth, although influenza vaccination is already recommended for high-risk populations (Grohskopf et al., 2021; Committee on Infectious Diseases, 2021), some low-risk populations would also benefit from vaccination (Table 4). This is consistent with previous results demonstrating that the effectiveness of influenza vaccines in reducing hospitalisation is greater in low-risk seniors than in high-risk seniors (Nichol et al., 1998). Fifth, even if the antigenic distance between the influenza vaccine strains and the circulating IFV strains is large, children would benefit from receiving the presently used quadrivalent influenza vaccine because immunisation against several IFV strains may protect children for a long time.

5. Conclusion

Toddlers aged 3 years who had a reported history of previous-season influenza vaccination were 25%–42% less likely to be infected by IFV in the current influenza season. Furthermore, a history of more episodes of prior IFV infection increased the risk of IFV infection in the current season. The results provide support that children should receive the influenza vaccine every winter season.

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CRediT authorship contribution statement

Hiroshi Yokomichi: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Mie Mochizuki:** Conceptualization, Writing – original draft. **Sayaka Horiuchi:** Project administration, Writing – original draft. **Ryoji Shinohara:** Supervision, Project administration. **Reiji Kojima:** Writing – original draft. **Tadao Ooka:** Writing – original draft. **Yuka Akiyama:** Writing – original draft. **Kunio Miyake:** Writing – original draft. **Sanae Otawa:** Writing – original draft. **Zentaro Yamagata:** Supervision, Project administration.

Declaration of Competing Interest

The authors have no conflicts of interest.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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