



Negative impact of prior influenza vaccination on current influenza vaccination among people infected and not infected in prior season: A test-negative case-control study in Japan



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ABSTRACT

Background: Accumulating evidences indicate that repeated influenza vaccination has negative impact on the vaccine effectiveness (VE). However no published studies considered past influenza infection when assessing the VE of repeated vaccination.

Methods: Prospective surveillance was conducted from 2009 to 2012 at a community hospital on a small island in Japan. The study included all outpatients with an influenza-like illness (ILI) who attended the hospital, and a rapid diagnostic test (RDT) was used to diagnose influenza A/B infection. The VE of trivalent inactivated influenza vaccine (TIV) against medically attended influenza A (MA-fluA) was estimated using a test-negative case-control study design. The influence of TIV in the prior season on VE in the current season was investigated in the context of MA-fluA during the prior season.

Results: During the three influenza seasons, 5838 ILI episodes (4127 subjects) were analysed. Subjects who had an episode of MA-fluA in the prior season were at a significantly lower risk of MA-fluA in the current season (adjusted odds ratio: 0.38, 95% CI: 0.30–0.50). The overall adjusted VE was 28% (95% CI, 14–40). VE was substantially lower in subjects vaccinated in the prior season compared to those who had not been vaccinated in prior season (19%; 95% CI: 0–35 vs 46%; 95% CI: 26–60, test for interaction, P value <0.05). In subjects who did not have MA-fluA in the prior season showed the attenuation of VE due to repeated vaccination (13%; 95% CI: –7 to 30 vs 44%; 95% CI: 24–59, test for interaction, P < 0.05). However this effect was not detected in subjects who had contracted MA-fluA in the prior season.

Conclusions: Negative effects of repeated vaccination were significant among those without history of MA-fluA in the prior season.

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1. Introduction

Every year, influenza epidemic has an enormous public health impact worldwide. The World Health Organization (WHO) has estimated around 3,000,000–5,000,000 severe cases and 250,000–500,000 deaths due to influenza infection each year and recommends annual vaccination for patients with chronic underlying diseases, pregnant women, children aged 6 months to 5 years and elderly people [1]. Vaccination is and has been the main strat-

egy for the control and prevention of influenza epidemics now and for the past 60 years [1–3]. Vaccination is considered the most effective strategy for mitigating an influenza epidemic, superior to other strategies including antiviral prophylaxis and non-pharmaceutical approaches such as early case isolation and school closure [2]. Annual vaccination is necessary because there is a continual antigenic drift of the influenza virus and vaccine compositions need to be regularly changed. Consequently vaccine effectiveness (VE) varies from one season to the next, and VE evaluation has been conducted every year [4–6].

Recently accumulating evidences indicate that repeated influenza vaccination have a negative impact on the immune response and VE [7–11]. Several observational studies have found a reduc-

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tion in VE among people who received a vaccination during the prior season [12–16]. The causal mechanism remains unclear but a common explanation of this phenomenon is the ‘original antigenic sin’ hypothesis that prior exposure to a virus or vaccination can dampen current immune response to a second virus [17]. However, one recent study showed that an increased B-cell response was induced by influenza vaccine if subjects were primed by natural influenza infection [8]. Another plausible explanation is that people without prior vaccination are more likely to have contracted natural infection in the prior season and that this exposure may have induced residual effects on the current vaccination [18]. Therefore it is crucial to consider past natural influenza infection. However, to our knowledge, no previously published study has investigated VE of repeated vaccination, simultaneously addressing this issue. Thus, the purpose of this study was to elucidate the effect of the trivalent inactivated influenza vaccine (TIV) in the prior season on VE of TIV in the current season by considering various interactive factors, including natural infection in the prior season.

2. Methods

2.1. Study design

This was a population-based study conducted in a semi-closed community in a single hospital where influenza and influenza-like illnesses (ILIs) were actively recorded.

2.2. Study setting

Kamigoto is a rural town consisting of one main island and several small islands, off the western coast of Japan (Fig 1). The community is semi-closed due to limited transportation to the Japanese mainland. According to the resident registration, the total population of the island was 24,102 in December 2008, declining to 22,599 in December 2011. The population is rapidly ageing, with one-third of the population aged 66 years or more, and the proportion of children aged 0–14 years decreasing from 17% to 11.5% between 2008 and 2011. The island has a single hospital, Kamigoto Hospital and six clinics. The hospital has 186 beds and provides primary, secondary and tertiary care; it is the only health facility on the island that has a paediatrician.

In Japan, the Ministry of Health, Labour and Welfare recommends that all children younger than 13 years of age receive two doses of TIV each season and that all others receive one dose. The cost of TIV at the time of the study was around 3600 yen (about 30 USD) per dose. This cost is not covered by national health insurance, but is partially, or fully, subsidised by local government. The vaccination status of individual residents has been available electronically, apart from data regarding the monovalent inactivated influenza A (H1N1) 2009 vaccine (MIV), which were not provided via the health department of local government during the 2009–2010 influenza pandemic.

2.3. Data collection

For the current data analysis, we obtained information on all patients who visited Kamigoto Hospital with an ILI between December 2008 and April 2012. This was possible because Kamigoto Hospital has systematically registered all ILI cases since 2007. Information about previous episodes of Influenza A was collected from this database and an electronic medical chart in the hospital. A case was defined as an ILI if the patient showed a sudden onset of fever and at least one sign of coughing, a runny nose, sore throat, headache, myalgia, or fatigue. A commercial rapid diagnostic test

(RDT; Esplini Influenza A and B[®], Fujirebio Inc, Japan) was routinely used for all patients to diagnose influenza. In our previous study conducted in the 2011–12 season, the sensitivity and specificity of rapid diagnostic test for detecting influenza A and/or B were 78.6% (95% CI: 73.9–83) and 95.3% (95% CI: 93–97.7), respectively [19]. When a patient had multiple ILI episodes within the same season, we included all the episodes as a cluster. However, once a patient was enrolled as having an RDT-positive episode, all ILI episodes that occurred after the positive event were excluded. We treated multiple ILI episodes that occurred within seven days as a sole ILI episode. Sociodemographic and clinical information for the patients were collected from the hospital database. The presence of cancer, diabetes, pulmonary diseases, cardiovascular diseases and others were treated as chronic conditions. Vaccine status was defined as ‘vaccinated’ 14 days after vaccine administration.

2.4. Data analysis

A test-negative case-control study design was used to estimate the VE of current-season TIV compared to medically attended influenza A (MA-fluA). The cases were ILI episodes positive by RDT for influenza A, and controls were ILI episodes negative by RDT for both influenza A and B. We excluded episodes that were RDT-positive for influenza B. The characteristics of enrolled episodes were compared between cases and controls using Pearson’s chi-squared test or Fisher’s exact test for categorical variables and *t*-tests or ANOVA for numerical variables. Ages of patient were categorised into four groups; 0–5 years, 6–18 years, 19–65 years and ≥ 66 years. Types of health insurance were categorised into three groups; employee health insurance, national health insurance and other insurance types. This was done because insurance may influence healthcare-seeking behaviour, even though the influenza vaccine is not covered by any kind of insurance.

The VE against MA-fluA was calculated as $[1 - \text{odds ratio (OR)}] \times 100$. Logistic regression models were applied to calculate unadjusted and adjusted OR; 95% confidence intervals were adjusted for clustering of episodes within the same individual. In multivariable analyses, sex, age group, chronic condition, health insurance type, visiting season/year and the period of the season/year were considered to be potential confounders and included in the final model.

We investigated the impact of prior-season TIV on current-season TIV, taking into account each subject’s MA-fluA status for the prior season. The VE of current-season TIV was separately estimated by prior-season vaccination status, and the stratum-specific VE estimates were compared using the likelihood ratio test (test for interaction). These VE estimates were further stratified by prior-season MA-fluA status. In addition, we estimated VE for four combinations of prior and current vaccine status; unvaccinated in both seasons, vaccinated only in the prior season, vaccinated only in the current season and vaccinated in both seasons. Subjects unvaccinated in both seasons acted as the reference group. In order to evaluate the effect of the repeated vaccination, we compared the VE between subjects vaccinated only in the current season and in both seasons. To exclude the potential unmeasured impact of MIV on our VE estimates during 2009–10 season, we conducted a sensitivity analysis restricting the subjects to those who visited the hospital during 2010–11 and 2011–12 seasons only.

Data were managed using Microsoft Access, and statistical analyses were performed using Stata software (Stata Statistical Software Release 13; Stata Corp., College Station, Texas, USA). Values of $P < 0.05$ were considered significant.

This study was approved by the Institutional Review Boards of Kamigoto Hospital and the Institute of Tropical Medicine at Nagasaki University, Japan. Verbal informed consent was obtained by

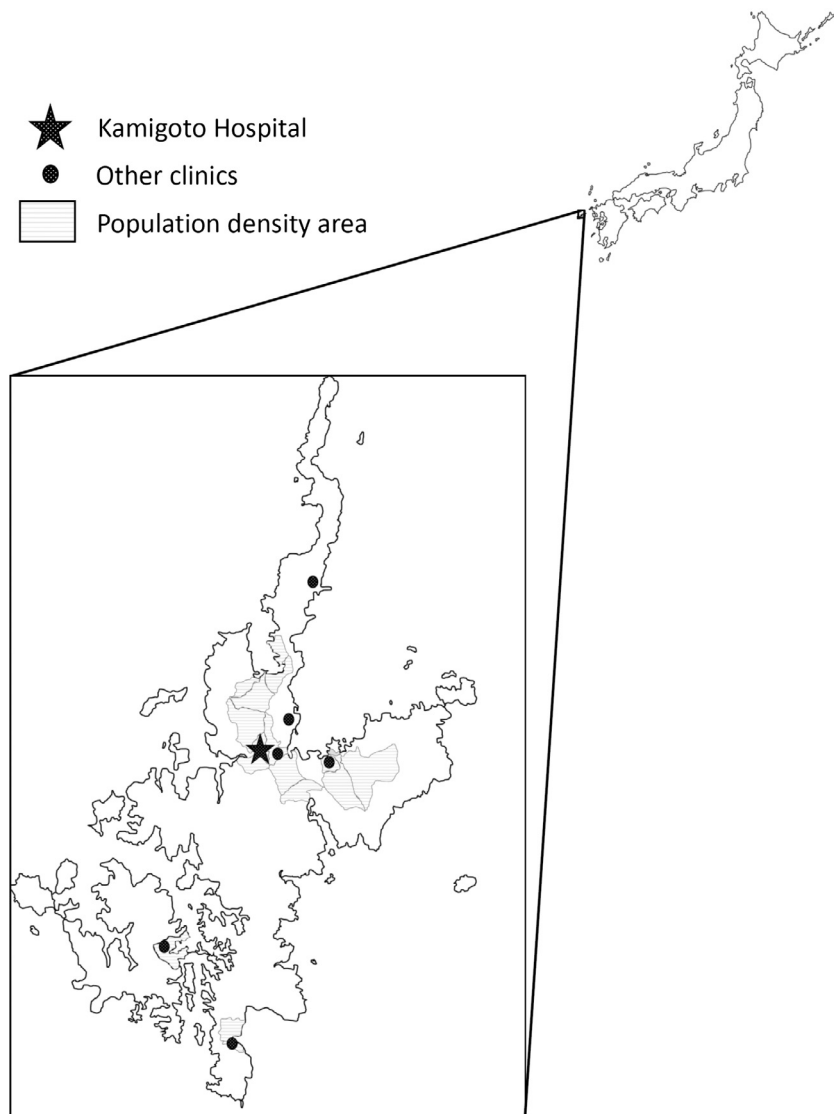


Fig. 1. Map of Kamigoto island and the locations of its health facilities.

attending physicians or nurse in all cases, information about the study was provided to interested parties by a researcher and poster presentations were available for public viewing at the fever clinic in Kamigoto Hospital. Both IRBs granted waivers for obtaining written informed consent from subjects because this study required no further investigation of subjects apart from the usual standard of care. Anonymised data were employed in the study.

3. Results

During three consecutive seasons, 7352 ILI episodes were observed at Kamigoto Hospital; 996 episodes due to the repeated visits within 7 days (320 episodes in 2009–2010 seasons, 202 episodes in 2010–2011 seasons and 474 episodes in 2011–2012 seasons) and 154 episodes due to the repeated visits after the RDT-positive episodes in the same season (30 episodes in 2009–2010 seasons, 27 episodes in 2010–2011 seasons and 97 episodes in 2011–2012) were subsequently excluded from our study. In total, 364 episodes of influenza B were also excluded from the analysis: 173 episodes in the 2010–2011 and 184 episodes in 2011–2012 seasons (Supplementary Fig. 1). A total of 5838 ILI episodes (4127 subjects), including 1896 RDT-positive MA-fluA and 3942

RDT negative episodes were included in our analysis. The characteristics of the episodes are shown in Table 1. During the 2009–2010 season, the pandemic influenza started in August 2009 and ended in February 2010, resulting in the highest number of RDT-positive MA-fluA episodes. During this season, 1502 ILI episodes (1400 subjects) and 838 ILI episodes were detected at the hospital before the seasonal vaccine campaign and after the campaign, respectively. During the overall study period, the highest number of RDT-positive MA-fluA episodes was found in school children aged between 6 and 18 years old, whereas it was lowest in those aged 66 years or more. Compared with RDT-negative ILI episodes, RDT-positive MA-fluA episodes occurred in younger people (mean age \pm SD, 26.9 \pm 28.5 vs. 18.7 \pm 17.8 years old, $P < 0.05$). Comorbidities were less frequent in subjects with RDT-positive MA-fluA ($P < 0.05$). Subjects who had an episode of MA-fluA in prior season were at a significantly lower risk of RDT-positive episodes in the current season (adjusted OR: 0.38, 95% CI: 0.30–0.50). This reduced risk was more apparent in 2010–2011 (adjusted OR: 0.11, 95% CI: 0.30–0.50) and in 2011–2012 (0.15, 95% CI: 0.04–0.62) than in 2009–2010 (0.63, 95% CI: 0.43–0.93) (Supplementary Table 1).

Characteristics of the four groups according to 2-year vaccination status are also shown in Table 1. The majority of subjects were

Table 1
Characteristics of enrolled influenza-like illness (ILI) episodes during the 2009–2010, 2010–2011 and 2011–2012 influenza seasons, by medically attended influenza A (MA-fluA) status and vaccination status.

	Total ILI episodes	RDT-positive MA-fluA episodes	RDT-negative ILI episodes	Vaccination status in the current and prior season			
				Neither season	Prior season only	Current season only	Both seasons
Overall	5838	1896 (32.5)	3942 (67.5)	1719 (29.5)	1373 (23.5)	512 (8.8)	2234 (38.3)
Season							
2009–10	2340	1189 (50.8)	1151 (49.2)	779 (33.3)	1071 (45.8)	74 (3.2)	416 (17.8)
2010–11	1483	210 (14.1)	1273 (85.8)	426 (28.7)	69 (4.7)	222 (15.0)	766 (51.7)
2011–12	2015	497 (24.7)	1518 (75.3)	514 (25.5)	233 (11.6)	216 (10.7)	1052 (52.2)
Male	2849	950 (33.4)	1899 (66.6)	834 (48.5)	702 (51.1)	257 (50.2)	1056 (47.3)
Age group ^a							
0–5 y	1408	261 (18.5)	1147 (81.5)	367 (26.1)	222 (15.8)	271 (19.3)	547 (38.9)
6–18 y	2312	1138 (49.2)	1174 (50.8)	458 (19.8)	804 (34.8)	101 (4.4)	949 (41.1)
19–65 y	1429	438 (30.7)	991 (69.3)	756 (52.9)	224 (15.7)	97 (6.8)	352 (24.6)
≥66 y	689	59 (8.6)	630 (91.4)	138 (20.0)	123 (17.9)	42 (6.1)	386 (56.0)
Comorbidity							
Any	1524	336 (22.1) ^a	1188 (77.9)	389 (25.5)	337 (22.1)	104 (6.8)	694 (45.5)
Cancer	118	9 (7.6) ^a	109 (92.4)	36 (30.5)	23 (19.5)	6 (5.1)	53 (44.9)
Diabetes	329	51 (15.5) ^a	278 (84.5)	95 (28.9)	61 (18.5)	21 (6.4)	152 (46.2)
Pulmonary	848	197 (23.2) ^a	651 (76.8)	206 (24.3)	203 (23.9)	50 (5.9)	389 (45.9)
Cardiovascular	638	112 (17.6) ^a	526 (82.4)	170 (26.7)	129 (20.2)	37 (5.8)	302 (47.3)
Others	651	74 (11.4) ^a	577 (88.6)	161 (24.7)	119 (18.3)	48 (7.4)	323 (49.6)
Health insurance							
Employee	4088	1425 (34.9) ^a	2663 (65.1)	1218 (30.0)	976 (23.9)	372 (9.1)	1522 (37.2)
National	1294	425 (32.8) ^a	869 (67.2)	403 (31.1)	324 (25.0)	107 (8.3)	460 (35.6)
Other	456	46 (10.1) ^a	410 (89.9)	98 (21.5)	73 (16.0)	33 (7.2)	252 (55.3)
MA-fluA in prior season	405	84 (20.7) ^a	321 (79.3)	90 (22.2)	84 (20.7)	37 (9.1)	194 (47.9)

Abbreviations: ILI: Influenza-Like Illness, RDT: Rapid Diagnostic Test, MA-fluA, Medically Attended Influenza A.

Numbers (%) of episodes are shown.

^a $P < 0.05$ by Pearson's chi-square test, comparing case (RDT-positive MA-fluA episode) and control (RDT negative ILI episode).

vaccinated in current season or prior season or both. About half of the enrolled subjects underwent repeated vaccinations in both current and prior seasons. A greater number of subjects with comorbidities and elderly people underwent a greater number of repeated vaccinations.

Results of the test-negative analysis investigating VE stratified according to vaccination status of the prior season are shown in Table 2; overall adjusted VE was 28% (95% CI, 14–40). Stratified analysis revealed significantly lower VE in subjects who had received TIV in the prior season than those who had not (19%; 95% CI: 0–35 vs 46%; 95% CI: 26–60, test for interaction, $P < 0.05$). This observation was clear for the 2011–2012 season (–15% vs 44%, $P < 0.05$) but not for the 2009–2010 season (35% vs 19%, $P = 0.457$). This trend was observed among subjects without prior MA-fluA episodes (13%; 95% CI: –7 to 30 vs 44%; 95% CI: 24–59, test for interaction, $P < 0.05$). However, among the subjects who had contracted MA-fluA in the prior season, unadjusted VE estimates suggested a high protection regardless of the prior vaccination status (91%; 95% CI: 83–96 vs 91%; 95% CI: 33–99, test for interaction, $p = 0.988$), though the adjusted VE for the non-vaccinated group did not reach a statistically significant level (81%; 95% CI: –32 to 97), probably due to a small sample size. Because the trend in the 2009–2010 season was different from the other two seasons, we conducted a sensitivity analysis for the MA-fluA stratified VE estimates that only include data from 2010 to 2011 and 2011 to 2012. The above observations did not change in the sensitivity analysis: the overall VE was lower among the prior-season vaccinated group than prior-season not-vaccinated group (–5%; 95% CI: –46 to 24 vs 49%; 95% CI: 24–66, test for interaction, P value < 0.01). This trend was also similar in the sensitivity analysis for the subjects without MA-fluA in the prior season (–7%; 95% CI: –49 to 23 vs 50%; 95% CI: 25–66, test for interaction, P value < 0.01). However the sensitivity analysis

could not be done for the subjects with MA-fluA in the prior season due to limited number of subjects.

We also estimated VE for four categories according to prior- and current-season TIV status using different reference subjects, namely those who had not been vaccinated in either season (Table 3). Highest VE was found in the group vaccinated only in the current season, significantly higher than that observed for the group vaccinated in both the prior and the current seasons (46%; 95% CI: 26–60 vs 2%; 95% CI: –17 to 17, $P < 0.01$). In analysis restricted to subjects who experienced episodes of MA-fluA in the prior season, unadjusted VEs for subjects vaccinated only in the current season and for those vaccinated in both seasons were both high, 91% (95% CI: 33–99) and 70% (95% CI: 40–85), respectively, though adjusted VE in the current season only was not significant, probably due to a small sample size. Conversely, the decrease in VE with repeated vaccination was obvious among subjects who had not suffered an MA-fluA episode during the prior season (44%; 95% CI: 24–59 vs –2%; –22 to 15, $p < 0.01$). Intriguingly vaccination in the prior season only showed a significant negative overall VE (adjusted VE –22%, 95% CI: –2 to –47). However, this association disappeared when we conducted a sensitivity analysis by restricting the subjects to those who visited the hospital during the 2010–2011 and 2011–2012 seasons only (adjusted VE –3%; 95% CI: –46 to 28).

4. Discussion

This is the first study demonstrating the negative effect of repeated vaccination in the context of influenza A infection during the prior season in analyses. We observed a profound protective effect of MA-fluA in the prior season against MA-fluA in the current season. Our stratified analysis revealed significantly lower overall VE of current vaccination in subjects who had vaccination in both

Table 2

Vaccine effectiveness (VE) of trivalent inactivated influenza vaccine (TIV) against medically attending influenza A (MA-fluA) and VE stratified by the prior-season vaccination status.

	Unadjusted VE (95% CI)			Adjusted ^b VE (95% CI)		
	Total	Stratified by prior-season vaccination		Total	Stratified by prior-season vaccination	
		Vaccinated	Not-vaccinated		Vaccinated	Not-vaccinated
Overall	52 (47–58)	62 (57–68)	69 (58–76)	28 ^a (14–40)	19 ^b (0–35)	46 ^{b,i} (26–60)
2009–2010 season	23 (6–37)	30 (12–44)	31 (–13 to 58)	32 ^c (3–52)	35 ^d (6–56)	19 ^d (–41 to 54)
2010–2011 season	49 (32–63)	38 (–18 to 68)	71 (49–84)	38 ^e (4–60)	16 (–73 to 60)	51 (9–74)
2011–2012 season	–15 (–43 to 8)	–12 (–57 to 19)	52 (23–71)	10 ^e (–20 to 32)	–15 ^f (–66 to 20)	44 ^f (6–67)
Restricted to subjects with MA-fluA in the prior season	86 (75–92)	91 (83–96)	91 (33–99)	75 ^g (56–86)	79 ^h (58–89)	81 ^h (–32 to 97)
Restricted to subjects without MA-fluA in the prior season	49 (42–55)	59 (52–65)	67 (56–75)	25 ^g (10–37)	13 ^h (–7 to 30)	44 ^{h, i} (24–59)

Abbreviations: VE: Vaccine Effectiveness, CI: Confidence Interval, MA-fluA: Medically Attended Influenza A.

^a Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season, vaccination status in the prior season and MA-fluA status in the prior season.

^b Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season, and MA-fluA status in the prior season.

^c Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season, vaccination status in the prior season and MA-fluA status in the prior season.

^d Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season, and MA-fluA status in the prior season.

^e Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season, vaccination status in the prior season, and MA-fluA status in the prior season.

^f Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season, and MA-fluA status in the prior season.

^g Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season, and vaccination status in the prior season.

^h Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season, and before or after the vaccination campaign during the 2009–2010 season.

ⁱ $P < 0.05$. Test for interaction. Comparison of adjusted VEs between vaccinated episodes and unvaccinated episodes in the prior season.

the current and prior seasons than those who had vaccination in the current season only. The trend was apparent among subjects without prior MA-fluA episodes: unadjusted VEs 13% (95% CI: 0–35) vs 46% (95% CI: 26–60); adjusted VEs 13% (95% CI: –7 to 30) vs 44% (95% CI: 24–59) (test for interaction, $P < 0.05$). However, this was not observed among subjects who had contracted MA-fluA in the prior season: adjusted VEs 79% (95% CI: 58–89) vs 81% (–32 to 97) (test for interaction, $P = 0.91$).

The negative effects of repeated vaccination have recently been reported in several published papers [7–16]. Ohmit et al. reported the unexpected findings of lower VE with repeated vaccination in a household cohort study during the 2010–2011 season which followed 1442 subjects and found 97 influenza A cases [16]. Another study assessed these effects using a different reference group, those not vaccinated in either the current or prior season [13]. However, confidence intervals in these two studies were wide due to the limited number of positive cases. In the 2011–2012 influenza season, the evidence of lower VE when analysis was restricted to type A(H3N2) by using test-negative design [15]. Furthermore, a reduced VE and attenuated immunologic response due to repeated vaccination were found in the 2012–2013 season when the A(H3N2) virus circulated in the house cohort study [20]. In contrast, negative effects were not observed in the 2013–2014 season when the 2009 pandemic influenza A(H1N1) virus predominated [21]. The authors of this report hypothesised that this phenomenon was more likely to occur when serotype H3N2 was predominant because antigenic drift is more common in serotype H3N2 viruses than in H1N1 pdm09 viruses. During our study period of three consecutive seasons, the proportion of serotype A (H3N2) among influenza A viruses was 0% in 2009–2010, 37.9%

in 2010–2011 and 99.7% in 2011–2012, according to surveillance of the National Institute of Infectious Diseases in Japan (Supplementary Table 4) [22]. Our results were consistent with previous reports because the negative effects of repeated vaccine were more obvious when the serotype H3N2 virus was more predominant. Our study provides further compelling evidence as it succeeded to demonstrate the statistical significance. Furthermore our study showed the effect of past exposure to the influenza A infection, which was suspected but not investigated [18].

The main mechanism for this phenomenon has been thought to be due to residual effects of prior vaccination on the current season's vaccination. One possible theory for this is the 'original antigenic sin' hypothesis, which proposes that prior exposure to a virus or vaccination can dampen current immune response [17]. However, this hypothesis was not supported by our finding that past exposure to influenza A infection did not attenuate VE in the current season. Recently published papers of serology analysis showed natural influenza virus infection elicited distinct patterns of B-cell activation and priming compared with inactivated influenza vaccination [8,9].

Our findings showed vaccination in the prior season only appeared 'harmful' with reference to vaccination in neither season. Inconsistent findings have been reported for the residual effect of prior-season vaccine: some studies confirmed its protective effect on current-season infection [14,4,23], while others failed to demonstrate it [15,16]. Although the VE for overall season was statistically significant negative VE in the group of "prior season only", the VE in 2010–2011 and 2011–2012 season was not significant. This negative VE result in 2009–2010 was possibly caused by the vaccine in 2008–2009 [24]. In our study, the 'harmful' effect was

Table 3
Vaccine effectiveness (VE) of trivalent inactivated influenza vaccine (TIV) during the 2009–2010, 2010–2011 and 2011–2012 influenza seasons according to vaccination status in the current and prior seasons.

Vaccination status	Total	MA-fluA, number (%)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)
Overall^a				
Neither season	1719	563 (32.8)	Ref	Ref
Prior season only	1373	673 (49.0)	−97 (−70 to −129)	−22 (−2 to −47)
Current season only	512	68 (13.3)	69 (58–76)	46 (26–60)
Both seasons	2234	592 (26.5)	26 (15–36)	2 (−17 to 17)
Restricted to the 2009–2010 season^b				
Neither season	779	366 (47.0)	Ref	Ref
Prior season only	1071	599 (50.4)	−43 (−73 to −19)	−23 (−58 to 3)
Current season only	74	28 (37.8)	31 (−13 to 58)	19 (−41 to 54)
Both seasons	416	196 (47.1)	−1 (−28 to 2)	20 (−12 to 43)
Restricted to the 2010–2011 season^c				
Neither season	426	86 (20.2)	Ref	Ref
Prior season only	69	13 (18.8)	8 (−76 to 52)	−7 (−126 to 49)
Current season only	222	15 (6.8)	71 (49–84)	51 (9–74)
Both seasons	766	96 (12.5)	43 (22–59)	10 (−30–38)
Restricted to the 2011–2012 season^c				
Neither season	514	111 (21.6)	Ref	Ref
Prior season only	233	61 (26.2)	−29 (−86 to 11)	−4 (−56 to 31)
Current season only	216	25 (11.6)	52 (23–71)	44 (6–67)
Both seasons	1052	300 (28.5)	−45 (−87 to −12)	−20 (−60 to 10)
Restricted to subjects with MA-fluA in the prior season^d				
Neither season	90	22 (24.4)	Ref	Ref
Prior season only	84	44 (52.4)	−240 (−79 to −547)	−138 (−360 to −23)
Current season only	37	1 (2.7)	91 (33–99)	81 (−32 to 97)
Both seasons	194	17 (8.8)	70 (40–85)	50 (2–74)
Restricted to subjects without MA-fluA in the prior season^d				
Neither season	1629	541 (33.1)	Ref	Ref
Prior season only	1289	629 (34.7)	−92 (−124 to −64)	−17 (−42 to 3)
Current season only	475	67 (3.7)	67 (56–75)	44 (24–59)
Both seasons	2040	575 (31.7)	21 (8–32)	−2 (−22 to 15)

VE was calculated as $100 \times (1 - \text{odds ratio})$.

Abbreviations: VE: Vaccine Effectiveness, CI: Confidence Interval, MA-fluA: Medically Attended influenza A, Ref: Reference.

^a Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season and MA-fluA status in the prior season.

^b Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season, before or after the vaccination campaign during the 2009–2010 season and MA-fluA status in the prior season.

^c Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting period of the season and MA-fluA status in the prior season.

^d Adjusted for sex, age group, presence of any comorbidity, type of health insurance, visiting season, visiting period of the season and before or after the vaccination campaign during the 2009–2010 season.

also observed for the subjects who experienced MA-fluA in the prior season. People who had been vaccinated with TIV but infected with influenza A in the prior season may have been more likely to be immune-compromised. However, the sample size of subjects with MA-fluA in the prior season was very small ($n = 405$) thus it requires special caution to draw any conclusion. Further studies are needed to understand the underlying mechanisms

In our study, overall estimate of VE for TIV was low relative to that previously published papers [4,15,25–27]. One contributing factor may be the negative effect of repeated vaccination since the rate of annual vaccine coverage was high in this community due to active vaccine campaign. Another possible reason is that during the 2009–2010 pandemic influenza season, the VE of TIV was low, because components of the seasonal TIV did not include the 2009 pandemic strain [24,28]. In addition, during our study period which encompassed the 2011–2012 season, other studies from Europe and USA have also reported low VE due to an antigenic shift for this season [16,27,29]. Furthermore the test-negative case control design may also be a reason [30,31].

There are several limitations. First, our study relied on RDTs as diagnostic tools, which are not as sensitive and specific as RT-PCR. However, to reduce false-negative cases, patients were routinely tested again on the following day if they visited the fever clinic within a 24 h onset period and the RDT was negative. The use of

RDT may result in underestimation of VE due to false negative results [31], and this may be another reason for relatively low VE in our study. However, this VE underestimation does not negate our findings about associations between TIV in the current season and TIV or MA-fluA in the prior season. Second, we did not determine the subtypes of influenza A. We believe that subtype-specific analysis could have disclosed more significant effects of repeated vaccination [15]. Third, our study did not collect vaccination history of MIV for influenza A (H1N1) 2009pdm and this could be potentially a significant confounder. However, it was assumed that most people who received TIV also received MIV because the total number of people vaccinated with MIV and seasonal TIV in the 2009–2010 influenza season were similar; 13,240 and 12,989 subjects (vaccine cover for the island, 56.1% and 55.0%, respectively). The vaccine campaign for MIV started just one week subsequent to the TIV campaign. Forth, we need to retain overall pooled data for estimating VEs because the sample size is limited. Therefore we demonstrated the results did not change in a sensitivity analysis. Lastly, our study investigated the effect of symptomatic influenza infection, which sought medical attention during the prior season. However, a recently published paper of five successive cohorts, using pre-season and post-season serology and weekly illness reporting, revealed a substantial rate of subclinical infection and most symptomatic cases were self-managing without medical consultation [32]. However, in our study, roughly one-half of the

subjects were schoolchildren aged between 6 and 18 years old, and symptomatic children were likely taken for medical consultation even with mild symptoms because this practice was encouraged by school teachers on the island for the purpose of controlling influenza epidemics in schools.

5. Conclusions

In conclusion, the current study conducted in a unique semi-closed community has provided further evidence that VE was reduced if repeatedly vaccinated and revealed that this attenuating effect was influenced by prior symptomatic infection with influenza A. Such attenuated VE was clearly observed in people who did not have MA-fluA during the prior season but not observed in people who suffered from MA-fluA during the prior season. In the latter group, high VEs were observed regardless of vaccine status in the prior season. However due to the small sample size in this group, further studies are needed to clarify the effects of repeated vaccination in this group.

Conflict of interest

None.

Author contributions

Conceived and designed the experiments: NS KK MS KA. Data collection: NS KK KT YT. Analysed the data: NS KK MS KA. Wrote the paper: NS MS KM KA.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2016.11.024>. These data include Google maps of the most important areas described in this article.

References

- [1] WHO. Influenza (seasonal): fact sheet number 211; 2014. <http://www.who.int/mediacentre/factsheets/fs211/en/> [accessed on 28 April 2016].
- [2] Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and control of influenza with vaccines: recommendations of the advisory committee on immunization practices, United States, 2015–16 influenza season. *MMWR Morb Mortal Wkly Rep* 2015;64(30):818–25.
- [3] Davenport FM. Current knowledge of influenza vaccine. *JAMA* 1962;182(1):11–3.
- [4] Skowronski DM, Janjua NZ, De Serres G, Winter AL, Dickinson JA, Gardy JL, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010–2011 season. *Clin Infect Dis* 2012;55(3):332–42.
- [5] Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. *Vaccine* 2007;25(39–40):6852–62.
- [6] Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12(1):36–44.
- [7] Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. *Proc Natl Acad Sci USA* 1999;96(24):14001–6.
- [8] He XS, Holmes TH, Sanyal M, Albrecht RA, Garcia-Sastre A, Dekker CL, et al. Distinct patterns of B-cell activation and priming by natural influenza virus infection versus inactivated influenza vaccination. *J Infect Dis* 2015;211(7):1051–9.
- [9] Kim JH, Liepkalns J, Reber AJ, Lu X, Music N, Jacob J, et al. Prior infection with influenza virus but not vaccination leaves a long-term immunological imprint that intensifies the protective efficacy of antigenically drifted vaccine strains. *Vaccine* 2016;34(4):495–502.
- [10] Castilla J, Navascues A, Fernandez-Alonso M, Reina G, Pozo F, Casado I, et al. Effectiveness of subunit influenza vaccination in the 2014–2015 season and residual effect of split vaccination in previous seasons. *Vaccine* 2016;34(11):1350–7.
- [11] Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Winter AL, Dickinson JA, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–2015 season. *Clin Infect Dis* 2016;63(1):21–32.
- [12] Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine* 1997;15(10):1114–22.
- [13] Sullivan SG, Kelly H. Stratified estimates of influenza vaccine effectiveness by prior vaccination: caution required. *Clin Infect Dis* 2013;57(3):474–6.
- [14] McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. *Clin Infect Dis* 2014;59(10):1375–85.
- [15] Ohmit SE, Thompson MG, Petrie JG, Thaker SN, Jackson ML, Belongia EA, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. *Clin Infect Dis* 2014;58(3):319–27.
- [16] Ohmit SE, Petrie JG, Malosh RE, Cowling BJ, Thompson MG, Shay DK, et al. Influenza vaccine effectiveness in the community and the household. *Clin Infect Dis* 2013;56(10):1363–9.
- [17] Kim JH, Skountzou I, Compans R, Jacob J. Original antigenic sin responses to influenza viruses. *J Immunol* 2009;183(5):3294–301.
- [18] Neuzil KM. How can we solve the enigma of influenza vaccine-induced protection? *J Infect Dis* 2015;211(10):1517–8.
- [19] Suzuki M, Minh Le N, Yoshimine H, Inoue K, Yoshida LM, Morimoto K, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011–2012 season. *PLoS ONE* 2014;9(2):e88813.
- [20] Ohmit SE, Petrie JG, Malosh RE, Fry AM, Thompson MG, Monto AS. Influenza vaccine effectiveness in households with children during the 2012–2013 season: assessments of prior vaccination and serologic susceptibility. *J Infect Dis* 2015;211(10):1519–28.
- [21] Ohmit SE, Petrie JG, Malosh RE, Johnson E, Truscon R, Aaron B, et al. Substantial influenza vaccine effectiveness in households with children during the 2013–2014 influenza season, when 2009 Pandemic influenza A(H1N1) virus predominated. *J Infect Dis* 2016;213(8):1229–36.
- [22] National Institute of Infectious Disease in Japan. Flash report of influenza virus in Japan. <http://www.nih.go.jp/niid/en/iasr-inf-e.html> [accessed on 28 April 2016].
- [23] Thompson MG, Li D, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. *Clin Infect Dis* 2014;58(4):449–57.
- [24] Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, Hottes TS, et al. Association between the 2008–09 seasonal influenza vaccine and pandemic H1N1 illness during spring-summer 2009: four observational studies from Canada. *PLoS Med* 2010;7(4):e1000258.
- [25] Valenciano M, Kissling E, Cohen JM, Oroszi B, Barret AS, Rizzo C, et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009–2010: results of influenza monitoring vaccine effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* 2011;8(1):e1000388.
- [26] Kissling E, Valenciano M, Cohen JM, Oroszi B, Barret A, Rizzo C, et al. I-move multi-centre case control study 2010–11: overall and stratified estimates of influenza vaccine effectiveness in Europe. *PLoS ONE* 2011;6(11).
- [27] Kissling E, Valenciano M, Larrauri A, Oroszi B, Cohen JM, Nunes B, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. *Euro Surveill* 2013;18(5).
- [28] Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009;361(20):1945–52.
- [29] Kissling E, Valenciano M, Buchholz U, Larrauri A, Cohen JM, Nunes B, et al. Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case-control study, influenza season 2012/13. *Euro Surveill* 2014;19(6):20701.
- [30] Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol* 2007;36(3):623–31.
- [31] Suzuki M, Yoshimine H, Harada Y, Tsuchiya N, Shimada I, Ariyoshi K, et al. Estimating the influenza vaccine effectiveness against medically attended influenza in clinical settings: a hospital-based case-control study with a rapid diagnostic test in Japan. *PLoS ONE* 2013;8(1):e52103.
- [32] Hayward AC, Fragaszy EB, Bermingham A, Wang L, Copas A, Edmunds WJ, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir Med* 2014;2(6):445–54.