Table 4 Reasons for having influenza vaccination(%)

Choices	Male						Female					
	Total	20-29	30-39	40-49	50-59	60-69	Total	20-29	30-39	40-49	50-59	60-69
	(n = 380)	(n = 54)	(n = 80)	(n = 79)	(n = 68)	(n = 99)	(n = 431)	(n = 68)	(n = 93)	(n = 75)	(n = 85)	(n = 110)
Wanted to avoid becoming infected with influenza virus.	84.0	83.8	87.8	88.5	84.6	77.1	82.6	84.0	84.2	84.5	80.3	80.9
	(80.3-87.7)	(74.0-93.6)	(80.6-95.0)	(81.5-95.5)	(76.0-93.2)	(68.8-85.4)	(79.0-86.2)	(75.3-92.7)	(76.8-91.6)	(76.3-92.7)	(71.8-88.8)	(73.6-88.2)
Even if infected with influenza, wanted to prevent the symptoms from becoming serious.	60.7	52.2	61.3	66.5	62.3	58.9	66.4	40.0	71.1	73.2	72.4	69.5
	(55.8-65.6)	(38.9-65.5)	(50.6-72.0)	(56.1-76.9)	(50.8-73.8)	(49.2-68.6)	(61.9-70.9)	(28.4-51.6)	(61.9-80.3)	(63.2-83.2)	(62.9-81.9)	(60.9-78.1)
Living with family members at high risk of influenza becoming serious	18.4	5.8	33.7	27.3	15.1	7.8	31.5	21.1	52.8	38.3	25.2	20.3
	(14.5-22.3)	(0.0-12.0)	(23.3-44.1)	(17.5-37.1)	(6.6-23.6)	(2.5-13.1)	(27.1-35.9)	(11.4-30.8)	(42.7-62.9)	(27.3-49.3)	(16.0-34.4)	(12.8-27.8)
Received financial assistance for vaccination.	18.6	3.6	22.3	27.9	15.9	18.3	21.0	13.3	21.5	23.4	22.3	22.7
	(14.7-22.5)	(0.0-8.6)	(13.2-31.4)	(18.0-37.8)	(7.2-24.6)	(10.7-25.9)	(17.2-24.8)	(5.2-21.4)	(13.2-29.8)	(13.8-33.0)	(13.5-31.1)	(14.9-30.5)
At high risk of becoming infected with influenza.	13.1	16.1	19.0	15.2	7.7	8.6	12.6	13.8	13.2	8.9	14.6	12.2
	(8.3-14.7)	(6.3-25.9)	(10.4-27.6)	(7.3-23.1)	(1.4-14.0)	(3.1-14.1)	(9.5-15.7)	(5.6-22.0)	(6.3-20.1)	(2.5-15.3)	(7.1-22.1)	(6.1-18.3)
Employer ordered the vaccination	13.9	16.9	16.9	16.6	13.7	7.8	11.1	22.3	16.2	9.5	9.8	2.0
	(10.4-17.4)	(6.9-26.9)	(8.7-25.1)	(8.4-24.8)	(5.5-21.9)	(2.5-13.1)	(8.1-14.1)	(12.4-32.2)	(8.7-23.7)	(2.9-16.1)	(3.5-16.1)	(0.0-4.6)
At high risk of influenza symptoms becoming serious if infected.	11.5	7.6	11.1	10.4	10.5	15.7	11.2	6.8	6.4	5.7	15.7	18.0
	(8.3-14.7)	(0.5-14.7)	(4.2-18.0)	(3.7-17.1)	(3.2-17.8)	(8.5-22.9)	(8.2-14.2)	(0.8-12.8)	(1.4-11.4)	(0.5-10.9)	(8.0-23.4)	(10.8-25.2)
Family, friends, and acquaintances recommended it.	8.9	20.4	5.0	9.6	5.6	7.4	11.4	16.5	8.0	4.9	7.4	18.8
	(6.0-11.8)	(9.7-31.1)	(0.2-9.8)	(3.1-16.1)	(0.1-11.1)	(2.2-12.6)	(8.4-14.4)	(7.7-25.3)	(2.5-13.5)	(0.0-9.8)	(1.8-13.0)	(11.5-26.1)
Family doctor recommended it.	7.9	3.3	5.7	2.8	6.2	17.6	6.8	1.4	2.0	3.0	7.3	16.5
	(5.2-10.6)	(0.0-8.1)	(0.6-10.8)	(0.0-6.4)	(0.5-11.9)	(10.1-25.1)	(4.4-9.2)	(0.0-4.2)	(0.0-4.8)	(0.0-6.9)	(1.8-12.8)	(9.6-23.4)

Table 5 Reasons for not having influenza vaccination (%)

Choices	Male						Female					
	Total	20-29	30-39	40-49	50-59	60-69	Total	20-29	30-39	40-49	50-59	60-69
	(n = 1143)	(n = 197)	(n = 242)	(n = 231)	(n = 226)	(n = 247)	(n = 1113)	(n = 174)	(n = 231)	(n = 245)	(n = 213)	(n = 250)
No time to visit a medical institution.	32.0	42.8	33.7	36.6	32.3	17.3	22.4	33.9	23.5	25.9	21.0	11.1
	(29.3-34.7)	(35.9-49.7)	(27.7-39.7)	(30.4-42.8)	(26.2-38.4)	(12.6-22.0)	(20.0-24.8)	(26.9-40.9)	(18.0-29.0)	(20.4-31.4)	(15.5-26.5)	(7.2-15.0)
Believed oneself unlikely to be infected with influenza	25.1	26.1	15.3	19.5	25.1	39.2	22.7	24.8	22.4	19.8	19.3	27.1
	(22.6-27.6)	(20.0-32.2)	(10.8-19.8)	(14.4-24.6)	(19.4-30.8)	(33.1-45.3)	(20.2-25.2)	(18.4-31.2)	(17.0-27.8)	(14.8-24.8)	(14.0-24.6)	(21.6-32.6)
Could not afford vaccination.	20.1	22.7	19.2	26.7	20.2	12.4	23.8	28.4	35.2	28.6	18.2	10.4
	(17.8-22.4)	(16.9-28.5)	(14.2-24.2)	(21.0-32.4)	(15.0-25.4)	(8.3-16.5)	(21.3-26.3)	(21.7-35.1)	(29.0-41.4)	(22.9-34.3)	(13.0-23.4)	(6.6-14.2)
Lack of confidence that influenza vaccinations are effective	19.0	7.5	20.0	21.4	18.9	24.9	22.2	10.5	20.4	23.3	22.0	31.0
	(16.7-21.3)	(3.8-11.2)	(15.0-25.0)	(16.1-26.7)	(13.8-24.0)	(19.5-30.3)	(19.8-24.6)	(5.9-15.1)	(15.2-25.6)	(18.0-28.6)	(16.4-27.6)	(25.3-36.7)
Believed that disease would not likely become severe even if infected with influenza	19.3	15.2	13.6	17.0	19.0	30.6	17.5	14.3	14.4	17.0	22.0	19.4
	(17.0-21.6)	(10.2-20.2)	(9.3-17.9)	(12.2-21.8)	(13.9-24.1)	(24.9-36.3)	(15.3-19.7)	(9.1-19.5)	(9.9-18.9)	(12.3-21.7)	(16.4-27.6)	(14.5-24.3)
Concerned about adverse reactions that might occur with vaccinations	12.3	10.1	11.6	12.3	11.6	15.6	18.0	8.7	11.9	15.5	22.7	28.5
	(10.4-14.2)	(5.9-14.3)	(7.6-15.6)	(8.1-16.5)	(7.4-15.8)	(11.1-20.1)	(15.7-20.3)	(4.5-12.9)	(7.7-16.1)	(11.0-20.0)	(17.1-28.3)	(22.9-34.1)
Dislike of injections	13.9	13.5	16.3	15.9	10.7	12.8	14.1	19.2	12.9	13.2	11.1	15.1
	(11.9-15.9)	(8.7-18.3)	(11.6-21.0)	(11.2-20.6)	(6.7-14.7)	(8.6-17.0)	(12.1-16.1)	(13.3-25.1)	(8.6-17.2)	(9.0-17.4)	(6.9-15.3)	(10.7-19.5)
Lack of knowledge about where to be vaccinated	6.1	9.1	6.5	3.3	5.6	6.6	3.4	8.0	5.2	1.8	1.0	2.1
	(4.7-7.5)	(5.1-13.1)	(3.4-9.6)	(1.0-5.6)	(2.6-8.6)	(3.5-9.7)	(2.3-4.5)	(4.0-12.0)	(2.3-8.1)	(0.1-3.5)	(0.0-2.3)	(0.3-3.9)
Prior experience of an adverse reaction after being vaccinated for influenza or another disease	2.1	1.4	2.6	1.7	3.1	1.7	3.6	2.0	3.2	5.1	3.5	3.9
	(1.3-2.9)	(0.0-3.0)	(0.6-4.6)	(0.0-3.4)	(0.8-5.4)	(0.1-3.3)	(2.5-4.7)	(0.0-4.1)	(0.9-5.5)	(2.3-7.9)	(1.0-6.0)	(1.5-6.3)

vaccine [22]. There appear to be various misconceptions that stop people from perceiving vaccination as an important measure and one that deserves priority over other matters in their daily lives. There have been some measures that can ensure access to vaccination such as providing vaccination in pharmacies [26], and an incentive for vaccination, an intensified advertising campaign, and offering a choice of influenza vaccines can improve vaccination rates in the workplace [27]. Among men aged 60–69 years, the main reasons for not being vaccinated were the belief that they would not be infected with the influenza virus and that the disease would not become severe[28]. In Japan, influenza vaccination is recommended for people 65 years of age or older, and some local governments are providing financial support for vaccination [29]. Although men aged 60–69 may believe that they will not be infected or become seriously ill with influenza based on their experience, they should be given accurate information about the risk of infection, which increases with age.

The reasons for not receiving influenza vaccination varied more widely according to age among women than among men. The most frequent reason for not being vaccinated was lack of time to visit a medical institution in women aged 20–29, not being able to afford vaccination in those aged 30-49[30], concerns about adverse reactions in those aged 50–59, and doubts about vaccine efficacy in those aged 60–69. The avoidance of influenza vaccination among women aged 50–69 may be attributable to unfavorable views related to changes in influenza vaccination policy as a result of severe side effects and lawsuit judgments for compensation at the time their children were vaccinated [31]. If these women retain negative impressions of influenza vaccination after reaching the age of 65 when vaccination is recommended, it may be difficult to increase the influenza vaccination rate in this age group.

This study was limited because all study participants were internet users, thus its generalizability to the wider population in Japan may be restricted. It is possible that there are differences in educational status and income between internet users and non-users. In particular, internet users aged 60 or older may be better at assimilating information than are the general population. Another limitation is that because each individual chose multiple choices for questionnaire responses, and choices were not independent, we were not able to apply chi-square analysis or other statistical analysis to determine the differences according to sex and age.

Conclusions

This study suggests that the reasons for not accepting influenza vaccination vary according to sex and age in the Japanese working age population. We recommend using different education and intervention approaches according to sex and age to increase awareness of influenza vaccination among unvaccinated participants.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KW conceived and implemented the study. TI and KW contributed equally to writing and revising the manuscript as the first author. All authors read and approved the final manuscript.

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References

1. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M: **The Japanese experience with vaccinating schoolchildren against influenza.** *N Engl J Med* 2001, 344(12):889–896.
2. Practices ACoI: **Recommended adult immunization schedule: United States, 2012 (1).** *Ann Intern Med* 2012, 156(3):211–217.
3. Nichol KL: **Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza.** *Arch Intern Med* 2001, 161(5):749–759.
4. Bridges CB, Thompson WW, Meltzer MI, Reeve GR, Talamonti WJ, Cox NJ, Lilac HA, Hall H, Klimov A, Fukuda K: **Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial.** *JAMA* 2000, 284(13):1655–1663.
5. Centers for Disease Control and Prevention: *Flu Vaccination Coverage United States, 2011–12 Influenza Season.* 2012. Available at http://www.cdc.gov/flu/professionals/vaccination/nfs-survey-march2012.htm.
6. Nobuhara H, Watanabe Y, Miura Y, K N: **Prediction of influenza vaccination uptake in Japan in 2006.** *Journal of Health and Welfare Statistics* 2007, 54(13):44–52.
7. Kumar S, Quinn SC, Kim KH, Musa D, Hilyard KM, Freimuth VS: **The Social Ecological Model as a Framework for Determinants of 2009 H1N1 Influenza Vaccine Uptake in the United States.** *Health Educ Behav* 2012, 39(2):229–243.
8. Bone A, Guthmann JP, Nicolau J, Lévy-Bruhl D: **Population and risk group uptake of H1N1 influenza vaccine in mainland France 2009–2010: results of a national vaccination campaign.** *Vaccine* 2010, 28(51):8157–8161.
9. Maurer J, Uscher-Pines L, Harris KM: **Perceived seriousness of seasonal and A (H1N1) influenzas, attitudes toward vaccination, and vaccine uptake among US adults: Does the source of information matter?** *Prev Med* 2010, 51(2):185–187.
10. Yi S, Nonaka D, Nomoto M, Kobayashi J, Mizoue T: **Predictors of the uptake of A (H1N1) influenza vaccine: findings from a population-based longitudinal study in Tokyo.** *PLoS One* 2011, 6(4):e18893.
11. Sypsa V, Livanios T, Psichogiou M, Malliori M, Tsiodras S, Nikolakopoulos I, A H: **Public perceptions in relation to intention to receive pandemic influenzavaccination in a random population sample: evidence from a cross-sectional telephone survey.** *Euro Surveill* 2009, 14(49):19437.
12. Schwarzinger M, Flicoteaux R, Cortarenoda S, Obadia Y, Moatti JP: **Low acceptability of A/H1N1 pandemic vaccination in French adult population: did public health policy fuel public dissonance?** *PLoS One* 2010, 5(4):e10199.
13. Barriere J, Vanjak D, Kriegel I, Otto J, Peyrade F, Esteve M, Chamorey E: **Acceptance of the 2009 A(H1N1) influenza vaccine among hospital workers in two French cancer centers.** *Vaccine* 2010, 28(43):7030–7034.

14. Hothersall EJ, de Bellis-Ayres S, Jordan R: **Factors associated with uptake of pandemic influenza vaccine among general practitioners and practice nurses in Shropshire, UK.** *Prim Care Respir J* 2012, 21(3):302–307.
15. Blank PR, Freiburghaus AU, Schwenkglenks M, Szucs TD: **Trends in influenza vaccination coverage rates in the United Kingdom over six seasons from 2001–2 to 2006–7.** *Euro Surveill* 2008, 13(43):19014.
16. Blank PR, Schwenkglenks M, Szucs TD: **Influenza vaccination coverage rates in five European countries during season 2006/07 and trends over six consecutive seasons.** *BMC Publ Health* 2008, 8:272.
17. Holm MV, Blank PR, Szucs TD: **Trends in influenza vaccination coverage rates in Germany over five seasons from 2001 to 2006.** *BMC Infect Dis* 2007, 7:144.
18. Ma X, He Z, Wang Y, Jiang L, Xu Y, Qian C, Sun R, Chen E, Hu Z, Zhou L, *et al*: **Knowledge and attitudes of healthcare workers in Chinese intensive care units regarding 2009 H1N1 influenza pandemic.** *BMC Infect Dis* 2011, 11:24.
19. Gargano LM, Painter JE, Sales JM, Morfaw C, Jones LM, Murray D, Wingood GM, DiClemente RJ, Hughes JM: **Seasonal and 2009 H1N1 influenza vaccine uptake, predictors of vaccination, and self-reported barriers to vaccination among secondary school teachers and staff.** *Hum Vaccin* 2011, 7(1):89–95.
20. Akan H, Gurol Y, Izbirak G, Ozdatlı S, Yilmaz G, Vitrinel A, Hayran O: **Knowledge and attitudes of university students toward pandemic influenza: a cross-sectional study from Turkey.** *BMC Publ Health* 2010, 10(1):413.
21. Esposito S, Bosis S, Pelucchi C, Tremolati E, Sabatini C, Semino M, Marchisio P, della Croce F, Principi N: **Influenza vaccination among healthcare workers in a multidisciplinary University hospital in Italy.** *BMC Publ Health* 2008, 8:422.
22. Hollmeyer HG, Hayden F, Poland G, Buchholz U: **Influenza vaccination of health care workers in hospitals–a review of studies on attitudes and predictors.** *Vaccine* 2009, 27(30):3935–3944.
23. 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.
24. Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E: **Vaccines for preventing influenza in healthy adults.** *Cochrane Database Syst Rev* 2010(7). doi:10.1002/14651858.CD001269.pub4.
25. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, Omer SB, Shahid NS, Breiman RF, Steinhoff MC: **Effectiveness of maternal influenza immunization in mothers and infants.** *N Engl J Med* 2008, 359(15):1555–1564.
26. Crawford ND, Blaney S, Amesty S, Rivera AV, Turner AK, Ompad DC, Fuller CM: **Individual- and neighborhood-level characteristics associated with support of in-pharmacy vaccination among ESAP-registered pharmacies: pharmacists' role in reducing racial/ethnic disparities in influenza vaccinations in New York City.** *J Urban Health* 2011, 88(1):176–185.
27. Nowalk MP, Lin CJ, Toback SL, Rousculp MD, Eby C, Raymund M, Zimmerman RK: **Improving influenza vaccination rates in the workplace: a randomized trial.** *Am J Prev Med* 2010, 38(3):237–246.
28. Liao Q, Cowling BJ, Lam WW, Fielding R: **Factors affecting intention to receive and self-reported receipt of 2009 pandemic (H1N1) vaccine in Hong Kong: a longitudinal study.** *PLoS One* 2011, 6(3):e17713.
29. Lee JS, Kawakubo K: **Influenza vaccination coverage in Japan.** *Lancet* 2003, 362(9397):1767.
30. Lau JTF, Yeung NCY, Choi K, Cheng MYM, Tsui H, Griffiths S: **Acceptability of A/H1N1 vaccination during pandemic phase of influenza A/H1N1 in Hong Kong: population based cross sectional survey.** *BMJ: British Medical Journal* 2009, 339:b4164.
31. Hirota Y, Kaji M: **History of influenza vaccination programs in Japan.** *Vaccine* 2008, 26(50):6451–6454.

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Influenza Vaccination Uptake among the Working Age Population of Japan: Results from a National Cross-Sectional Survey

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Abstract

Background: Influenza vaccination rates among Japanese people of working age (20–69 years) is currently suboptimal, and the reasons for this have not been clearly elucidated. This study examined factors associated with vaccination intention among the working age population in Japan during September 2011, one-month prior to influenza vaccination becoming available.

Methodology/Principal Findings: A web-based survey of intention to be vaccinated against influenza in the coming season was undertaken among 3,129 Japanese aged 20 to 69 years. Multinomial logistic regression analysis was used to explore the associations between vaccination intent and other variables. Influenza vaccination intent was associated with having been vaccinated in the previous year (Odds Ratio (OR): 3.81; 95% Confidence Interval (CI): 3.75–3.86), the number of children per household (one compared with zero; OR: 1.37; 95%CI: 1.11–1.65), and household income ($50,000 to <$100,000 compared with $0 to <$50,000; OR: 1.30; 95%CI: 1.07–1.54). Smoking was inversely associated with influenza vaccine uptake (current smokers compared with non-smokers; OR: 0.79; 95%CI: 0.61–0.98). A history of either the survey respondent or a household member having being medically diagnosed with influenza in the previous year was not statistically associated with future influenza vaccination intent.

Conclusions/Significance: Overall, this suggests that intention to be vaccinated among working age Japanese is associated with a past history of influenza vaccination, having children, and the household's income. As such, consideration of these factors should now form the cornerstone of strategies to encourage increased uptake of vaccination against influenza in future years.

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Introduction

Influenza vaccination coverage in adults is relatively low in many countries, and low coverage was also observed during the H1N1 influenza pandemic of 2009 [1,2]. The Japanese government procured influenza vaccine for the entire population in 2009, but more than 99.7 million doses of the stockpiled vaccine (81.8% of the total ordered) ended up not being used [3]. The reasons for this low coverage are unknown, although possible reasons may relate to concerns of vaccine safety [4] and efficacy [5] – concerns that have been voiced for more than 20 years by an anti-vaccination lobby in Japan claiming that influenza vaccine is of limited efficacy and causes side effects [6]. Other reasons for suboptimal influenza vaccination coverage might relate to limited motivation, insufficient income or not living in households considered to be at risk [7,8].

Influenza vaccination is recommended for individuals over 6 months of age by the United States Centers for Disease Control and Prevention [9]. On the other hand, in Japan, the working age population has not been recommended to receive influenza vaccine, and influenza vaccination coverage is relatively low in this group (around 25%) [10]. As such, predictors of influenza vaccination intention should be addressed to build strategies to encourage yearly influenza vaccination.

Predictors of influenza vaccination among the working age Japanese population were previously investigated in a study of 428 adults that found that vaccinated individuals tended to have underlying diseases, perceived themselves as being susceptible to influenza, and found the vaccines to be affordable [11]. Other predictors such as demographic characteristics, a prior history of vaccination, and history of influenza infection for survey respondents or household members, have not been well studied and therefore need to be investigated in a larger sample of Japanese people. As such, this study aimed to determine the factors associated with the intention to be vaccinated against influenza in

September 2011 (one-month before the influenza vaccine became available) among the working age population of Japan.

Materials and Methods

Ethics statement

This study was approved by the Human Research Committee at the Kitasato University School of Medicine.

Data collection

This study sought to recruit a total of 3,000 Japanese individuals aged 20 to 69 years who had been registered by a web-based survey company. Registrants were individuals interested in participating in a survey that provided financial incentives. In September 2011, the survey company randomly selected persons from this list and invited them to participate in the current study. Recruitment was intended to cease when the number of participants had reached the target (3,000), although 3,129 persons eventually agreed to participate from a total of 7,937 individuals initially contacted. Participants were classified into five groups by age range: 20–29, 30–39, 40–49, 50–59 and 60-69 years. Individuals who agreed to participate were then directed to complete an anonymous online questionnaire.

Questions included basic demographic information (including age, gender, number of children living in the household, household income in Yen [1US$ = 80Yen at the time], and smoking status), influenza vaccination status in the previous year, and whether the participant or any member of their household had been medically diagnosed with influenza in the previous year. The survey also enquired about other hygiene practices that had been associated with vaccination in a previous study (wearing a face mask in public and hand washing); as these factors were to be used during multivariate analysis of data [12].

To determine vaccination intent, the question "Do you intend to receive an influenza vaccine in this coming influenza season?" was asked, with possible answers of "Yes", "Not decided yet", or "No". To determine vaccination status in the previous year, we asked: "Did you receive an influenza vaccine in the previous year?" with possible answers of "Yes" or "No". We also enquired about their prior history of influenza infection with the following two questions: "During the period from October 2010 to March 2011, were you medically diagnosed with influenza?" and "During the period from October 2010 to March 2011, was a member of your family who lives with you medically diagnosed with influenza?"

Statistical analysis

We conducted univariate analysis using Pearson's chi-squared test to examine the potential relationships between vaccination intent and other demographic variables. Multinomial logistic regression analyses was then used to explore possible associations between predictor variables and the outcome of vaccination intent in the coming year. The three outcome categories were as follows: "I will not receive a vaccine" (referent), "I am not decided yet", and "I am intending to receive a vaccine". All analyses were performed using IBM SPSS Statistics 19, with statistical significance being set at $p<0.05$.

Results

A total of 3,129 persons, including 1,572 men and 1,557 women, participated in the study. Table 1 indicates the characteristics of participants. A total of 25.4% expressed an intention to be vaccinated in the coming influenza season and 27.7% were undecided, even though the survey was conducted only 1 month before the start of influenza vaccine becoming available. In the previous influenza season, 7.3% of respondents had been medically diagnosed with influenza and 15.3% of respondents reported having had a household member who was diagnosed with influenza.

Table 2 shows associations between vaccination intent and other study variables. A strong association was seen between prior vaccination status and intention to be vaccinated in the coming season. In fact, 72.7% of respondents who were vaccinated in the previous year also intended to be vaccinated in the coming season, while only 9.0% of unvaccinated respondents in the previous year expressed vaccination intent for the coming season. Thirty-three percent of respondents with at least one child in their household intended to be vaccinated. Intention to be vaccinated against influenza was also related to household income, with respondents from higher-income households more likely to express an intention for future vaccination. A significantly higher number of participants who had been diagnosed with influenza in the previous year intended to be vaccinated in the coming period. Similarly, participants with household members who had been diagnosed with influenza were more likely to express an intention to be vaccinated in future when compared to household members without a previous history of influenza diagnosis.

Table 3 details the results of multinomial logistic regression analysis when considering intention to be vaccinated and other study variables. Compared with participants who had not been vaccinated in the previous year, respondents who *were* vaccinated had a higher odds of vaccination intent in the coming season (Odds Ratio (OR): 3.81; 95% Confidence Interval (CI): 3.75–3.86). Similarly, respondents who were vaccinated in the previous year were more likely to have not yet decided whether or not they would be vaccinated in the coming season (OR: 2.41; 95%CI: 2.14–2.66). The number of children per household (one compared with zero; OR: 1.37; 95%CI: 1.11–1.65) and household income ($50,000 to $100,000 compared with $0 to <$50,000; OR: 1.30; 95%CI: 1.07–1.54) were both positively associated with vaccination intent in the coming season. Current smoking status (OR: 0.79; 95%CI: 0.61–0.98) was negatively associated with future intention to be vaccinated. A history of prior influenza infection for either the survey participant or any of their household members was not significantly associated with intention to receive influenza vaccine.

Discussion

The current study investigated predictors associated with intent to receive influenza vaccine among the working age population of Japan. The official Japanese influenza vaccine provision begins in October every year, and as such, our study was undertaken in September to determine the participants' intentions immediately prior to the national vaccine provision. We found that influenza vaccination in the previous year, the number of children per household, and household income were all associated with an intention to receive influenza vaccination. A prior diagnosis of influenza infection in the previous year was not associated with vaccination intent, although current smoking status was generally associated with a lower influenza vaccine uptake.

Some of our current findings are consistent with previous research, with various studies demonstrating that a history of influenza vaccination is a strong predictor of vaccination in the following year, in Japan as well as some other countries [11,13–15]. Vaccinated individuals appear to have confidence in the safety and effectiveness of influenza vaccines, and this phenom-

Table 1. Participant Characteristics.

	n (3,129)	(%)
Age (years)		
20–29	510	(16.3)
30–39	659	(21.1)
40–49	647	(20.7)
50–59	601	(19.2)
60–69	712	(22.8)
Gender		
Male	1,572	(50.2)
Intention to be vaccinated in the coming season		
Yes, I intend to be vaccinated	796	(25.4)
Not yet decided	867	(27.7)
Will not be vaccinated	1,466	(46.9)
Influenza vaccination in the previous year		
Vaccinated	809	(25.9)
Not vaccinated	2,320	(74.1)
Number of children in household		
None	1,821	(58.2)
One	645	(20.6)
Two or more	663	(21.2)
Yearly household income (USD)		
\$0 to <\$50,000	1,213	(38.8)
\$50,000 to <\$100,000	1,326	(42.4)
\$100,000+	590	(18.9)
Smoking		
Current smoker	663	(21.1)
Former smoker	700	(22.4)
Never smoked	1,766	(56.4)
Medically diagnosed with influenza in the previous year	229	(7.3)
Household member medically diagnosed with influenza in the previous year (n = 2,899; excluding 230 who did not have household members)	444	(15.3)

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enon is not limited to Japan. A recent study from Turkey, for example, found that the leading factor negatively influencing vaccine uptake was a disbelief in the vaccine's effectiveness [16]. Interestingly, 30.6% of respondents in the current study who were not vaccinated in the previous year had not yet decided if they would be vaccinated in the current year. Such a finding suggests that this group may be an ideal target to help increase vaccination uptake in Japan, as elsewhere.

The number of children per household was an important predictor of vaccination intent for working age adults in the current study. When compared with respondents with no children, there were significant associations between households with one child and their intention to be vaccinated, as well as a weak association between households with two or more children and their vaccination intent. It is well-known that children can be vulnerable to influenza, being at an increased risk of infection from schools and nursery schools, and also being at greater risk of developing a more severe illness if the disease is contracted [17]. Similarly, working age populations with children are also at risk of contracting influenza if their children are infected [18,19]. For these reasons, individuals with children would likely have additional motivation to prevent influenza infection in themselves and their children, compared with people living without children. Despite this fact, however, not all studies have demonstrated such a trend. For example, a recent investigation of parents from the United Kingdom [20] found that while 61% would accept influenza vaccination for their children, the most common reasons for declining were concerns about safety and potential side effects.

Cost may also contribute to low influenza vaccination coverage rates in Japan as elsewhere, given that in Japan, people of working age must pay for influenza vaccination themselves. During the 2009 influenza pandemic, for example, one dose of influenza vaccine cost 3,600 yen for adults (around US \$45) in this country [11]. Compared with other countries, this may be seen as relatively expensive [21], and as a result, individuals with limited income may simply be unable to afford the vaccine [7]. As a result, financial support for the working age population and/or subsidizing vaccination may be one strategy to help improve this situation in Japan. Offering free influenza vaccination days in Japan's Municipal Health Centers (MHC), for example, might

Table 2. Associations between intention to receive influenza vaccine in the coming influenza season and other study variables (n = 3,129).

	Intend to be vaccinated in the coming season		Not yet decided		Will not be vaccinated		
	n = 796	(%)	n = 867	(%)	n = 1466	(%)	*P* value[a]
Age (years)							
20–29	148	(29.0)	195	(38.2)	167	(32.7)	<0.001
30–39	169	(25.6)	175	(26.6)	315	(47.8)	
40–49	151	(23.3)	174	(26.6)	322	(49.8)	
50–59	156	(26.0)	162	(27.0)	283	(47.1)	
60–69	172	(24.2)	161	(22.6)	379	(53.2)	
Gender							
Male	431	(27.4)	457	(29.1)	684	(43.5)	<0.001
Female	365	(23.4)	410	(26.3)	782	(50.2)	
Influenza vaccination in the previous year							
Vaccinated	588	(72.7)	158	(19.5)	63	(7.8)	<0.001
Not vaccinated	208	(9.0)	709	(30.6)	1403	(60.5)	
Number of children in household							
None	383	(21.0)	532	(29.2)	906	(49.8)	<0.001
One	213	(33.0)	173	(26.8)	259	(40.2)	
Two or more	200	(30.2)	162	(24.4)	301	(45.4)	
Household income (USD)							
$0 to <$50,000	240	(19.8)	366	(30.2)	607	(50.0)	<0.001
$50,000 to <$100,000	369	(27.8)	369	(27.8)	588	(44.3)	
$100,000+	187	(31.7)	132	(22.4)	271	(45.9)	
Smoking							
Current smoker	134	(20.2)	174	(26.2)	355	(53.5)	<0.001
Former smoker	169	(24.1)	202	(28.9)	329	(47.0)	
Never smoked	493	(27.9)	491	(27.8)	782	(44.3)	
Medically diagnosed with influenza in the previous year							
Yes	89	(38.9)	73	(31.9)	67	(29.3)	<0.001
No	707	(22.8)	794	(25.6)	1599	(51.6)	
Household member diagnosed with influenza in the previous year							
Yes	162	(36.5)	104	(23.4)	178	(40.1)	<0.001
No	634	(23.6)	763	(28.4)	1288	(48.0)	

[a]Statistical differences by intention to receive influenza vaccine with Chi-square test.
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help raise coverage rates among those unwilling or unable to pay for influenza vaccines. MHCs represent an important component of the national public health system in Japan, and already perform a variety of preventive services [22]. As such, adding influenza vaccination days at MHCs is a feasible option to increase influenza vaccination coverage. Further benefits might also arise from having designated "influenza vaccination days" at MHCs in Japan, not the least being increased public awareness as well as providing healthy role modeling behavior for children – similar to current, routine vaccination schedules.

The current study revealed a statistically significant relationship between some aspects of vaccination status and tobacco use. This is consistent with some previous research which revealed that smokers are unlikely to receive influenza vaccine [23], even though they have a high risk of influenza virus infection [24] and chronic obstructive pulmonary disease (COPD). Patients with COPD are strongly encouraged to be vaccinated against influenza [25]. Such a result is not entirely surprising however, as smokers tend to have mixture of unhealthy behaviors; including lower vegetable intake and higher alcohol consumption when compared to non-smokers [26]. As a result, any interventions to increase influenza vaccination uptake among smokers will clearly need to consider these issues in their design.

Interestingly, the current study revealed that previous influenza infection for survey participants and their household members was not significantly associated with an intention to receive influenza vaccine. To our knowledge, no similar studies have investigated the association between history of infection and future intention to be vaccinated. We found that among 805 participants who had been vaccinated in the previous year, 111 were diagnosed with influenza virus infection in the previous influenza season. Despite this fact, only 13.5% of them decided not to receive influenza vaccination in the coming season. On the other hand, 123 individuals out of 2,324 who did not receive a vaccine in the

Table 3. Multinomial logistic regression analysis of associations between study variables and intention to be vaccinated in the coming influenza season (reference category: will not be vaccinated).

	Intend to be vaccinated in the coming season				Not yet decided			
	Crude		Multivariate[a]		Crude		Multivariate[a]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Influenza vaccination in the previous year								
Vaccinated versus unvaccinated (ref)	3.82	(3.76–3.86)	3.81	(3.75–3.86)	2.44	(2.17–2.67)	2.41	(2.14–2.66)
Number of children in household								
None	ref		ref		ref		ref	
One	1.61	(1.41–1.83)	1.37	(1.11–1.65)	1.13	(0.97–1.31)	1.11	(0.94–1.30)
Two or more	1.41	(1.22–1.61)	1.21	(0.96–1.50)	0.97	(0.82–1.13)	0.97	(0.81–1.16)
Household income (US $)								
0 to <50,000	ref		ref		ref		ref	
50,000 to <100,000	1.44	(1.27–1.63)	1.30	(1.07–1.54)	1.08	(0.94–1.22)	1.04	(0.90–1.19)
100,000+	1.53	(1.31–1.76)	1.17	(0.92–1.47)	0.90	(0.74–1.07)	0.83	(0.68–1.01)
Smoking (versus not smoking)								
Current smoker	0.70	(0.58–0.84)	0.79	(0.61–0.98)	0.87	(0.74–1.02)	0.91	(0.76–1.07)
Former smoker	0.89	(0.75–1.05)	0.81	(0.64–1.02)	1.02	(0.87–1.18)	1.01	(0.86–1.18)
Never smoked	ref		ref		ref		ref	
Medically diagnosed with influenza in the previous year	1.82	(1.51–2.14)	1.08	(0.73–1.53)	1.49	(1.21–1.80)	1.20	(0.89–1.55)
Household member diagnosed with influenza in the previous year	1.56	(1.34–1.79)	0.74	(0.51–1.04)	1.02	(0.84–1.22)	0.82	(0.62–1.07)

[a]Adjusted for age and gender OR: odds ratio, CI: confidence interval, ref: referent.
[a]Multivariate model: adjusted for all independent variables, including hand washing and wearing a facemask in public.
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previous year had been diagnosed with influenza in the previous year. Of these 2,324, only 15.4% intended to be vaccinated in the coming vaccination provision. As such, this finding suggests that influenza infection itself, might not play a large role in determining future influenza vaccination uptake.

Limitations of the current study include the fact that the study population was recruited through a web-based survey company, and it might be expected that individuals who can access the internet can also seek information more easily and tend to take healthy behaviors more seriously [27]. Such factors will need to be investigated in future research. In addition, while the current study investigated intention to receive influenza vaccine, participants were not followed up and as such, we were unable to determine if participants subsequently received the vaccination or not. This may be a relevant consideration for future investigations, as a previous study by Yi and colleagues [11], for example, found that while 57% of people were willing to be vaccinated, only 12.1% actually ended up doing so. A result which suggests that individuals who state a willingness to be vaccinated at one point in time, might later change their mind. Future studies would do well to incorporate intervention strategies to increase motivation to receive influenza vaccine in such groups.

Conclusion

Overall, this study found that among Japanese people of working age, intention to be vaccinated against influenza is associated with a prior history of influenza vaccination, number of children, and household income. These factors should form the cornerstone of strategies to encourage higher vaccination rates among working age populations in Japan, as elsewhere.

Author Contributions

Conceived and designed the experiments: KW. Performed the experiments: KW. Analyzed the data: KW. Contributed reagents/materials/analysis tools: KW. Wrote the paper: KW DRS.

References

1. Schwarzinger M, Flicoteaux R, Cortarenoda S, Obadia Y, Moatti JP (2010) Low acceptability of A/H1N1 pandemic vaccination in French adult population: did public health policy fuel public dissonance? PLoS One 5: e10199.
2. Rachiotis G, Mouchtouri VA, Kremastinou J, Gourgoulianis K, Hadjichristodoulou C (2010) Low acceptance of vaccination against the 2009 pandemic influenza A(H1N1) among healthcare workers in Greece. Euro Surveill 15: pii: 19486.
3. Wada K (2011) Pandemic (H1N1) 2009 in Japan: Chuouhouki, Tokyo.
4. Hothersall EJ, de Bellis-Ayres S, Jordan R (2012) Factors associated with uptake of pandemic influenza vaccine among general practitioners and practice nurses in Shropshire, UK. Prim Care Respir J 21: 302–307.
5. Hollmeyer HG, Hayden F, Poland G, Buchholz U (2009) Influenza vaccination of health care workers in hospitals – a review of studies on attitudes and predictors. Vaccine 27: 3935–3944.
6. Hirota Y, Kaji M (2008) History of influenza vaccination programs in Japan. Vaccine 26: 6451–6454.
7. Armstrong K, Berlin M, Schwartz JS, Propert K, Ubel PA (2001) Barriers to influenza immunization in a low-income urban population. Am J Prev Med 20: 21–25.
8. SteelFisher GK, Blendon RJ, Bekheit MM, Lubell K (2010) The Public's Response to the 2009 H1N1 Influenza Pandemic. N Engl J Med 362: e65.
9. Advisory Committee on Immunization Practices (2012) Recommended Adult Immunization Schedule: United States, 2012. Ann Intern Med 156: 211–217.

10. Nobuhara H, Watanabe Y, Miura Y, Nakai K (2007) Prediction of influenza vaccination uptake in Japan in 2006. Journal of Health and Welfare Statistics 54: 44–52.
11. Yi S, Nonaka D, Nomoto M, Kobayashi J, Mizoue T (2011) Predictors of the uptake of A (H1N1) influenza vaccine: findings from a population-based longitudinal study in Tokyo. PLoS One 6: e18893.
12. Wada K, Oka-Ezoe K, Smith DR (2012) Wearing face masks in public during the influenza season may reflect other positive hygiene practices in Japan. BMC Public Health 12: 1065.
13. Maurer J, Uscher-Pines L, Harris KM (2010) Perceived seriousness of seasonal and A (H1N1) influenzas, attitudes toward vaccination, and vaccine uptake among US adults: Does the source of information matter? Prev Med 51: 185–187.
14. Seale H, Heywood AE, McLaws ML, Ward KF, Lowbridge CP, et al. (2010) Why do I need it? I am not at risk! Public perceptions towards the pandemic (H1N1) 2009 vaccine. BMC Infect Dis 10: 99.
15. Eastwood K, Durrheim DN, Jones A, Butler M (2010) Acceptance of pandemic (H1N1) 2009 influenza vaccination by the Australian public. Med J Aust 192: 33–36.
16. Ciblak MA, Grip P (2013) Influenza vaccination in Turkey: Prevalence of risk groups, current vaccination status, factors influencing vaccine uptake and steps taken to increase vaccination rate. Vaccine 31:518–23.
17. Bagdure D, Curtis DJ, Dobyns E, Glode MP, Dominguez SR (2010) Hospitalized children with 2009 pandemic influenza A (H1N1): comparison to seasonal influenza and risk factors for admission to the ICU. PLoS One 5: e15173.
18. Hirotsu N, Wada K, Oshitani H (2012) Risk Factors of Household Transmission of Pandemic (H1N1) 2009 among Patients Treated with Antivirals: A Prospective Study at a Primary Clinic in Japan. PloS one 7: e31519.
19. O'Riordan S, Barton M, Yau Y, Read SE, Allen U, et al. (2010) Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. CMAJ 182: 39–44.
20. Janks M, Cooke S, Odedra A, Kang H, Bellman M, et al. (2012) Factors Affecting Acceptance and Intention to Receive Pandemic Influenza A H1N1 Vaccine among Primary School Children: A Cross-Sectional Study in Birmingham, UK. Influenza Res Treat 2012: 182565.
21. Khazeni N, Hutton DW, Garber AM, Hupert N, Owens DK (2009) Effectiveness and Cost-Effectiveness of Vaccination against Pandemic (H1N1) 2009. Ann Intern Med 151: 829.
22. Smith DR (2009) Public health centres in contemporary Japan. Public Health 123: 196–197; author reply 198.
23. Mangtani P, Breeze E, Kovats S, Ng ESW, Roberts JA, et al. (2005) Inequalities in influenza vaccine uptake among people aged over 74 years in Britain. Prev Med 41: 545–553.
24. Nicholson K, Kent J, Hammersley V (1999) Influenza A among community-dwelling elderly persons in Leicestershire during winter 1993-4; cigarette smoking as a risk factor and the efficacy of influenza vaccination. Epidemiol Infect 123: 103–108.
25. Plans-Rubio P (2007) Prevention and control of influenza in persons with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2: 41–53.
26. Subar AF, Harlan LC, Mattson ME (1990) Food and nutrient intake differences between smokers and non-smokers in the US. Am J Public Health 80: 1323–1329.
27. Kontos EZ, Emmons KM, Puleo E, Viswanath K (2012) Contribution of communication inequalities to disparities in human papillomavirus vaccine awareness and knowledge. Am J Public Health 102: 1911–1920.

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Effectiveness of Trivalent Influenza Vaccine among Children in Two Consecutive Seasons in a Community in Japan

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Influenza vaccination is considered the single most important medical intervention for the prevention of influenza. The dose of trivalent influenza vaccine in children was increased almost double since 2011/12 season in Japan. We estimated the influenza vaccine effectiveness for children 1-11 years of age using rapid test kits in Isahaya City, involving 28,884 children-years, over two consecutive influenza seasons (2011/12 and 2012/13). Children were divided into two groups, vaccinated and unvaccinated, according to their vaccination record, which was obtained from an influenza registration program organized by the Isahaya Medical Association for all pediatric facilities in the city. There were 14,562 and 14,282 children aged from 1-11 years in the city in 2011 and 2012 respectively. In the 2011/12 season, the overall vaccine effectiveness in children from 1-11 years of age, against influenza A and B were 23% [95% confidence interval (CI): 14%-31%] and 20% [95% CI: 8%-31%], respectively. In the 2012/13 season, vaccine effectiveness against influenza A and B was 13% (95% CI: 4%-20%) and 9% (95% CI: −4%-21%), respectively. The vaccine effectiveness was estimated using the rapid diagnosis test kits. Age-stratified estimation showed that vaccine effectiveness was superior in younger children over both seasons and for both virus types. In conclusion, the trivalent influenza vaccine has a significant protective effect for children 1-11 years of age against influenza A and B infection in the 2011/12 season and against influenza A infection in the 2012/13 season in a community in Japan.

Keywords: children; community; influenza virus; trivalent influenza vaccine; vaccine effectiveness
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Introduction

Influenza virus is responsible for acute respiratory infections in every winter, and it is an important cause of morbidity and mortality. Epidemic resulted in approximately 3-5 million cases of severe illnesses and 250-500 thousand deaths (World Health Organization 2009). Vaccination is considered as the single most important medical intervention for prevention of influenza (Palache 2011; Centers for Disease Control and Prevention 2012).

In general, vaccine efficacy/effectiveness is expressed as a proportionate reduction in the disease attack rate between the vaccinated and unvaccinated study cohorts, and it can be calculated from the relative disease risk among the vaccinated group (Weinberg and Szilagyi 2010). Vaccine efficacy is best measured by double-blind, randomized controlled clinical trials, providing "best case scenarios" of vaccine protectiveness under controlled conditions and are commonly required before a new vaccine is licensed by the Food and Drug Administration and other global regulatory authorities (Clemens et al. 1996). The advantages of a vaccine efficacy study include rigorous control for biases afforded by randomization as well as prospective and active monitoring for disease attack rates and careful tracking of the vaccination status. In contrast, vaccine effectiveness is a "real world" view of how a vaccine actually reduces disease in a population. A study design capable of measuring vaccine effectiveness in this way is the "indirect cohort" or "quasi-cohort" study, in which different responses in the same vaccinated population are examined (Clemens and Shapiro 1984). The other option is "case-cohort" method, in which vaccination rates among cases are compared with those in a similar cohort as well as ecologic or observational studies. A meta-analysis of the

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Cochrane Database showed that vaccine efficacy of the trivalent inactivated vaccine against laboratory-confirmed influenza in healthy children is approximately 59% (Jefferson et al. 2012). Influenza vaccine efficacy/effectiveness considerably varies according to the time, place, and the degree of antigenic distance between the vaccine and circulating strains in each season (Osterholm et al. 2012). Therefore, it is necessary to assess vaccine efficacy/effectiveness in every season, at each study site.

The doses of trivalent vaccine used in Japan before the 2010/11 season were two doses of 0.1 ml for children less than 1 year of age, two doses of 0.2 ml for 1-5 years, two doses of 0.3 ml for 6-12 years, and a dose of 0.5 ml for 13 years and over. However, the amount was smaller than that is administered in the US or Europe, and thus, it was disputable whether such a low dose leads to sufficient seroresponse (Ochiai et al. 2009). Accordingly, from the 2011/12 season, the recommended dose of trivalent inactivated influenza vaccine for children was increased almost double to two doses of 0.25 ml for 6-24 months of age and two doses of 0.5 ml for 3-12 years, which met the recommendations of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommendations (Health Service Bureau, Ministry of Health, Labour and Welfare 2011). However, there was no report estimating the influenza vaccine efficacy/effectiveness following the increase in the vaccine dosage for children in Japan.

In Isahaya City, Nagasaki Prefecture, Japan, the local government supports the expense of seasonal influenza vaccination for children less than 13 years of age every year. At the same time, Isahaya Medical Association conducts active influenza case surveillance and registration of all patients diagnosed as influenza using rapid test kits at nearly 80 internal medicine and pediatric facilities. In Japan, the rapid diagnostic test for influenza has been effectively used in routine medical practice. Rapid influenza diagnostic test has a high overall sensitivity of 82.8%-96.8% and specificity of 95.3%-97.6% (Kubo et al. 2003; Mitamura et al. 2004).

In the present study, we estimated vaccine effectiveness of influenza during the two influenza seasons following the introduction of the higher trivalent influenza vaccine dose for children, and assessed the protective effect of the vaccine against influenza A and B in a community in Japan.

Methods

Study site

The study was conducted in Isahaya City in Nagasaki Prefecture, located in southwestern Japan. According to the 2010 census, the region's population is about 140,000 and the total area is about 320 square-kilometers.

In Isahaya City, the local government subsidizes the expense of seasonal influenza vaccination for all children who wish to receive vaccines from 6 months to 11 or 12 years of age (until graduation of elementary school). Subsidies were given from October 1st to February 28th in every season.

The vaccine

The vaccine used in this study contained 30 μg/ml of hemagglutinin for each of the recommended components as follows: A/California/7/2009(H1N1), A/Perth/16/2009(H3N2), and B/Brisbane/60/2008 in the 2011/12 season, and A/California/7/2009(H1N1), A/Victoria/361/2011(H3N2), and B/Wisconsin/01/2010 in the 2012/13 season. The influenza vaccine was given a dose of 0.25 ml per injection for children aged 6 month through 2 years of age, and a dose of 0.5 ml for children aged 3 through 12 years, following the Japanese guidelines. Children received influenza vaccine once or twice at medical facilities before the start of the influenza season. Children who received two vaccine doses were given 2-4 weeks apart according to the recommendation of the Ministry of Health, Welfare, and Labor in Japan.

Vaccinees were registered at the Health and Welfare Center of Isahaya City with their name and age data for the subsidy. Individual data were aggregated into the number of children in the vaccinated group (vaccinated at least once in a season) and unvaccinated group and stratified according to age. The information without individual records was sent to Niigata University for further analysis of vaccine effectiveness. The use of data without individual records for this study was approved by the Health and Welfare Center of Isahaya City and Isahaya Medical Association.

Case surveillance and definition

Isahaya Medical Association in Isahaya City, Nagasaki Prefecture has conducted an influenza registration program since the 2003/04 season (Kimura et al. 2011). The number of medical facilities that participated in this study was 80 in the 2011/12 season and 78 in the 2012/13 season. All 17 pediatric facilities and almost all 56 internal medicine outpatient medical facilities were enrolled. When patients visited the medical facilities with influenza-like-illness (ILI), such as having a sudden onset of fever (> 37.5°C) and sore throat, cough, or myalgia; clinicians used influenza rapid diagnostic test kits to screen for influenza A or B. Informed consent was obtained and the following information of the patients was collected: age, day of onset, diagnosis (influenza type A or B by rapid diagnosis test or clinically diagnosed), influenza vaccination status, and "most likely" route of transmission. In terms of the question for route of transmission, patient or patient's parent chose a single answer where they thought they got infected with influenza, from a set of multiple choices; at home, at school/preschool, at the crowded place, or the other including unknown. Registration was commenced when the first ILI case occurred and ended in the end of April (week 18 of epidemic week) every season. This influenza case surveillance program was approved by the Ethical Committee of Niigata University Graduate School of Medical and Dental Sciences and Isahaya Medical Association. The overall study to evaluate influenza vaccine effectiveness is approved by the committee of Isahaya Medical Association.

Measurement of incidence rates of influenza and vaccine effectiveness

Overall incidence rate of influenza A or B infections in Isahaya City was calculated from the number of children who were positive with rapid test kits from the case surveillance program, divided by the population of children aged 1-11 years in each season. Age specific data, 1-2 years, 3-5 years, and 6-11 years, were also calculated by type and season. Vaccine effectiveness was estimated as [(1 − relative risk) × 100%] where the relative risk is the ratio of the incidence of vaccinated group over unvaccinated group. Incidence rate of vaccinated group was obtained by dividing the number of influenza cases in the respective type (A or B) diagnosed using the rapid diagnostic test kits who received influenza vaccination at least once, by the number of vaccinated children in 1-11 years from the record of the municipal registration program. On the other hand, incidence rate of unvaccinated group was obtained by dividing the number of unvaccinated influenza patients from the respective type registered to the case surveillance program, by the number of the unvaccinated population aged 1-11 years. The unvaccinated population was calculated by subtracting the number of vaccinated population in municipal registration record from the total population obtained by the city census. We computed vaccine effectiveness against influenza A and influenza B with all age and with subdivided age groups (1-2 years, 3-5 years, and 6-11 years). The chi-square test was used to compare the incidence rates between the vaccinated and unvaccinated groups. For all hypothesis tests, p value < 0.05 was considered statistically significant. Statistical analyses were conducted using R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Laboratory analysis

Virological confirmation of influenza A (H3N2 and H1N1pdm09) or B that circulated in the two seasons in Isahaya City was performed with selected samples collected at one of the pediatric clinics in the city. Throat swabs were obtained from patients positive with influenza rapid diagnostic test kits and kept in viral transport medium upon collection. The samples were sent to Niigata University for further laboratory analysis. Influenza virus isolation was performed by using Madin-Darby canine kidney (MDCK) cells. Typing and subtyping were done by Real-Time PCR as reported previously (Dapat et al. 2012).

Results

Vaccination coverage rate

The city census showed that the number of children from 1 to 11 years of age in Isahaya City was 14,562 and 14,282 on the first date of vaccination for seasonal influenza (October 1st) in 2011 and 2012, respectively.

According to the municipal vaccination record, 9,864 children were vaccinated and 4,698 were not vaccinated in 2011, and the numbers of the respective groups were 8,773 and 5,509 in 2012 (Table 1). Overall vaccination coverage rates in the two seasons were 67.7% and 61.4%. In the 2011/12 season, aggregated vaccination coverage rates were 75.3% in the 1-2 years of age group, 74.4% in the 3-5 years, and 62.2% in the 6-11 years. In the 2012/13 season, the figures for the respective groups were 66.4%, 66.0%, and 57.7%. The older children had a lower vaccination coverage rate in both seasons, and the vaccination coverage decreased in the second season.

Influenza epidemiology and the incidence rates

In Isahaya City, 2,412 children in 1-11 years of age were diagnosed as influenza A or B infections at the medical facilities between the week 52 of 2011 and the week 18 of 2012 in the first season, and 3,346 were diagnosed between the week 48 of 2012 and the week 18 of 2013 in the second season. In both seasons, co-circulation of influenza A and B was observed (Fig. 1).

The overall incidence rates of influenza A were 10.4% in the 2011/12 season, and was 16.8% in the 2012/13 season. The figures for influenza B were 5.9% and 6.6%, respectively (Table 2). For influenza A, the incidence rates were higher in the second season than the first season, but the rates over age groups (1-2 years, 3-5 years, and 6-11 years) did not show difference. For influenza B, the incidence rates were low in both two seasons, and the rates increased as children became older.

Table 1. Age distribution and proportion of vaccinated and unvaccinated children in Isahaya City in 2011 and 2012.

Age (years)	2011			2012		
	No. of Population*	Vaccinated (%)	Unvaccinated (%)	No. of Population*	Vaccinated (%)	Unvaccinated (%)
Total	14,562	9,864 (67.7%)	4,698 (32.3%)	14,282	8,773 (61.4%)	5,509 (38.6%)
1	1,268	957 (75.5%)	311 (24.5%)	1,217	848 (69.7%)	369 (30.3%)
2	1,268	953 (75.2%)	315 (24.8%)	1,261	797 (63.2%)	464 (36.8%)
3	1,300	969 (74.5%)	331 (25.5%)	1,246	842 (67.6%)	404 (32.4%)
4	1,275	972 (76.2%)	303 (23.8%)	1,305	854 (65.4%)	451 (34.6%)
5	1,302	942 (72.4%)	360 (27.6%)	1,272	826 (64.9%)	446 (35.1%)
6	1,285	894 (69.6%)	391 (30.4%)	1,291	826 (64.0%)	465 (36.0%)
7	1,301	905 (69.6%)	396 (30.4%)	1,287	783 (60.8%)	504 (39.2%)
8	1,346	875 (65.0%)	471 (35.0%)	1,303	795 (61.0%)	508 (39.0%)
9	1,377	865 (62.8%)	512 (37.2%)	1,359	751 (55.3%)	608 (44.7%)
10	1,351	796 (58.9%)	555 (41.1%)	1,380	743 (53.8%)	637 (46.2%)
11	1,489	736 (49.4%)	753 (50.6%)	1,361	708 (52.0%)	653 (48.0%)

*The number of population by each age in Isahaya City was as of October 1st, the first date of vaccination for seasonal influenza in each year.

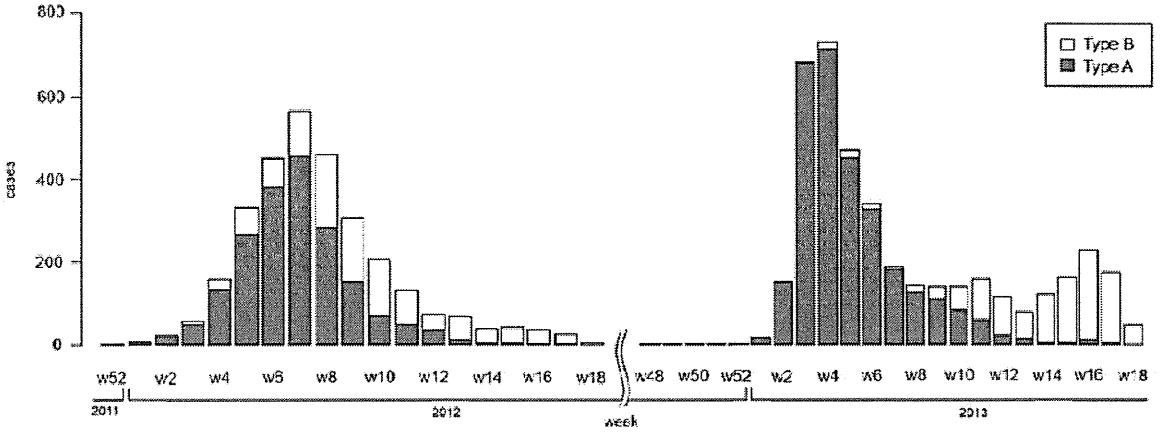

Fig. 1. Weekly incidence of influenza virus infection by type.
An epidemic curve of influenza type A and B in Isahaya, Japan in 2011-2013. The number of cases was obtained from an influenza registration program conducted by Isahaya Medical Association. Registration was commenced when the first case occurred and ended in the end of April (week 18 of epidemic week) every season.

Table 2. Age distribution of incidence of influenza virus infection and vaccine effectiveness.

	Incidence of confirmed influenza in children (%)			Relative risk (95% CI)	Vaccine effectiveness (95% CI)	*P*-value
	Total	Vaccinated*	Unvaccinated			
2011/12 season						
Influenza A						
1-2 years	231/ 2,536 (9.1%)	134/1,910 (7.0%)	97/ 626 (15.5%)	0.45 (0.34-0.60)	55% (40-66)	< 0.001
3-5 years	478/ 3,877 (12.3%)	317/2,883 (11.0%)	161/ 994 (16.2%)	0.68 (0.55-0.83)	32% (17-45)	< 0.001
6-11 years	781/ 8,149 (9.6%)	471/5,071 (9.3%)	310/3,078 (10.1%)	0.92 (0.79-1.07)	8% (−7-21)	0.244
1-11 years	1,490/14,562 (10.2%)	922/9,864 (9.3%)	568/4,698 (12.1%)	0.77 (0.69-0.86)	23% (14-31)	< 0.001
Influenza B						
1-2 years	62/ 2,536 (2.4%)	40/1,910 (2.1%)	22/ 626 (3.5%)	0.60 (0.35-1.01)	40% (−1-65)	0.046
3-5 years	150/ 3,877 (3.9%)	100/2,883 (3.5%)	50/ 994 (5.0%)	0.69 (0.48-0.98)	31% (2-52)	0.028
6-11 years	650/ 8,149 (8.0%)	400/5,071 (7.9%)	250/3,078 (8.1%)	0.97 (0.82-1.14)	3% (−14-18)	0.705
1-11 years	862/14,562 (5.9%)	540/9,864 (5.5%)	322/4,698 (6.9%)	0.80 (0.69-0.92)	20% (8-31)	0.001
2012/13 season						
Influenza A						
1-2 years	376/ 2,478 (15.2%)	231/1,645 (14.0%)	145/ 833 (17.4%)	0.81 (0.65-1.01)	19% (−1-35)	0.027
3-5 years	665/ 3,823 (17.4%)	404/2,522 (16.0%)	261/1,301 (20.1%)	0.80 (0.67-0.95)	20% (5-33)	0.002
6-11 years	1,359/ 7,981 (17.0%)	762/4,606 (16.5%)	597/3,375 (17.7%)	0.94 (0.83-1.05)	6% (−5-17)	0.179
1-11 years	2,400/14,282 (16.8%)	1,397/8,773 (15.9%)	1,003/5,509 (18.2%)	0.87 (0.80-0.96)	13% (4-20)	< 0.001
Influenza B						
1-2 years	51/ 2,478 (2.1%)	34/1,645 (2.1%)	17/ 833 (2.0%)	1.01 (0.56-1.82)	−1% (−82-44)	0.966
3-5 years	190/ 3,823 (5.0%)	110/2,522 (4.4%)	80/1,301 (6.1%)	0.71 (0.53-0.95)	29% (5-47)	0.016
6-11 years	705/ 7,981 (8.8%)	415/4,606 (9.0%)	290/3,375 (8.6%)	1.05 (0.90-1.23)	−5% (−23-10)	0.516
1-11 years	946/14,282 (6.6%)	559/8,773 (6.4%)	387/5,509 (7.0%)	0.91 (0.79-1.04)	9% (−4-21)	0.126

*Vaccinated group include those who were vaccinated at least once in each influenza season.

Vaccine effectiveness

The overall vaccine effectiveness against influenza A virus in children from 1-11 years of age in Isahaya City, was 23% (95% CI: 14%-31%) in the 2011/12 season and 13% (95% CI: 4%-20%) in the 2012/13 season, with statistical significance (Table 2). In the 2011/12 season, vaccine effectiveness against influenza A virus was apparent in 1-5 years [1-2 years: 55% (95% CI: 40%-66%); 3-5 years: 32% (95% CI: 17%-45%)]. However, there was no significance in those aged 6-11 years [8% (95% CI: −7%-21%)]. Similarly, in the 2012/13 season, vaccine effectiveness against influenza A virus was apparent in 1-5 years [1-2

Table 3. Route of transmission of influenza virus infection by age group in 2011/12 and 2012/13 season.

Route of transmission*	2011/12 season			2012/13 season		
	1-2 years (n = 293)	3-5 years (n = 628)	6-11 years (n = 1,431)	1-2 years (n = 427)	3-5 years (n = 855)	6-11 years (n = 2,064)
At home	78 (26.6%)	110 (17.5%)	177 (12.4%)	113 (26.5%)	181 (21.2%)	284 (13.8%)
At school/preschool	140 (47.8%)	383 (61.0%)	1,015 (70.9%)	185 (43.3%)	452 (52.9%)	1,387 (67.2%)
At the crowded place	7 (2.4%)	10 (1.6%)	40 (2.8%)	12 (2.8%)	29 (3.4%)	45 (2.2%)
Other/Unknown	68 (23.2%)	125 (19.9%)	199 (13.9%)	117 (27.4%)	193 (22.6%)	348 (16.9%)

*Interview was conducted to each patient or patient's parent chose a single answer where they thought they got infected with influenza virus from a set of multiple choices; at home, at school/preschool, at the crowded place, or the other including unknown.

years: 19% (95% CI: −1%-35%); 3-5 years: 20% (95% CI: 5%-33%)], but no significant effect was found in those aged 6-11 years [6% (95% CI: −5%-17%)].

The overall vaccine effectiveness in children against influenza B was 20% (95% CI: 8%-31%) in the 2011/12 with statistical significance. However, it was not significant in the 2012/13 season at 9% (95% CI: −4%-21%). In the 2011/12 season, the vaccine effectiveness against influenza B virus was apparent in 1-5 years [1-2 years: 40% (95% CI: −1%-65%); 3-5 years: 31% (95% CI: 2%-52%)], but there was no significance in 6-11 years [3% (95% CI: −14%-18%)]. In the 2012/13 season, vaccine effectiveness against type B was apparent in 3-5 years [29% (95% CI: 5%-47%)]. However, there was no significance for those under 2 years [−1% (95% CI: −82%-44%)] and more than 6 years [−5% (95% CI: −23%-10%)].

Route of transmission

Majority of patients (65.4% in the first season and 60.5% in the second season) replied that they thought they contracted the infection either at their school or preschool, and the rates increased with age (47.8% at 1-2 years, 61.0% at 3-5 years, and 70.9% at 6-11 years in the 2011/12 season, and 43.3%, 52.9% and 67.2%, respectively, in the 2012/13 season) (Table 3). In contrast, those who replied they contracted the infection at home reduced by age group (26.6% at 1-2 years, 17.5% at 3-5 years, 12.4% at 6-11 years in the 2011/12 season, and 26.5%, 21.2% and 13.8%, respectively, in the 2012/13 season). These results suggested that the school and the preschool are an important source of infection among children.

Virological confirmation of circulating strains

A total of 11 and 25 influenza isolates in the 2011/12 and the 2012/13 seasons, respectively, were obtained from influenza patients diagnosed using rapid test kits at the sentinel pediatric clinic in Isahaya City. Of the 11 isolates obtained in the 2011/12 season, 5 were influenza A (H3N2) and 6 were influenza B. Of the 6 of influenza B isolates, 4 (66.7%) belonged to the Victoria-lineage viruses, and the rest 2 (33.3%) were in Yamagata-lineage. Of the 25 isolates in the 2012/13 season, 18 were influenza A (H3N2) and 7 were influenza B. All influenza B isolates belonged to the Yamagata-lineage viruses. Influenza A (H1N1) pdm09 was not detected during either season.

Discussion

This study was conducted during two consecutive seasons in a community involving a total of 28,884 children-years in Japan. The trivalent influenza vaccine demonstrated a significant protective effect against both influenza A and B infections in the 2011/12 season and against influenza A infections in the 2012/13 season. Stratified by age, vaccine effectiveness was higher for younger children aged less than 6 years compared with those in children 6 years old and over, for both types of influenza infections during two seasons.

In Japan, some studies reported on influenza vaccine effectiveness but only a few found significant protective effects. A significant vaccine efficacy of 52% in influenza A and 59% in influenza B were found during 6 consecutive seasons diagnosed using rapid test kits among children less than 6 years in a community in Japan (Katayose et al. 2011). Other studies that estimated vaccine effectiveness among children in Japan during a single influenza season was to be 24%-44% (Fujieda et al. 2008; Ochiai et al. 2009; Yamaguchi et al. 2010). However, some vaccine effectiveness studies showed no statistical significance (Ohkuma et al. 2002; Maeda et al. 2004). One of the strengths of this study is that our investigation had larger sample size (28,884 children-years) than other vaccine effectiveness studies in Japan (346-14,788 children-years) (Ohkuma et al. 2002; Maeda et al. 2004; Fujieda et al. 2008; Ochiai et al. 2009; Yamaguchi et al. 2010; Katayose et al. 2011). To evaluate vaccine effectiveness, the community cohort that involved the entire local city area like this study is essential.

Although the vaccine dose has been doubled, our study demonstrated lower vaccine effectiveness, compared to the previous reports. There are several reasons for lower vaccine effectiveness. There was a mismatch between the circulating influenza strains and the vaccine strain in the 2011/12 season in Japan. According to the antigenic analysis of influenza A (H3N2) circulated in Japan in 2011/12 season, 34% had an eight-fold or greater reduction in hemagglutination-inhibition titer compared with the vaccine virus (Infectious Disease Surveillance Center, National

Institute of Infectious Diseases 2012). Of all the Influenza B strains collected in Japan, two-thirds belonged to the Victoria lineage, contained the trivalent influenza vaccine in the 2011/12 season, whereas the remainder belonged to the Yamagata lineage (Infectious Disease Surveillance Center, National Institute of Infectious Diseases 2012). The proportion of the Victoria lineage and the Yamagata lineage was almost same in Isahaya City. Thus, for both subtypes A (H3N2) and B, antigenic differences may have existed between the circulating and vaccine strains in 2011/12 season, and this may be the reason for lower vaccine effectiveness.

For the 2012/13 season, the decreased effectiveness of A (H3N2) may be explained by a mismatch between egg-derived vaccine strain and circulating strains (Infectious Disease Surveillance Center, National Institute of Infectious Diseases 2013, WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research 2013). According to the reports, 94% of circulated A(H3N2) showed 8-16 times reductions of hemagglutination-inhibition titer compared to egg-derived vaccine strain, A/Victoria/361/2011. In contrast, the MDCK isolated vaccine strain (A/Victoria/361/2011) matched with the circulating strains. This can be the reason for the lower vaccine effectiveness for influenza A in the second season due to antigenic mismatch. For influenza B, there was no antigenic difference in the 2012/13 season, having both vaccine and circulating strains to be in Yamagata lineage. However, the vaccine effectiveness was lower than the 2011/12 season. It is conceivable that children who were infected in the previous season have already obtained an antibody against the strains in the following season of the same antigenicity. The certain immune level by infections, which surpass the responses induced by vaccination, was already obtained in both vaccinated and unvaccinated groups. As a result, it led to lower vaccine effectiveness in the season because of a smaller difference between vaccinated and unvaccinated groups in terms of proportions of subjects who had protective antibody levels.

For influenza B, the vaccine effectiveness was generally lower than influenza A for both seasons. In some of the previous Japanese reports, vaccine effectiveness for influenza B was lower than influenza A (Sugaya et al. 1994) or did not show statistical significance even though the vaccine strain and the circulating strains matched (Yamaguchi et al. 2010). The comprehensive reasons remained unknown, but one of the explanations from our study is that the incidence rate was always higher in the school-age children compared to the younger children with influenza B for the two seasons. Age stratified vaccine effectiveness showed that the protection is smaller in the school-age children compared to the younger children. It may be the reason for the diminished vaccine effectiveness for influenza B.

Age-stratified estimation showed that vaccine effectiveness was superior in younger children over both seasons and for both virus types. In general, young children with no detectable antibody to influenza are less likely to develop immunologic response to the influenza vaccine than are older children with a preexisting antibody (Hurwitz et al. 2000; Jefferson et al. 2012). However in this study, children less than 6 years of age had benefited from improved effectiveness compared with school-age children. One of the reasons for children less than 6 years showed significant vaccine effectiveness is that younger children have a higher vaccination coverage rate. High vaccination coverage rate reduces the risk of infection due to herd effect (Van Vlaenderen et al. 2013). In addition, children aged less than 6 years could have less chance of infection than school-age children. It is presumed that school-age children have a wider range of activities and a higher frequency of contact with other children at school, compared with younger children who are likely to stay at home with less contact often limited to their guardians. According to the question for the route of transmission, as children grow older, the opportunity for contracting infection at their school increased. School-age children spend more time with other children at school (Vazquez-Prokopec et al. 2013). As they contact with others more frequently at school, they would be exposed more to virus and have more chance of infection for both vaccinated and unvaccinated groups. Thus, the vaccine effectiveness in school-age children may be diminished. The increase of vaccination dose for children is a probable cause of significant vaccine effectiveness for children less than 6 years, although we were not able to estimate the effectiveness before the change of vaccination dose.

Apart from vaccine effectiveness, the vaccination coverage gradually decreased with advancing age. Cost of subsidy for children in Isahaya City was the same from infants until the graduation of elementary school. In a previous study conducted among children, the vaccination coverage rate was 41.6% for children aged from 6-23 months and 26.1% for those aged 2-8 years (Ritzwoller et al. 2005). One of the reasons for the lower vaccination rate in older children was that their parents tended to visit the pediatric facilities less frequently and get less information about influenza vaccination (Ando 2012). Furthermore, it was reported that as the children get older, some parents believe that their children are already immune to influenza infections (Toyoshima 2012). For these reasons, higher age children withhold of vaccination and the vaccination coverage decreased with age.

This study has several limitations. Firstly, the study was not double-blind or randomized by design and choice of vaccinated or non-vaccinated was self-selected by parents. Thus, some bias could be introduced if the behavior of seeking medical care was different between vaccinated and unvaccinated. It is likely that those who did not go to vaccination tend not to consult with medical facilities even though they developed ILI. This may lead to underestimation of the vaccine effectiveness. Secondly, vaccination registration included only information of vaccinees. Thus the number of unvaccinated was calculated by the differences in number of vaccinees and the city census population. No authentic figures of unvaccinated group could be obtained. Thirdly, missed influenza cases in the community may have existed. Although all pediatric facilities in the city participated in the registration program, a certain number of children may have not consulted to the facilities due to low motivation for medical seeking, or they consulted to the facilities for medical care in other towns adjacent to the Isahaya City. Fourthly, bias may occur while estimating vaccine effectiveness with case findings using the rapid diagnosis test kits due to the relative lack of sensitivity and specificity compared with those using molecular techniques (Orenstein et al. 2007). If the number of patients with ILI was large in the season, more children were likely to have been misclassified, which have caused the bias in the estimation of vaccine effectiveness (Hirota et al. 2008). Because we could not obtain the data on the number of children who were vaccinated in Isahaya city before the increase of vaccine dose for children, we were not able to estimate the effectiveness before the change. In addition, in this study, it was unknown whether children less than 6 years attended preschools or day cares. The vaccine effectiveness might be variable, depending on the attendance of day cares or staying at home in terms of the chance of contact, although we could not obtain the relevant information.

In conclusion, a significant protective effect was found for children 1-11 years of age with trivalent influenza vaccine over two consecutive seasons. Of note, vaccine effectiveness was higher in influenza A compared to influenza B and protection was higher in infants than older children. Our community study encourages vaccination prior to influenza seasons to protect children from influenza infections. We plan to continue this study in the same cohort and to investigate other areas in Japan to monitor the effectiveness of the vaccination.

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Conflict of Interest

The authors declare no conflict of interest.

References

Ando, Y. (2012) The questionnaire survey for guardians about Haemophilus influenza type b conjugated vaccine and 7-valent pneumococcal conjugated vaccine. *J. Natl. Inst. Public Health*, **61**, 492-493 (in Japanese).

Centers for Disease Control and Prevention (2012) Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2012-13 influenza season. *MMWR Morb. Mortal. Wkly. Rep.*, **61**, 613-618.

Clemens, J., Brenner, R., Rao, M., Tafari, N. & Lowe, C. (1996) Evaluating new vaccines for developing countries. Efficacy or effectiveness? *JAMA*, **275**, 390-397.

Clemens, J.D. & Shapiro, E.D. (1984) Resolving the pneumococcal vaccine controversy: are there alternatives to randomized clinical trials? *Rev. Infect. Dis.*, **6**, 589-600.

Dapat, I.C., Dapat, C., Baranovich, T., Suzuki, Y., Kondo, H., Shobugawa, Y., Saito, R. & Suzuki, H.; Japanese Influenza Collaborative Study Group (2012) Genetic characterization of human influenza viruses in the pandemic (2009-2010) and post-pandemic (2010-2011) periods in Japan. *PLoS One*, **7**, e36455.

Fujieda, M., Maeda, A., Kondo, K., Fukushima, W., Ohfuji, S., Kaji, M. & Hirota, Y. (2008) Influenza vaccine effectiveness and confounding factors among young children. *Vaccine*, **26**, 6481-6485.

Health Service Bureau, Ministry of Health, Labour and Welfare (2011) For stable supply measures of influenza vaccine. [*Cited*: August 8, 2011]
http://www.jshp.or.jp/cont/11/0812-2.pdf
[*Accessed*: January 15, 2014] (in Japanese).

Hirota, Y., Fukushima, W., Fujieda, M., Ohfuji, S. & Maeda, A. (2008) Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: a Japanese perspective. *Vaccine*, **26**, 6455-6458.

Hurwitz, E.S., Haber, M., Chang, A., Shope, T., Teo, S.T., Giesick, J.S., Ginsberg, M.M. & Cox, N.J. (2000) Studies of the 1996-1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infection, and clinical effectiveness. *J. Infect. Dis.*, **182**, 1218-1221.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases (2012) Analysis of influenza virus isolates in 2011-12 season. *Infectious Agents Surveillance Report*, **33**, 288-294 (in Japanese).

Infectious Disease Surveillance Center, National Institute of Infectious Diseases (2013) Analysis of influenza virus isolates in 2012-13 season. *Infectious Agents Surveillance Report*, **34**, 328-334 (in Japanese).

Jefferson, T., Rivetti, A., Di Pietrantonj, C., Demicheli, V. & Ferroni, E. (2012) Vaccines for preventing influenza in healthy children. *Cochrane Database Syst. Rev.*, **8**, CD004879.

Katayose, M., Hosoya, M., Haneda, T., Yamaguchi, H., Kawasaki, Y., Sato, M. & Wright, P.F. (2011) The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons. *Vaccine*, **29**, 1844-1849.

Kimura, Y., Saito, R., Tsujimoto, Y., Ono, Y., Nakaya, T., Shobugawa, Y., Sasaki, A., Oguma, T. & Suzuki, H. (2011) Geodemographics profiling of influenza A and B virus infections in community neighborhoods in Japan. *BMC Infect. Dis.*, **11**, 36.

Kubo, N., Ikematsu, H., Nabeshima, S., Yamaji, K., Nabeshima, A., Kondou, H., Chong, Y., Kashiwagi, S. & Hayashi, J. (2003) Evaluation of an immunochromatography test kit for rapid diagnosis of influenza. *The Journal of the Japanese Association for Infectious Diseases*, **77**, 1007-1014 (in Japanese).

Maeda, T., Shintani, Y., Nakano, K., Terashima, K. & Yamada, Y. (2004) Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. *Pediatr. Int.*, **46**, 122-125.

Mitamura, K., Yamazaki, M., Ichikawa, M., Kimura, K., Kawakami, C., Shimizu, H., Watanabe, S., Imai, M., Shinjo, M., Takeuchi, Y. & Sugaya, N. (2004) Evaluation of an immunochromatography test using enzyme immunoassay for rapid detection of influenza A and B viruses. *The Journal of the Japanese Association for Infectious Diseases*, **78**, 597-603 (in Japanese).

Ochiai, H., Fujieda, M., Ohfuji, S., Fukushima, W., Kondo, K., Maeda, A., Nakano, T., Kamiya, H. & Hirota, Y.; Influenza

Vaccine Epidemiology Study Group (2009) Inactivated influenza vaccine effectiveness against influenza-like illness among young children in Japan: with special reference to minimizing outcome misclassification. *Vaccine*, **27**, 7031-7035.

Ohkuma, K., Teramoto, Y., Fukuta, M., Takahashi, H., Yano, T., Sugiyama, A., Nakayama, O. & Kamiya, H. (2002) Efficacy and safety of influenza vaccine for infants in Mie Prefecture in 2000/2001 prevalent season. *Annual Report of Mie Prefecture Health and Environment Research Institute*, **4**, 86-93 (in Japanese).

Orenstein, E.W., De Serres, G., Haber, M.J., Shay, D.K., Bridges, C.B., Gargiullo, P. & Orenstein, W.A. (2007) Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int. J. Epidemiol.*, **36**, 623-631.

Osterholm, M.T., Kelley, N.S., Sommer, A. & Belongia, E.A. (2012) Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect. Dis.*, **12**, 36-44.

Palache, A. (2011) Seasonal influenza vaccine provision in 157 countries (2004-2009) and the potential influence of national public health policies. *Vaccine*, **29**, 9459-9466.

Ritzwoller, D.P., Bridges, C.B., Shetterly, S., Yamasaki, K., Kolczak, M. & France, E.K. (2005) Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. *Pediatrics*, **116**, 153-159.

Sugaya, N., Nerome, K., Ishida, M., Matsumoto, M., Mitamura, K. & Nirasawa, M. (1994) Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. *JAMA*, **272**, 1122-1126.

Toyoshima, Y. (2012) How the novel influenza (pandemic 2009) can influence the attitudes of elementary and junior high school students toward vaccination. *Jpn. J. Public Health*, **59**, 390-398 (in Japanese).

Van Vlaenderen, I., Van Bellinghen, L.A., Meier, G. & Nautrup, B.P. (2013) An approximation of herd effect due to vaccinating children against seasonal influenza: a potential solution to the incorporation of indirect effects into static models. *BMC Infect. Dis.*, **13**, 25.

Vazquez-Prokopec, G.M., Bisanzio, D., Stoddard, S.T., Paz-Soldan, V., Morrison, A.C., Elder, J.P., Ramirez-Paredes, J., Halsey, E.S., Kochel, T.J., Scott, T.W. & Kitron, U. (2013) Using GPS technology to quantify human mobility, dynamic contacts and infectious disease dynamics in a resource-poor urban environment. *PLoS One*, **8**, e58802.

Weinberg, G.A. & Szilagyi, P.G. (2010) Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J. Infect. Dis.*, **201**, 1607-1610.

WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research (2013) September 2013 interim report.
http://www.nimr.mrc.ac.uk/documents/about/NIMR-report-Sep2013final.pdf
[*Accessed*: January 15, 2014].

World Health Organization (2009) Influenza fact sheet No. 211. April 2009.
http://www.who.int/mediacentre/factsheets/fs211/en/index.html.
[*Accessed*: October 31, 2013].

Yamaguchi, S., Ohfuji, S. & Hirota, Y. (2010) Influenza vaccine effectiveness in primary school children in Japan: a prospective cohort study using rapid diagnostic test results. *J. Infect. Chemother.*, **16**, 407-413.

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特集 インフルエンザ ーその現状と対応ー

1．インフルエンザ流行の世界的動向

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インフルエンザの流行はパンデミックインフルエンザだけでなく，季節性インフルエンザも世界規模で流行が起きる。温帯地域では冬から春にかけて流行が起きるが，熱帯・亜熱帯地域では1年を通してインフルエンザウイルスが検出される。近年，このような熱帯・亜熱帯地域が新たなインフルエンザウイルスの変異株が発生する場所として注目されてきている。インフルエンザの流行状況を正しく理解するためには世界規模でインフルエンザをモニタリングする必要がある。インフルエンザサーベイランスネットワークは急速に充実しつつあり，インフルエンザ流行が世界規模で解析できる体制が整いつつある。

Key Words：インフルエンザ／WHO／グローバルサーベイランス

I はじめに

インフルエンザは人類にとってもっとも罹患率の高い急性感染症である。季節性インフルエンザの流行でも毎年，人口の5～15%程度が罹患しているとされており，パンデミックインフルエンザでは人口の20～30%が罹患すると考えられている。また，パンデミックインフルエンザだけでなく，季節性インフルエンザも同じようなウイルスが世界規模の流行を起こすことが知られている。

しかし，従来，インフルエンザの疫学的・ウイルス学的データは温帯地方に位置する先進国からのものがほとんどであり，世界規模でのインフルエンザの疫学にはまだ不明な点が多く残されている。

近年，アジア，中南米，中近東などの多くの国でインフルエンザサーベイランスが行われるようになり，世界規模でのインフルエンザの理解が深まってきている。

II グローバルサーベイランスネットワーク

世界規模でのインフルエンザの発生状況をモニタリングしているのがWHO（世界保健機関）のGlobal Influenza Surveillance and Response System (GISRS) である。これは，Global Influenza Surveillance Network (GISN) をその前身としており，もともとのネットワークは1952年に確立されたものである。現在では106の国と地域にある136のNational Influenza Centerと，わが国の感染症研究所を含む6つのWHO協力センターがこのネットワークを形成している（図1）[1]。

このGISRSの目的は世界規模でインフルエンザの流行状況および流行ウイルスの解析をすることで，ワクチン株の選定やパンデミックインフルエンザのリスクを評価することである。これらの結果はホームページでリアルタイムに発表されるようになっており（図2），世界中でどのようなウイルスが流行しているかが常にモニタリングでき

Global epidemiology of influenza

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