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Field Study

An Effective Quarantine Measure Reduced the Total Incidence of Influenza A H1N1 in the Workplace: Another Way to Control the H1N1 Flu Pandemic

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Abstract: An Effective Quarantine Measure Reduced the Total Incidence of Influenza A H1N1 in the Workplace: Another Way to Control the H1N1 Flu Pandemic: Koichi Miyaki, *et al.* Department of Clinical Research and Informatics, National Center for Global Health and Medicine—Objectives: To evaluate the effectiveness of a non-vaccine quarantine measure against pandemic influenza A H1N1 in workplaces. **Methods:** Design was quasi-cluster randomized controlled trial in two sibling companies (Cohort 1 n=6,634, Cohort 2 n=8,500). The follow-up period was from July 1st, 2009 to February 19th, 2010 (233 days). Intervention was voluntary waiting at home on full pay if the family became Influenza like Illness (ILI). The incidences of influenza A H1N1 and those of the subgroups whose families got ILI in both cohorts were compared by a Cox regression model and log-rank test. **Results:** There were 189 and 270 workers who got H1N1 infection during the follow-up period in each cohort. In this period 317 workers in Cohort 1 were asked to wait at home for several days (100% obeyed). The intervention group (Cohort 1) showed a statistically significant lower risk (p for log-rank test=0.033) compared with the control (Cohort 2), and the hazard ratio of the intervention was 0.799 [0.658–0.970] after adjusting for age, sex, BMI and smoking status. The workers who were asked to wait at home showed H1N1 infection more frequently (49 out of 317) compared with the workers whose family got ILI but were not asked to wait and work regularly (77 out of 990, RR=2.17 [1.48–3.18]). **Conclusions:** The waiting on full pay policy in the workplace reduced the overall risk of influenza A H1N1 by about 20% in one flu season in Japan. This kind of non-vaccine measure will be a promising option in workplaces to control the next flu pandemic.
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Key words: Controlled trial, H1N1, Influenza, Pandemic, Prevention, Quarantine

One year has passed since a novel swine-origin influenza A H1N1 virus was isolated in Mexico and the USA in April 2009[1)]. The virus spread all over the world and the WHO (World Health Organization) raised the pandemic alert level to phase 6 in June 2009[2)]. As of August 1, 2010, more than 214 countries and overseas territories or communities have reported laboratory-confirmed cases of pandemic influenza H1N1 2009, and over 18,449 deaths have been reported worldwide[4)]. Since August 10, 2010, the pandemic alert level had been in the highest phase. In Japan, influenza activity continued to decrease towards seasonal baselines in February 2010, and the number of cases reported per sentinel in Japan (consisting of approximately 3,000 pediatric and 1,800 internist hospitals/clinics around the country) was less than 1 in the first week of March 2010[5)].

Although122 persons died as a result of this virus by December 15, 2009[6)], we got over the first flu season under the pandemic of influenza A H1N1 last year.

In such a situation, development of strategies for mitigating the severity of a new influenza pandemic is a top global public health priority[7)]. Last year, we focused our attention on the fact that being a member of a household with a flu case is the largest single risk factor for being infected oneself [8, 9)]. So we invented a feasible quarantine measure for workplaces and applied it to a large Japanese company in the car industry from September

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2009, and followed up the cohort with a control until February 2010. In this report, we will introduce our preventive intervention in Japanese workplaces and verify the effectiveness of our intervention statistically in order to cope with the next flu pandemic.

Methods

The study participants were 15,134 general employees (age, 19–72 yr old in 2009) of two sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to be the workplace were included, regardless of treatment for chronic diseases. All of the workers in these two companies were covered by the same health insurance society, underwent the same medical checkup every year and were followed up in the same way.

The intervention involved asking workers whose family members developed an influenza-like illness (ILI) to stay at home. If any co-habitating family members showed signs of ILI, employees of one company (intervention group, Cohort 1, n=6,634) were asked to stay at home voluntarily until 5 days had passed since the resolution of ILI symptoms or 2 days after alleviation of fever. The company paid full wages during this time. ILI was defined as a body temperature greater than 38°C or more than 1°C above the normal temperature accompanied with more than two of these symptoms: nasal mucus, pharyngeal pain, cough, chills or heat sensation. To ensure the validity of the diagnosis, the following measures were taken by the health management department:

1) Each day before leaving work body temperature was measured and whether the employees had the symptoms mentioned above was recorded.

2) If the symptoms of a worker met the ILI case definition, he/she was asked to report this to the company and stay at home.

3) If it was doubtful whether the symptoms met the ILI case definition, the industrial physicians made a judgmental decision.

4) Whether a stay-home order could be canceled was decided according to the record of the employees staying at home. If the standard for cancelling a stay-home order was not met, or the judgment was not made strictly, the employee could not return to work.

The standard for cancelling a stay-home order was established strictly as follow:

a. Swine-origin influenza virus (S-OIV) infection ruled out by a doctor even though the ILI case definition was met, or the doctor provided a definite diagnosis that the employee who was ill could go to work.

b. Even though a doctor had not made a definite diagnosis of S-OIV infection, a stay-home order could not be canceled until five days after the onset of the symptoms mentioned in the ILI case definition or until after a two-day observation period after defervescence.

Moreover, even if the result of a fast diagnostic kit was negative, if a doctor did not make a definite diagnosis of other illness, a stay-home order could not be canceled until five days after the onset of the symptoms mentioned in the ILI case definition or until after a two-day observation period after defervescence.

Employees at the other company (control group, Cohort 2, n=8,500) did not participate in the intervention and reported to work as usual even if a co-habitating family member developed ILI. The follow-up period was from July 1, 2009 to February 19, 2010 (233 days).

The objective of this study was to statistically verify the effectiveness of the intervention from the viewpoint of suppressing the H1N1 pandemic in workplaces. The measured outcome was the incidence of influenza A H1N1 in the two cohorts. Company doctors diagnosed the disease through a positive result of an influenza A test or clinical symptoms. Compliance with the intervention was confirmed in Cohort 1 (the intervention group). Though there was no intervention in Cohort 2 (the control group), workers in this group whose family members did or did not develop ILI were also recorded.

The study design was a quasi-cluster randomized controlled trial.

The sample size was set on the assumption that the incidence of influenza A H1N1 during the season was 0.05. Because the intervention suppressed the incidence by 20%, 3,189 subjects per group were needed for the log-rank test with a two-sided alpha of 0.05 and an 80% statistical power[10]. If the incidence was 0.05 and our intervention suppressed the influence by 15%, 5,902 subjects per group were needed for the same alpha and beta level.

As for statistical methods, Kaplan-Meier plots and the log-rank test were used to compare the cumulative incidences of influenza A H1N1 in the two cohorts. The Cox regression model was used to estimate the hazard ratio and for multivariable adjustment. Proportions were compared by Fisher's exact test. All statistical analyses were performed using SPSS for Windows version 17.0 (Statistical Product and Service Solutions, Chicago, IL, USA), and statistical significance was accepted for a two-tailed $p<0.05$. No interim analysis was performed.

Results

Participant flow was quite simple. The follow-up period was from July 1, 2009 to February 19, 2010; all 15,134 workers were followed up during the period, and none were lost to follow-up. By the end of the follow-up period, 459 (3.03%) of the 15,134 workers experienced H1N1 infection. No one died, and no one was infected more than once. Three hundred and seventeen workers in Cohort 1 whose family members had ILI were asked to stay at home, and none declined to follow the intervention protocol (i.e., the compliance rate was 100%). All cases are included in the analysis, so the flow chart of participant flow has been

Table 1. Baseline characteristics of all the subjects and the subjects of the intervention (Cohort 1) and control groups (Cohort 2)

	Total subjects (N=15,134)	Intervention group (Cohort 1) (n=6,634)	Control group (Cohort 2) (n=8,500)
Male/Female	14,093/1,041	6,263/371	7,830/670
Age (yr)	40.9 ± 10.0	41.9 ± 11.0	40.0 ± 9.1
Height (cm)	170.2 ± 6.6	169.5 ± 6.6	170.7 ± 6.6
Weight (kg)	67.4 ± 11.2	66.8 ± 11.3	68.0 ± 11.0
BMI (kg/m^2)	23.2 ± 3.3	23.2 ± 3.4	23.3 ± 3.2
Systolic blood pressure (mmHg)	123.0 ± 14.3	126.7 ± 16.3	120.0 ± 11.8
Diastolic blood pressure (mmHg)	74.7 ± 10.6	74.9 ± 12.2	74.6 ± 9.1
Total cholesterol (mg/d*l*)	206.8 ± 32.6	210.0 ± 31.0	206.0 ± 32.9
Triglycerides (mg/d*l*)	141.3 ± 107.3	150.5 ± 111.9	130.3 ± 100.3
HDL-cholesterol (mg/d*l*)	57.6 ± 14.2	56.8 ± 14.7	58.5 ± 13.5
LDL-cholesterol (mg/d*l*)	123.1 ± 28.8	120.9 ± 29.4	125.1 ± 28.0
Blood urea nitrogen (mg/d*l*)	13.7 ± 3.5	13.8 ± 3.6	13.7 ± 3.4
Creatinine (mg/d*l*)	0.8 ± 0.4	0.8 ± 0.3	0.9 ± 0.5
GOT (IU/*l*)	23.2 ± 13.5	22.3 ± 9.4	24.2 ± 17.0
GPT (IU/*l*)	27.0 ± 18.6	26.0 ± 18.0	28.2 ± 19.1
γ-GTP (IU/*l*)	45.2 ± 53.4	42.3 ± 45.5	48.7 ± 61.4
Uric acid (mg/d*l*)	5.9 ± 1.3	5.8 ± 1.4	6.0 ± 1.2
Under hypertension treatment (%)	6.66	8.82	4.89
Under diabetes treatment (%)	2.05	2.83	1.40
Under hyperlipidemia treatment (%)	4.07	4.28	3.91
Current smoking (%)	39.8	46.4	34.4

Data are presented as the mean ± SD or percentage. The total subjects were from two sibling companies and divided into two groups: one company was assigned as the intervention group (Cohort 1), in which the workers were asked to wait at home voluntarily on full pay if the family of the worker got an influenza-like illness (ILI); the other company was assigned as the control group (Cohort 2). All of the workers in Cohort 1 obeyed the instructions of this intervention.

omitted.

The basic characteristics of the subjects, as well as respective characteristics of the subjects in the intervention group (Cohort 1, n=6,634) and the control group (Cohort 2, n=8,500), are shown in Table 1. The mean ages (± SD) of the two groups were 41.9 ± 11.0 and 40.0 ± 9.1, the male-to-female ratios were 6,263/371 and 7,830/670, and the mean BMI values were 23.2 ± 3.4 and 23.3 ± 3.2, respectively. The characteristics of the two groups were statistically similar.

Next, the incidences of influenza A H1N1 were compared between the two groups during the intervention period. At the end of the follow-up period, 189 subjects in Cohort 1 and 270 in Cohort 2 were diagnosed as having contracted influenza A H1N1. The proportions of infectors in the two groups were 2.75% and 3.18%, respectively. As shown in Figure, the cumulative disease-free survival rate of Cohort 1 was higher during the intervention and follow-up period. The intervention group showed a significantly lower risk by time series analysis, and the p value for the log-rank test, adjusted for age, sex, BMI and smoking status was 0.033.

The Cox regression model was used to assess the impact of the intervention on influenza A H1N1 infection (Table 2). Briefly, the intervention group had about a 20% lower risk of infection than the control group. The hazard ratio was 0.799 (95% CI: 0.658–0.970; p=0.023). Age was also associated with infection risk; younger persons were more easily infected (p<0.001). Female sex, higher BMI and being a current smoker were also related with a higher infection rate, but these differences did not reach statistical significance.

Thus, these results indicated that the overall risk for influenza A H1N1 infection in the workplace was significantly reduced by the intervention. However, as an important adverse event, attention should be paid to the excess risk in workers who obeyed the intervention and maintained close contact with infected family members. Thus, the incidence of influenza A H1N1 for workers whose family members developed ILI was compared between the two cohorts. In the intervention group, 49 workers were infected out of a total of 317 asked to stay

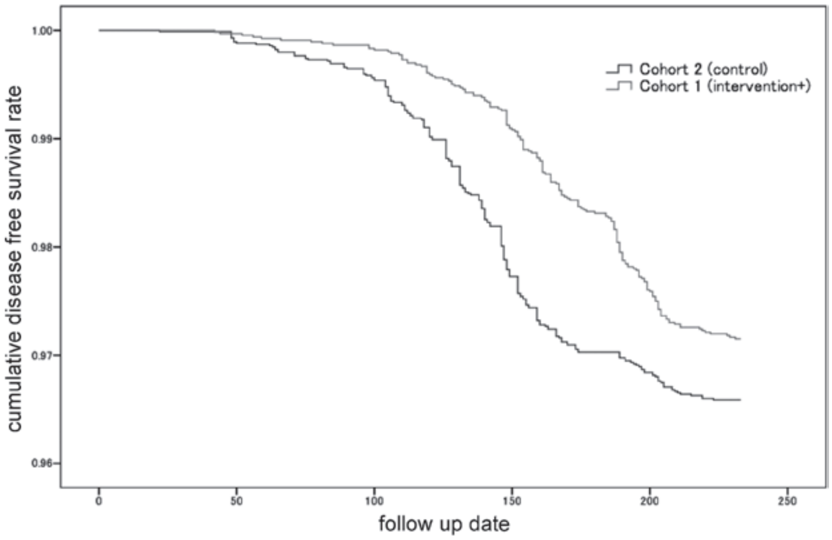

Figure. Comparison of the cumulative incidences of influenza A H1N1 between two cohorts. This Kaplan-Meier Plots show the cumulative disease free survival rates of Cohort 1 and Cohort 2. At the end of this follow-up, 189 of 6,634 (2.85%) and 270 of 8,500 (3.18%) subjects were infected in Cohort 1 and 2, respectively. p value for the log-rank test is 0.033, and the hazard ratio of the intervention is 0.799 [0.658–0.970], adjusted for age, sex, BMI and smoking status.

Table 2. Odds ratios for the infection of influenza A H1N1 in the intervention group (Cohort 1) compared with the control group (Cohort 2)

	Odds ratio	95% confidence interval	*p* value
Intervention	0.799	0.658–0.970	0.023
Age	0.957	0.947–0.966	<0.001
Sex	0.993	0.696–1.417	0.970
BMI	1.024	0.996–1.053	0.100
Smoking	1.041	0.854–1.268	0.693

The odds ratios (ORs) and p values were derived from a Cox regression model adjusted for age, sex, BMI and smoking. In the sex item, female is the referent group; as for the smoking item, non-current smoker is the reference. The proportionalities of hazards are satisfied.

Table 3. Comparison of the incidences of influenza A H1N1 between the close contact subgroups of the two cohorts

	Total number	Number of infection	*p* value	Relative risk (95%CI)
Workers whose family got ILI in Cohort 1	317	49	<0.001	2.17 [1.48–3.18]
Workers whose family got ILI in Cohort 2	990	77		

p value is derived from Fisher's exact test. The former indicates workers who were asked to be absent from work in Cohort 1, and all of them obeyed this instruction. The latter indicates workers who were not asked to be absent and worked regularly in Cohort 2. The incidences of influenza A H1N1 of the former and the latter were 15.5% and 7.8%, respectively.

at home. In the control group, 990 workers had infected family members but continued to work regularly, and 77 were confirmed to be infected themselves. As shown in Table 3, the relative risk of infection was 2.17-fold higher in the intervention group than in the control group (p<0.001).

Discussion

The main results of the study (Figure and Table 2) indicate that the policy of staying at home on full pay reduced the overall risk of influenza A H1N1 infection in the workplace by about 20% in one flu season. Fortunately, all 459 infected workers recovered without any deaths. We think this was by the grace of a kind of "healthy workers' effect".

There was a plateau in the Kaplan-Meier curve of Cohort 1 between day 182 and day 186, and the curve of Cohort 2 also changed little during the same time. This may be attributable to the New Year holidays in Japan, as many people stayed home and did not seek treatment.

Table 2 also shows that age significantly affected the risk of infection in addition to the intervention. Younger individuals seemed to be more prone to infection. These findings are compatible with a study that indicated that pre-existing antibodies in the elderly protect against H1N1 infection[11]. Another reasonable explanation might be that young people are more active in their daily lives than the older people and therefore have more opportunity to contract a viral infection.

Ancillary analysis (Table 3) showed that workers who obeyed the intervention were exposed to twice the risk of infection despite being careful not to be infected. Closer contact with infected family members may explain this additional risk.

The current study revealed that asking employees whose family members have contracted ILI to stay at home reduced the overall incidence of influenza A H1N1 in the workplace. However, subjects who obeyed the intervention and were absent from work showed an increased risk of infection compared with those who worked as usual. The self-sacrifice of these workers may have produced the overall decrease in H1N1 infection observed in the community in this study.

Ferguson NM *et al.* pointed out that household quarantine is effective at reducing attack rates in the community, but only if compliance is high[7]. We also think keeping a high compliance rate is very important. Our intervention was not compulsory; we only asked the employees to leave the workplace for a while on full pay, and we succeeded in getting all workers' agreement. In our case, explaining that the home waiting policy might be beneficial to the whole workers and help to avoid stopping the manufacturing lines (explaining it is for the benefit of the public) and guaranteeing payment during the leave (financial support) helped them to obey our request.

This is why we consider fostering public health mind-set and financial support to keep high compliance are very important. In this study, the company itself bore the expenses, but the government and municipalities should also discuss financially supporting such measures. The initial goal of this study was to sustain production lines in factories during the flu season. This endpoint was achieved, but future cost effective analysis is needed.

There were some limitations in the present study. First of all, participants could not be individually randomized in this trial because of the characteristics of the intervention. Methodological issues in cluster randomized trials have been widely discussed[12–14], and the effective sample size tends to be less than the total number of individual participants. Nevertheless, the sample size in the present study was large enough to detect a significant preventive effect.

Next, there were some differences in the baseline characteristics between the groups. The proportions of current smokers and those under treatment for hypertension and diabetes were higher in Cohort 1 than in Cohort 2. Since these two companies were in the same business and under the same capital and the same health insurance society, these differences seemed to be the result of chance. If the characteristics were equal, higher rates of chronic disease treatment may have suggested higher health consciousness in Cohort 1. However, this may not be a valid assumption, as the proportion of smokers was comparatively high in Cohort 1. Even if the true causes are unknown, these differences tended to dilute the effect of the intervention, since impaired glucose tolerance and smoking increase susceptibility to respiratory infections. Therefore, we concluded that these differences did not change the direction of the conclusion. In addition, although we could not confirm the number of children of the participants in the two companies, since they were sibling companies of a major automotive industry and there was no difference between the two groups in age and sex ratio, that is, all of the workers in these two companies participate in the same benefit program (such as health insurance society, employment regulations, pay system and personnel evaluations.), thus, we do not think there is significant difference in number of children. Moreover, the vaccination in Japan was under government control, therefore, those susceptible individuals should be given priority to be vaccinated. In the two sibling companies, all of the employees obeyed the rules, and it is reasonable to consider they were under the same conditions because their backgrounds did not differ. Hence, we believe that there was little sampling bias.

The next limitation was the diagnosis of influenza A H1N1. H1N1 was diagnosed by a positive result of an influenza A test kit (rapid test) or by clinical symptoms, not by culture or molecular diagnostic techniques. The sensitivity of the rapid test is said to be about 50%, and an extreme report found only 11% sensitivity compared with PCR[15]. Thus, diagnosis using only the rapid test may miss a large number of true infections. A Japanese national weekly survey showed that almost all of the ILI in the 2009 season was genotyped as influenza A H1N1[16]. The test kit also included suspicious ILI as influenza A H1N1.

However, the national data above suggest a rather high percentage of correct diagnosis. Moreover, the percentages were expected to be common in the two cohorts, and this problem did not seem to change the conclusion.

In Japan, the supply of H1N1 vaccine was not sufficient in 2009, and vaccinations were prioritized to medical professionals and high-risk people only. Healthy workers were therefore unable to be vaccinated, and companies were unable to provide vaccines to their employees. A report concerning patients in California showed that mortality was higher among hospitalized adults than among hospitalized children, and the infection in healthy adults was shown to be life-threatening[17].

The present data have the advantage of evaluating non-vaccine interventions because the preventive effect without vaccination could be appraised. As for generalizability (external validity), the study also has strength when considering the application of evidence to future prevention, because the supply of new vaccines might not be sufficient in the future. This is especially true for healthy people in the early stages of infection.

As the CDC (Centers for Disease Control and Prevention) in the United States recommends, influenza vaccination is the first and most important step in protecting against the flu[18], and a single 15-μg dose of 2009 H1N1 vaccine is immunogenic in adults[19]. However, the supply and distribution of the vaccine can be delayed. Even after vaccination, non-vaccine interventions such as the one described in this study should be considered as additional measures to control future flu pandemics. Fostering a public health mind-set and financial support, as well as establishing usual prevention strategies (such as hand washing and avoiding people with flu), are keys to minimizing flu pandemics.

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