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Extreme influenza epidemics and out-of-hospital cardiac arrest

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ABSTRACT

Introduction: There is compelling evidence for an association between influenza epidemics and major adverse cardiovascular events. However, the role of extreme influenza epidemics as a trigger of out-of-hospital cardiac arrest (OHCA) is unclear. Thus, we evaluated the potential association between extreme influenza epidemics and incidence of OHCA.

Methods: We used a quasi-experimental design with time-series analysis of national registry data for cases of OHCA from all 47 prefectures of Japan during influenza seasons between 2005 and 2014. A Poisson regression time-series model with a distributed lag non-linear model was used to estimate prefecture-specific effects of influenza epidemics on OHCA. A multivariate meta-analysis was conducted for nationally pooled estimates.

Results: In total, 481,516 OHCAs of presumed cardiac origin were reported during the study period. The minimum morbidity percentile (MMP) was estimated as the 0th percentile for influenza incidence. The overall cumulative relative risk versus the MMP was 1.25 (95% confidence interval, 1.16–1.34) for extreme influenza epidemics (at the 99th percentile of influenza incidence). The effect of extreme influenza epidemics was significant for lag periods of 1.5–7.1 and 17.9–21 days. Multivariate random-effects meta-analysis indicated significant spatial heterogeneity among prefectures (Cochran Q test, $p = 0.011$; $I^2 = 23.2\%$).

Conclusion: Extreme influenza epidemics are associated with higher risk of OHCA. Our findings suggest that several weeks' prevention for extreme influenza infections should be implemented to reduce the risk of OHCA.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) constitutes a significant public health issue in industrialized countries [1]. Although survival following an OHCA has improved in recent years, the survival rate remains low at 8% [2,3]. Coronary artery disease is a known major risk factor for sudden cardiac arrest, while a family history of cardiac arrest and lifestyle factors, such as smoking, physical activity, diet, and weight, can raise the risk of OHCA [4]. In addition to these traditional risk factors, influenza is considered to be an important causative factor for cardiovascular disease mortality and morbidity [5–8]. The influenza virus has been linked to the development and progression of atherosclerosis and has been found in atherosclerotic plaques [9]. The mechanisms underlying the association between the influenza virus and cardiovascular disease include direct influenza-induced cardiac changes, such as asymptomatic electrocardiogram abnormalities [10,11], myopericarditis [9], and acute myocardial infarction [12], and subsequent systemic effects caused by the release of inflammatory cytokines and prothrombotic changes [13,14].

Influenza is a viral infection that is associated with seasonal outbreaks of respiratory illness during winter in regions with temperate climates and during rainy seasons in tropical regions. Further, influenza epidemics are associated with large numbers of deaths and serious complications in vulnerable populations [15]. Several studies have established an association between influenza epidemics and major adverse cardiovascular events, and influenza may be an important causative factor for cardiovascular disease morbidity and mortality [16,17]. However, the association between extreme influenza epidemics and OHCA are yet to be studied. Improved understanding of these associations might enable the development of strategies to prevent influenza-related OHCA.

Therefore, we investigated the potential association between influenza epidemics and OHCA using national registry data for all OHCA cases of presumed cardiac origin occurring between 2005 and 2014 in Japan.

2. Materials and methods

2.1. Study design

A quasi-experimental design with time-series analysis was used to investigate the association between seasonal influenza epidemics and OHCA from January 1, 2005, to December 31, 2014, in all 47 Japanese prefectures. We examined the impact of influenza by narrowing the focus of our analysis to the influenza seasons (defined as week 40 of a given year through week 20 of the following year).

This study was approved by the Ethics Committee of the Kyushu University Graduate School of Medical Sciences. The need for written informed consent was waived because of the study's retrospective observational design using national registry data and the de-identification of enrolled individuals.

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2.2. Data sources

2.2.1. OHCA morbidity

We collected data on OHCA cases that arose between 2005 and 2014 in all 47 Japanese prefectures listed by the Fire and Disaster Management Agency (FDMA). According to Japan's Fire Service Act, municipal governments provide emergency medical services (EMSs) at approximately 800 fire stations and related dispatch centers. Since EMS providers cannot terminate resuscitation in the field, all EMS-treated OHCA patients are transferred to hospital. EMS personnel, with the assistance of the physician in charge, summarize each OHCA case in accordance with the Utstein-style guidelines [18]. The fire stations and dispatch centers send this data to the FDMA, where it is entered into the FDMA database server's national registry system. In Japan, registration of OHCA episodes is required under the Fire Service Act; therefore, the OHCA data registry is considered complete across the country. The data were checked for consistency by the computer system, and were validated by the FDMA. Detailed information on Japan's EMS system has been previously reported [19].

We extracted a daily time-series of OHCA cases. The physician in charge in cooperation with EMS staff determined whether the clinical cause of the cardiac arrest was of cardiac or non-cardiac origin; the arrest was considered cardiac in origin unless it was due to drowning, trauma, overdose, exsanguination, asphyxia, or other obvious non-cardiac causes. All included patients had an OHCA of presumed cardiac origin.

2.2.2. Influenza morbidity

We obtained data on influenza cases occurring between 2005 and 2014 in all 47 Japanese prefectures from the National Institute of Infectious Diseases, which is organized by the Ministry of Health, Labour and Welfare. Under Japan's Infectious Disease Control Law, influenza has been a notifiable disease under systematic surveillance since 1999. This surveillance involves approximately 5000 sentinel medical institutions, comprising approximately 8% of clinics and hospitals in Japan [20,21]. A case definition of influenza includes sudden fever (>38 °C), respiratory symptoms, general malaise, and myalgia, and these clinical symptoms are backed up by viral load measurement. All clinical data are reported electronically to the National Institute of Infectious Diseases. To calculate daily influenza cases, weekly surveillance data was used and converted to daily values using linear interpolation.

2.3. Statistical analysis

2.3.1. First-stage time-series model

For the first stage, we used a Poisson regression time-series model with a distributed lag non-linear model to evaluate the prefecture-specific non-linear lag effects of influenza on OHCA [22]. To simultaneously describe relationships with influenza data and lags, spline functions were used to define the cross-basis. A cross-basis matrix was obtained by estimating the exposure-response function modeled with quadratic B-splines, with one internal knot at the 75th percentiles of the influenza distributions in each prefecture during the influenza seasons, and the lag-response function modeled with natural cubic B-splines, with an intercept and two internal knots that are equally spaced along the log scale. The maximum lag was set to 21 days to examine the delayed effects of influenza epidemics on OHCA [5]. A natural cubic B-spline with equally spaced knots and four degrees of freedom (df) for the day of the season was used to control for seasonality. A natural cubic B-spline with equally spaced knots and one degree of freedom for the year was used to adjust for long-term trends. Indicator variables for the day of the week and the 2009–2010 influenza season, the period during which the 2009 pandemic influenza A virus subtype H1N1 (A[H1N1]pdm09) first emerged and was circulated, were included in the model. Further, ambient temperature and relative humidity over 0–21 day lags were used to test for confounding and effect modification.

Although influenza-OHCA associations for each prefecture could be evaluated using absolute influenza case scales, the distributions and ranges of influenza cases differed among the 47 prefectures. Additionally, the overall effects of influenza on OHCA may be more meaningful on a relative influenza-case scale than on an absolute influenza-case scale due to influenza adaptation. Thus, the association between influenza and OHCA was assessed by standardizing the prefecture-specific absolute influenza cases to the prefecture-specific influenza case percentiles [22].

2.3.2. Second-stage meta-analysis.

For the second stage, we used a multivariate random-effects meta-regression model to estimate pooled effects at the national level and the best linear unbiased prediction of pooled associations between influenza and OHCA for all 47 prefectures [23]. As meta-predictors, the absolute mean and range of influenza cases in each prefecture were adjusted to account for heterogeneity between prefectures. Multivariate extension of the Cochran Q test and the I^2 index were used to assess residual heterogeneity among prefectures [22].

The minimum morbidity influenza incidence was derived from the weakest point of the overall cumulative association between influenza incidence and OHCA, and this value was interpreted as the minimum morbidity risk of OHCA. The minimum morbidity risk was represented as the minimum morbidity percentile (MMP) of influenza incidence and was estimated using the best linear unbiased prediction of the pooled relationships between influenza and OHCA in each prefecture. MMP values were used as references to estimate the risk of OHCA by re-centering the quadratic B-spline, which models the prefecture-specific overall cumulative influenza-OHCA association. We defined extreme influenza epidemics as influenza incidence above the 99th percentile of influenza cases and calculated the overall cumulative relative risk (RR) in the 90th and 99th percentiles.

For sensitivity analysis, we estimated influenza-OHCA associations by adopting different degrees of freedom for time trends (two and three degrees of freedom per year) or by including ambient temperature and relative humidity. All statistical analyses were carried out using the *dlnm* and *mvmeta* packages of R 3.3.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The significance level for all tests was $P < 0.05$ (two-sided).

3. Results

A total of 1,176,351 OHCA cases were registered between January 1, 2005 and December 31, 2014 in all 47 prefectures of Japan. We analyzed 481,516 OHCAs of presumed cardiac origin that occurred during influenza seasons (Table 1). During the study period, a total of 13,347,080 influenza cases were reported, with a daily mean of 122.3 influenza cases (Table 1). There was a broad range of daily influenza cases among the various prefectures, and the prefecture-specific daily influenza cases ranged from 29.3 cases in Tottori to 376.4 cases in Kanagawa (Supplementary Table S1).

The overall cumulative association between influenza incidence and OHCA is shown in Fig. 1 and Table 2. The corresponding relationships in each prefecture are shown in Supplementary Fig. S1. The MMP was estimated as the 0th percentile of the national daily influenza cases, and the morbidity risk for OHCA increased with increasing daily influenza incidence. The overall cumulative relative risk versus the MMP was 1.25 (95% confidence interval, 1.16–1.34) for extreme influenza epidemics (at the 99th percentile of influenza incidence). Multivariate random-effects meta-analysis indicated significant spatial heterogeneity between prefectures (Cochran Q test, $p = 0.011$; $I^2 = 23.2\%$).

The pooled lag-response relationship between extreme influenza epidemics and OHCA is shown in Fig. 2. The effect of extreme influenza epidemics was significant for lag periods of 1.5–7.1 and 17.9–21 days.

To determine whether our results were sensitive to our modeling choices, we performed sensitivity analysis by adopting different degrees of freedom for seasonality and lag period or by including ambient temperature and relative humidity. The sensitivity analysis revealed that the choice of model had little effect on the estimates (Supplementary Table S2). These results suggest that our findings were robust.

4. Discussion

We examined the correlation between influenza epidemics and OHCA incidence in Japan. Our study findings clearly show that extreme influenza epidemics are associated with significantly increased risk of OHCA. These findings agree with those of previous studies, which suggest that influenza infection is associated with increases in cardiovascular disease mortality and morbidity [6–8]. Influenza and respiratory infection have also been shown to increase the risk of myocardial infarction [17,24–26], and many coronary deaths may be attributable to respiratory infections [25,27]. Potential mechanisms to explain the increased risk for OHCA due to influenza infection include various direct actions of the influenza virus on inflammatory and coagulation pathways, which can lead to destabilization of vulnerable atherosclerotic plaques and subsequent coronary artery occlusion, the main factor underlying myocardial infarction [9]. Influenza infections can also lead to increases in proinflammatory cytokines caused by inflammatory and coagulation pathways [12] and promote macrophage infiltration into the artery wall [28,29]. These events lead to the release of endotoxins or lipopolysaccharides, which damage the vascular endothelium, eliciting an immune response and increasing plasma viscosity and clotting factors [30,31]. Thus, our findings are physiologically plausible and indicate that extreme influenza epidemics can have a substantial impact on OHCA.

Our analyses also demonstrated that the effects of extreme influenza epidemics were significant for lag periods of 1.5–7.1 and 17.9–21 days. This lag pattern in extreme influenza epidemic-related OHCA is