【 ORIGINAL ARTICLE 】

The Prophylactic Effect of Anti-influenza Agents for an Influenza Outbreak in a University Hospital

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Abstract:
Objective   From November 24 to December 9, 2013, an outbreak of the influenza (flu) A (H3) virus occurred in a tertiary-care university hospital (1,014 beds). We herein report the prophylactic effect of anti-flu agents for controlling the flu outbreak.
Methods   We administered pre- or post-exposure prophylaxis with anti-flu agents in flu outbreak. To test the effectiveness of prophylaxis in a flu outbreak, we used the posterior mean of the reproductive value during the pre- and post-intervention period. We also simulated the probability distribution of new flu cases. We performed an analysis to quantify the strength of the intervention effect.
Results   A total of 97 people were diagnosed with flu before the intervention, and 7 were diagnosed after the intervention. A molecular analysis of the flu virus revealed that this outbreak was due to the flu A (H3) virus. A total of 3,702 people received prophylaxis. There was a significant reduction in the reproductive value from 1.89 [95% confidence interval (CI), 1.59 to 2.24] to 0.65 (95% CI, 0.02 to 1.00) after the intervention ($p<0.001$).
Conclusion   Prophylaxis with anti-flu agents, along with prompt identification and isolation of infected individuals, was effective in reducing the impact of a flu outbreak in a hospital.

Key words: influenza (flu), outbreak, oseltamivir, zanamivir, prophylaxis

Introduction

Influenza (flu) outbreaks have been reported worldwide throughout the past century. While flu itself can lead to death, mortality can also occur during a flu outbreak due to secondary bacterial infections, specifically pneumococcal disease (1). Particularly among the elderly, flu outbreak is a regular occurrence during the annual flu season, despite high rates of flu vaccination (2). Flu outbreaks are also common in medical facilities, and attack rates vary from 25% to 70% (3-5).

In recent years, the main strategy for flu outbreak prevention has been annual flu vaccination. Previous studies have shown that flu vaccination provides around 30% protection against illness and is approximately 40% effective at preventing hospitalization and 60% effective at preventing death (6, 7). The Japanese Association of Infectious Disease recommends the use of anti-flu agents as prophylaxis for healthcare workers and patients (8), as clinical studies have shown that neuraminidase inhibitors, such as oseltamivir and zanamivir, are effective in preventing flu (9, 10) when used as primary or post-exposure prophylaxis in healthy adults (11-14). However, the effectiveness of prophylaxis with anti-flu agents during a flu outbreak has not been well documented.

We experienced an outbreak of flu A virus in 2013 that occurred in a tertiary-care university hospital. Several cases of flu infection were transmitted from patients to healthcare workers and other patients. The aim of our study was to as-

sess the effectiveness of prophylaxis with anti-flu agents during a flu outbreak in a hospital.

Materials and Methods

Protocols and management

A suspected flu case was defined as flu-like illness (temperature ≥38.0℃ with cough or sore throat) with an onset of symptoms within 7 days after close contact with a flu patient. During the outbreak in 2013, all persons with suspected flu infection were screened with the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay. Flu patients were isolated in our hospital or given home leave to prevent transmission. Contact tracing was performed to identify those with close contact with flu patients.

Prophylaxis with oseltamivir at 75 mg twice a day or zanamivir at 2 blisters twice a day, was administered for a period of 5 days after close contact with flu patients. More substantial prophylaxis was instituted when cases were present in many units. Interactions between affected units and other units were reduced during the outbreak.

The infection control committee at our hospital approved the pre- and post-exposure prophylaxis regimen at a therapeutic dosage (oseltamivir at 75 mg twice a day for 5 days and zanamivir at 2 blisters twice a day) to prevent the emergence of resistance to anti-flu agents (15). Written informed consent was obtained from all individuals prescribed the prophylaxis agents.

The epidemiologic investigation

Our investigation of the outbreak was approved by the Aichi Medical University Hospital committee. In addition, oral assent was provided by all others during the surveys. In each suspected case, a nasopharyngeal swab was obtained within one to two days of the onset of symptoms. Testing was continued until no further symptomatic patients or healthcare workers were identified. In addition, to confirm nosocomial transmission, medical records of the contacted patients were reviewed. We then investigated any underlying co-morbid illnesses, the treatment, and the timing of isolation as precautions.

The molecular diagnosis and sequencing

Laboratory confirmation of suspected cases was performed via an RT-PCR assay or viral culture. Nasopharyngeal swabs were collected, re-suspended in 2.0 ml of viral-transport medium, and sent for RT-PCR testing, all within a 24-h period. The RT-PCR assay involved protocols with flu A (H3) forward-reverse primer sets and a probe (QIAamp® Viral RNA Mini Kit and QuantiTect® Probe RT-PCR Kit; QIAGEN, Tokyo, Japan).

The cost evaluation

We evaluated the medical costs, such as the costs of pro-phylaxis and certain tests regarding the treatment for flu, during the outbreak. All costs were reported in Japanese Yen.

Statistical analyses

We calculated the probability distribution of the fitted model from the start of intervention as described below. An analysis was used to quantify the strength of the intervention effect. We distinguished the effects of prophylaxis from that of sending workers home for the outbreak. We also tested the hypothesis of a reduction in infection rates after the start of our intervention.

Following the statistical argument of a previous study (16), we assumed that each case of flu A (H3) led to new cases, distributed as a Poisson variate with a mean of λ or $\lambda\theta$ in the absence or presence of intervention, respectively, as well as a specific form for the generation interval. The λ variable represents the reproductive value in the absence of intervention and $\lambda\theta$ the reproductive value after intervention. The time between the onset of primary and secondary cases was independently distributed with a discretized gamma distribution, which we parameterized from the posterior mean and variance of the gamma distribution fitted to the data provided by Moser (17). The posterior distribution of the parameters conditional on the data was taken to be proportional to this, i.e., a pseudo-objective improper flat prior on the parameters λ and $\lambda\theta$ was assumed. Therefore, this analysis was performed within the Bayesian paradigm using improper flat priors on the parameter space, i.e., p (λ, θ) 1 if $\lambda>0$ and $\theta>0$, and 0 otherwise; the likelihood function has a finite integral, and so the posterior is proper (18). The posterior distribution is estimated via Markov chain Monte Carlo integration (19). The hypothesis of an effect $\theta<1$ is assessed via posterior hypothesis probabilities (20) by direct calculation from the posterior sample of p $(\theta>1$, data). The analysis was performed according to the Bayesian paradigm (18) and with the use of the statistical programing language R.

Results

Outbreak

The numbers of cases of flu A (H3) during the outbreak in 2013 are shown (Figure). At the start of the outbreak, one patient tested positive for flu. Four more patients hospitalized in the same room showed the same symptoms as the index patient and were confirmed to be infected on day 2. Sixteen more patients were confirmed to be infected on day 3 in different wards. We recommended that all healthcare workers receive prophylaxis from day 5. Consequently, 97 people were diagnosed with flu (48 confirmed with PCR, and 49 diagnosed based only on symptoms), and 3,702 (hospital personnel: n=2,680, patients: n=771, students and patient attendants: n=251) were given oseltamivir or zanamivir for prophylaxis during the flu outbreak. In addi-
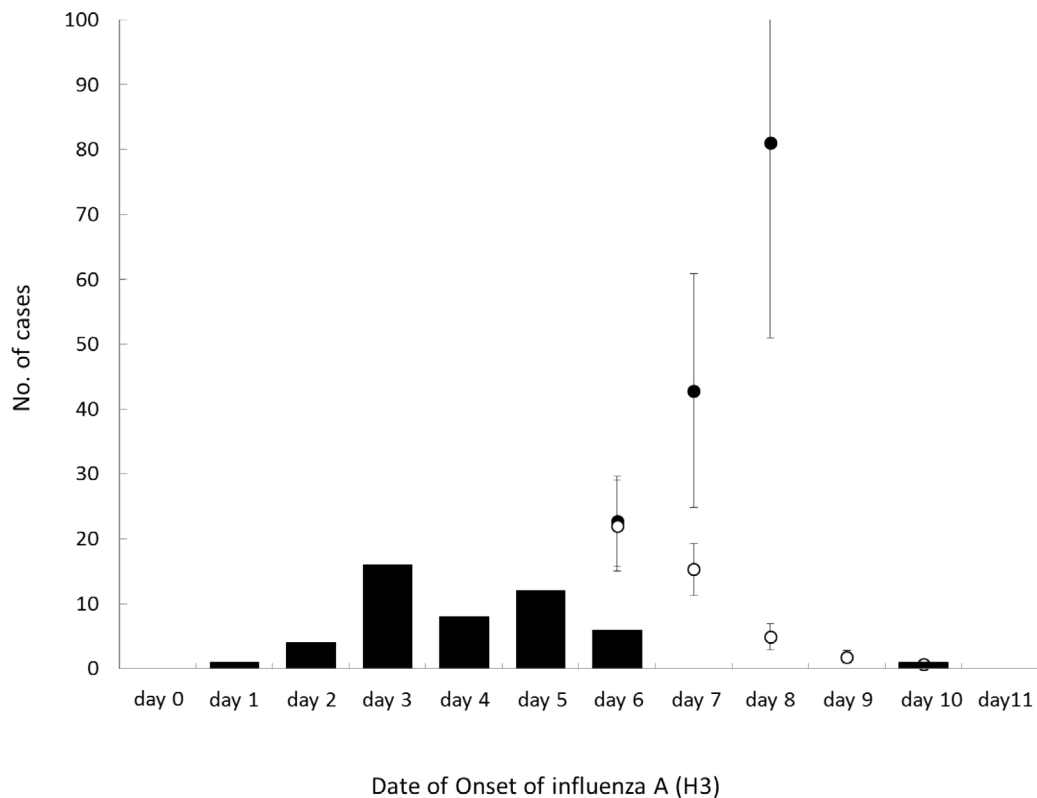
●: No control, ○: Home leave only

Figure. **The numbers of cases of influenza A (H3) during outbreak are shown. The predicted numbers of cases based on the assumptions that the apparent effect of the interventions was due to either chance alone or to sending personnel home rather than to the prophylaxis of anti-influenza agents are also shown in circles. The I bars indicate the 95% confidence intervals of the predicted values.**

tion, we restricted new admissions to our hospital for 14 days.

Rates of infection and efficacy of interventions

Before the start of oseltamivir or zanamivir prophylaxis or other interventions, the proportion of flu patients was 1.42%. After intervention, the infection rate was reduced to 0.23% (p<0.001).

We used mathematical modeling to investigate the effect of the interventions on the course of the outbreak. If we considered only confirmed cases, the global estimate of the reproductive value before intervention was 1.92 [95% confidence interval (CI), 1.59 to 1.89]. There was a significant reduction in the reproductive value after intervention (0.65; 95% CI, 0.02 to 1.00; posterior hypothesis probability, p<0.001).

To test the effectiveness of prophylaxis in the flu outbreak, we simulated the probability distribution of new flu cases. We estimated two distributions with the posterior mean of the reproductive value during the pre- and post-intervention period (Figure). These distributions represented what we would expect if the clear efficacy of the interventions was due to chance alone or due to the isolation measures rather than the oseltamivir and zanamivir prophylaxis. There was the large discrepancy between these distributions.

The sharp drop in the rate of flu infection was therefore deemed to be due to prophylaxis as well as isolation.

The cost evaluation

During the flu outbreak, prophylaxis with oseltamivir and zanamivir was found to have prevented 3,702 flu cases. The total cost for prophylaxis and rapid tests was ¥10,510,000 during the outbreak. The total cost for prophylaxis was ¥10,320,000. The number of rapid tests for flu was 273, and the cost was ¥190,000.

In this case, the flu virus was transmitted to many wards, so more substantial prophylaxis was instituted. Our mathematical models indicated that all medical staff and patients would have been infected by 13 days after the initiation of the flu outbreak if the intervention had not been implemented. The cost of the anti-flu agent would then exceed ¥12,711,000 if we prescribed only oseltamivir as prophylaxis to all medical staff and patients in our hospital. Therefore, our hospital would have lost at least ¥2,201,000 plus the cost of PCR for flu tests.

Discussion

Several studies have examined both the clinical and economic benefits of prophylaxis with anti-flu agents (21, 22).

However, few studies have estimated the efficacy and the cost of prophylaxis of anti-flu agents when an outbreak happens at a single hospital. Anti-flu prophylaxis strategies have been predicted to be effective in some mathematical models. However, data are still needed to document their actual effectiveness during an outbreak. We therefore describe our experience in responding to outbreak of flu A (H3) virus in our hospital. We also evaluated the role of prophylaxis in attenuating the transmission of the virus and its economic impact.

Several uncertainties still remain concerning prophylaxis with anti-flu agents. Van der Sande et al. observed no protective effect of post-exposure oseltamivir prophylaxis among Dutch nursing home residents (21). They therefore recommended only close observation of residents and the early start of therapy in case of disease during flu outbreaks. The development of resistance when using neuraminidase inhibitors is also unknown. However, the prophylactic usage of oseltamivir is now indicated to manage flu outbreaks for all nursing home residents, as the duration of flu outbreaks was shown to be the shortest in nursing homes where prophylaxis with oseltamivir was given to all residents (22).

However, the threshold for initiating neuraminidase inhibitor prophylaxis has not been well defined. A previous study showed that early prophylaxis with amantadine reduced the flu incidence. This strategy also reduced the mortality rate in outbreaks at long-term care facilities (23). Among those in contact with flu patients, the use of prophylaxis with oseltamivir has shown protective efficacy (24, 25). At our hospital, we recommend that all medical staff members take prophylaxis agents within 48 h of contact with flu patients. We have not experienced any similar flu outbreaks since the outbreak in 2013 in our hospital. We therefore feel that the prophylactic use of anti-flu agents may be justifiable for protecting against flu strains. This strategy may also protect particularly vulnerable populations in closed or semi-closed environments, such as elderly patients.

In addition, our mathematical models indicated that all medical staff and patients would have been infected by 13 days after the initiation of the flu outbreak if no intervention had been implemented. The cost of anti-flu agents would then be at least ¥12,711,000. In the flu outbreak of 2013, the total cost for prophylaxis and rapid tests was ¥10,510,000. In addition, our hospital experienced a reduced income ¥91,080,000 (mean ¥6,505,714/day) due to the restriction of any new admissions to our hospital for a 14-day period, compared with the same period in last year (November 26 to December 9, 2012). Furthermore, 95.8% of the workers (1,806/1,885) in our hospital received a flu vaccination in 2013, and the total cost of the vaccine was ¥1,896,300. As a result, this flu outbreak had a huge economic impact. Our experience is thus considered to support the use of prophylaxis with neuraminidase inhibitors during a flu outbreak.

Limitations associated with this study include the fact that the data were observational and that many interventions were applied in the outbreak. However, it would have been difficult to use prophylaxis as the sole control measure, due to external pressure to do everything possible to halt transmission and the spontaneous social-distancing measures people take. Furthermore, it is impossible to conduct non-intervention and non-pharmaceutical intervention in a real-world setting. It is also important to consider that all computer simulation models are simplifications of real life and cannot reflect every possible event that might result from flu infection. We therefore assumed that each case of flu A (H3) led to new cases in accordance with the statistical methods of previous studies (16).

In conclusion, our experience supports the use of large-scale anti-flu prophylaxis during a flu outbreak. The strategy may be able to slow or halt the spread of flu infection in outbreak. Prophylaxis with oseltamivir and zanamivir can also ease the economic impact of a flu outbreak.

The authors state that they have no Conflict of Interest (COI).

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