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Prediction, risk and control of anti-influenza drugs in the Yodo River Basin, Japan during seasonal and pandemic influenza using the transmission model for infectious disease

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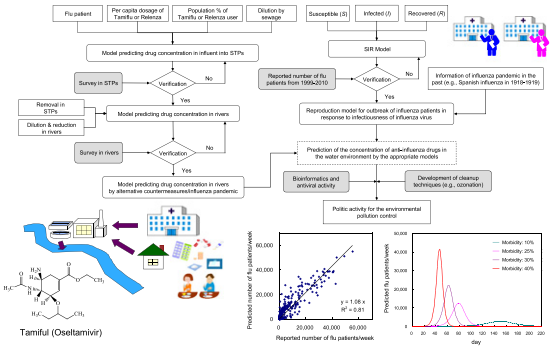
HIGHLIGHTS

- The transitional change in number of flu patient was firstly simulated by SIR model.
- Concentration of anti-influenza drugs under the several flu pandemics was estimated.
- The estimated concentration of anti-influenza drugs was higher than 1 μg/L in Japan.
- Application of ozonation at STP reduced the generation risk for drug-resistant virus.

GRAPHICAL ABSTRACT



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ABSTRACT

To reduce the risk of producing an anti-influenza drug-resistant virus from wildfowl, it is important to estimate the concentrations of anti-influenza drugs in river water during an influenza pandemic and to evaluate the concentrations that keep river basins safe. We first created a newly designed infectious disease transmission model based on the Susceptible–Infected–Recovered model. This model was then applied to replicate the transitional changes of three representative anti-influenza drugs, oseltamivir (OS), oseltamivir carboxylate (OC), and zanamivir (ZAN), in the urban area of the Yodo River system, which is one of the major basins in Japan with a population of 12 million; this region contains nearly 10% of the country's flu cases during the seasonal influenza outbreaks between 1999 and 2010. The results showed high correlations between the estimated number of influenza cases and the concentrations of the three investigated anti-influenza drugs with the reported values. We then extended the application of the model to estimate the concentration level of these anti-influenza drugs during the several influenza pandemics. The maximum estimated concentrations for OS, OC, and ZAN were known to be 260–450 ng/L, 1500–2600 ng/L and 40–70 ng/L, respectively, at the peak of the influenza pandemic. These results suggest that it is possible that a drug-resistant influenza virus can originate from wild mallard when there is a large-scale influenza pandemic. However, ozonation before discharge at sewage treatment plants is known to significantly reduce the release of such drugs into the aquatic environment to reduce the risk of a drug-resistant virus outbreak. It was also suggested that further environmental risk could be reduced by decreasing these concentrations further in river water.

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1. Introduction

In recent years, an issue with the anti-influenza drug, oseltamivir (Tamiflu®, OS), which is used to treat influenza, and its pharmacologically active metabolite (oseltamivir carboxylate: OC) being discharged into river environments has drawn significant attention (Söderström et al., 2009; Ghosh et al., 2010b; Prasse et al., 2010; Azuma et al., 2012, 2013; Singer et al., 2014). Wildfowl living in river basins carry all types of the influenza virus and are in fact the origins of type A influenza, which infect and spread throughout humans, poultry and swine (Suarez and Schultz-Cherry, 2000; Wang et al., 2008). For this reason, there are deep concerns about outbreaks of drug-resistant influenza viruses as a result of wildfowl consuming river water containing anti-influenza drugs and the risk for epidemics among humans (Singer et al., 2007; Straub, 2009).

Currently, two drugs, Tamiflu® and Relenza® (zanamivir: ZAN), are used for treatment and prophylaxis of influenza worldwide (WHO, 2009a). Both of these are recommended by the WHO for mitigation of seasonal influenza, which becomes an epidemic every year, as well as for the influenza pandemic caused by highly contagious new influenza viruses (WHO, 2009a).

Influenza pandemics in the past have included the Spanish flu outbreak of 1918, the Asian flu outbreak of 1957, the 1968 Hong Kong flu, and the swine influenza pandemic of 2009 (Schoenbaum, 2001; WHO, 2005; Fraser et al., 2009). Among these, the Spanish flu caused the greatest mortality (Schoenbaum, 2001; WHO, 2005), killing 20 to 50 million people worldwide (WHO, 2009a). Drugs to treat influenza infections had not been developed at that time; however, in modern society, the concern revolves around a rapid spread of influenza due to developed transportation networks and increased and concentrated populations (Ohkusa and Sugawara, 2009). If a pandemic of a new influenza virus were to occur, large quantities of anti-influenza drugs will be consumed on a worldwide scale; it is expected that the amount of anti-influenza drugs discharged into rivers will also increase. Unfortunately, attenuation of both Tamiflu® and Relenza® through water treatment processing at sewage treatment plants as well as by photolysis and biodegradation in river water is minimal (Saccà et al., 2009; Accinelli et al., 2010; Ghosh et al., 2010a; Gonçalves et al., 2011; Azuma et al., 2013). The possibility of these drugs remaining in river water at high concentrations is a significant concern (Singer et al., 2007, 2011; Straub, 2009; Chen et al., 2014). For this reason, it is important to estimate the actual concentrations of anti-influenza drugs in river water when there is an outbreak of influenza pandemic and then to examine methods to evaluate the environmental risks and measures to reduce the risks to make river basins safe.

Studies involving estimates of anti-influenza drug concentrations in river water during influenza pandemics have targeted OC concentration. The maximum estimated concentrations in the U.S. and Europe are 1 to 103 μg/L (Singer et al., 2007, 2008, 2011, 2014; Straub, 2009; Ellis, 2010; Chen et al., 2014). During an inter-pandemic period, Japan typically accounts for approximately 70% of the world's consumption of oseltamivir (Hoffmann-La Roche Inc., 2005; Yasui et al., 2007; Tashiro et al., 2009). Furthermore, there are no international reports on the concentrations of ZAN; thus, estimating ZAN concentrations is an important subject for study.

We have kept detailed records of the presence of OS, OC, and ZAN for two years (2010–2011) from the entire Yodo River Basin area, one of the major basins in Japan; this area is 8240 km^2 and has a population of 12 million from Shiga to Osaka Prefectures, accounting for approximately 10% of Japan's population (Azuma et al., 2013). One major source of the Yodo River is Lake Biwa whose water level is artificially adjusted by controlling the height of the Setagawa Araizeki Canal Gate at Nango, Ohtsu, Shiga Prefecture. The Yodo River is also equipped with several multipurpose dams including the Hiyoshi and Kizugawa dams to allow a wide-range development of water resources in and around the Yodo River basin (Lake Biwa-Yodo River Water Quality Preservation Organization, Japan, 2012).

We have also shown that there is a strong correlation between the time-dependent dynamics of the concentrations of OS, OC, and ZAN in the river water and the transitional changes in the number of flu patients (Azuma et al., 2012). In addition, the prediction of the actual concentrations of OS, OC, and ZAN was precisely made by a mathematical model based on the number of flu patients, the usage of Tamiflu® and Relenza®, the removal rate of these drugs at sewage treatment plants, and their attenuation in the river water environment (Azuma et al., 2012).

In this study, we have created an infectious disease transmission model that predicts the transitional changes in the number of patients when influenza becomes an epidemic based on the Susceptible–Infected–Recovered (SIR) model used in the field of infection control (Coen, 2007; Gerardo et al., 2009; Singer et al., 2011; Chen et al., 2014). We then combined this model with a model that predicts the concentrations of OS, OC, and ZAN in the river water environment during a seasonal influenza outbreak, based on the reported number of flu patients (Azuma et al., 2013), to evaluate the correlation with the actual concentrations. We further predicted the concentrations of OS, OC, and ZAN in the river water during different outbreak scenarios using an assumed infection rate of 25% (Ministry of Health Labour and Welfare, Japan, 2007) and 30 to 40% from a previous influenza pandemic (Longini et al., 2004; WHO, 2005) to examine the environmental risk during the outbreak of influenza pandemics and to make preliminary calculations of the effectiveness of risk reduction measures.

2. Materials and methods

2.1. SIR model

In this study, we developed a model that predicts the transitional changes in the number of flu patients during an influenza outbreak based on the SIR infectious disease transmission model (Brauer, 2005; Coen, 2007; Gerardo et al., 2009). The SIR model divides a population into three groups: S (Susceptible) describes those who are susceptible to being infected; I (Infected) describes those who have been infected and who are able to spread the disease to susceptible individuals; and R (Recovered) describes those who have recovered from the disease and are immune to subsequent re-infection. The model expresses infection transmissions by differential equations that indicate population changes in each group per time unit (Coen, 2007). The basic composition of the traditional SIR model is shown in Fig. S1. Because this traditional model expresses the fundamental transmission patterns of infectious disease in general (Coen, 2007; Towers et al., 2011), we partially modified the model for the purpose of this study to specifically apply to influenza. Fig. S2 shows the revised SIR model. For the parameters used in the model, we simulated the conditions described below.

First, we presumed that the first day (Day 1) was when one flu patient appeared in the subject area ($I = 1$) as determined in the SIR model. Further, we assumed that all individuals in the subject area were susceptible to influenza ($R = 0$) because an influenza outbreak is caused by a different subtype virus with a modified infectivity and pathogenicity every year (Cox et al., 2004). Furthermore, we presumed that the probability of an apparent infection in which influenza symptoms actually occur was 80% of individuals after being infected by the influenza virus (Kara et al., 2007); we also assumed that all individuals with an apparent infection visited medical facilities and received treatment because Japan has the highest annual level of oseltamivir usage in the world, and prescription drugs can be served as a good indicator of the overall number of influenza patients (Sugawara et al., 2012). In addition, we determined the incubation period of the virus up to the onset of typical influenza symptoms, which include high fever and cough, after contracting the influenza virus as being one full day (WHO, 2009b); the episode period in which the symptoms continued was considered to be four full days (Nicholson et al., 2000), and the spreadable period during which influenza patients were able to spread

the virus to others as five days, which is simply the summation of the incubation and episode periods.

Next, because the number of people who the infected patients have contact with, which is measured in persons/day, remains fixed in the traditional SIR model (Coen, 2007; Towers et al., 2011), varying contact ratios were considered by multiplying a coefficient with the passage of time, assuming that the number of people who influenza patients have contact with per unit of time (persons/day) decreases as the patient's influenza symptoms progress, leading to less mobility. The coefficients were calculated by parameter fitting (Fig. S3(a, b)) so that the differences between the transitional changes for the actual number of patients based on influenza case statistics in Japan from 1999 to 2010 (Infectious Disease Surveillance Center, Japan) and the transitional changes calculated by the SIR model were minimized and set as follows: Day 1 — ×1; Day 2 — ×1/20; Day 3 — ×1/40; and Day 4 and Day 5 — ×1/80.

Lastly, to examine the influence of the decline in population due to deaths from influenza pandemics, we subtracted the chronological number of deaths from the population. The fatality rates applied were 0.05% for seasonal influenza (Sugaya, 2006; Foppa and Hossain, 2008) and 2% for influenza pandemics (WHO, 2009a). On account of the fatality rate, the estimated values at the influenza pandemic are known to be substantially higher than those at the seasonal influenza with significant differences in age and countries (European Centre for Disease Prevention and Control, 2010; Wilking et al., 2010; Shrestha et al., 2011; Nicoll et al., 2012), but close to the average fatality value of 0.08% cited in the review (Girard et al., 2010). Therefore we took the value of 0.05% that was estimated in the same country (Japan) at the seasonal influenza by Sugaya (2006). Surprisingly the same mortality value was also estimated by Foppa and Hossain (2008) in the USA based on the monthly mortality data 1995–2005. In addition, we did not consider the increase in population through births because the seasonal influenza outbreak period in Japan usually lasts only 2 to 3 months (Infectious Disease Surveillance Center, Japan). We also assumed that there were no major changes in the population due to relocations between neighboring cities (Coen, 2007).

2.2. Replication of transitional changes in number of cases during seasonal influenza outbreak

To replicate the transitional changes in influenza cases during a seasonal influenza outbreak based on the SIR model, we validated its applicability by evaluating the correlation against actual reports with the chronological transition for the number of flu patients in Kyoto, Shiga, and Osaka Prefectures in the Yodo River Basin, which were obtained from influenza case statistics in Japan from 1999 to 2010 (Infectious Disease Surveillance Center, Japan); the results from the SIR model simulation and the basic reproduction number (R_0), which indicates the infectivity strength in the infection transmission model, were also included (Gerardo et al., 2009; Singer et al., 2011; Chen et al., 2014).

2.3. Simulation for transitional changes in number of patients during influenza pandemics

To estimate the transitional changes for influenza cases during influenza pandemics, we considered an incidence of 30% to 40% (Longini et al., 2004; WHO, 2005) from a previous pandemic in addition to the incidence of 25% (Ministry of Health Labour and Welfare, Japan, 2007) as the presumed damage rate for influenza pandemics in Japan; we also simulated conditions in which the total incidences throughout the pandemic period were 25%, 30%, and 40% (Mild, Medium, and Severe, respectively) of the population.

2.4. Estimates for OS, OC and ZAN concentrations in river water

To predict the concentrations of OS, OC, and ZAN in the river water, we calculated chronological estimates by combining the results obtained from the SIR model, which predicts the numbers of flu patients, with the model that allows the forecasting of OS, OC, and ZAN concentrations in the river water based on the number of flu patients (Azuma et al., 2012) (Fig. S4). The subject area for these estimates included the city of Kyoto and its surrounding area located in the middle of the Yodo River. More precisely, we chose Hirakata Bridge, a major bridge crossing the Yodo River, and another bridge, Miyamae Bridge, where high concentrations of OS, OC, and ZAN have been reported, with approximately 40% of the river water being treated at sewage treatment plants (Ghosh et al., 2010b; Azuma et al., 2013). In this study, we calculated these estimated concentrations by assuming the following: the rates of prescription of oseltamivir and zanamivir were 60% and 40%, which were used as the standard compliance rates in Japan (Ministry of Health Labour and Welfare, Japan, 2010; Azuma et al., 2012) in accordance with the former value with the upper limit of the reported value (Singer et al., 2013); the patient compliance rate was 94% (Healthy Nippon 21 Council Secretariat, Japan, 2010; Azuma et al., 2012); the excretion rates after compliance were 15% for OS, 80% for OC (George et al., 1999), and 80% for ZAN (Lindsey et al., 1999); the removal rate at sewage plants was 10% (Ghosh et al., 2010a; Azuma et al., 2012); the dilution rates in the river were five to ten times (Azuma et al., 2012); the annual flow volumes were 13,300,000 m^3/day (Hirakata Bridge) and 2,060,000 m^3/day (Miyamae Bridge) (Azuma et al., 2012); and the attenuation in the river water by photolysis and biodegradation were negligible (Saccà et al., 2009; Accinelli et al., 2010; Gonçalves et al., 2011; Azuma et al., 2013).

3. Results and discussion

3.1. Replication of transitional changes in number of patients during seasonal influenza outbreak using the SIR model, and evaluation of correspondence between OS, OC, and ZAN concentration predictions in river water

Fig. 1 shows the results of the correspondence evaluation for the transitional changes in the number of seasonal influenza cases by the SIR model against the reported number of seasonal flu patients in Kyoto Prefecture between 1999 and 2010 (Infectious Disease Surveillance Center, Japan).

The results show high correlations between the transitional change in the number of influenza cases simulated by the SIR model and the transitional change in the actual number of influenza cases ($R > 0.897$ with high linearity $r^2 > 0.809$). In addition, we evaluated the correlation for neighboring Shiga and Osaka Prefectures; both showed similar results ($R > 0.882$ with high linearity $r^2 > 0.778$) (Fig. S5). From these results, we determined that we are able to predict a transitional change in

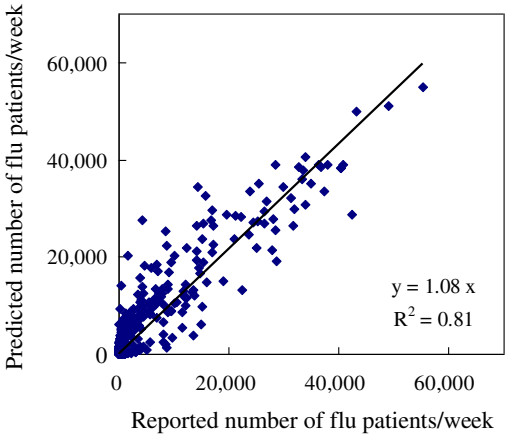

Fig. 1. Correlation between the reported number of patients with the predicted number of flu patients/week from 1999 to 2010 in the Kyoto Prefecture (n = 330).

the number of patients associated with a seasonal influenza outbreak. The seasonal influenza R_0 applied to construct the SIR model in this study was set to 1.1, which is an appropriate value when compared with the reported values of 1.1 to 1.3 (Chowell et al., 2010).

Next, based on the transitional change in the number of patients obtained by the SIR model, we estimated the mean concentrations of OS, OC, and ZAN to be 20 ng/L, 117 ng/L, and 6 ng/L, respectively, at Miyamae Bridge, and 12 ng/L, 69 ng/L, and 3 ng/L at Hirakata Bridge during the peak of a seasonal influenza outbreak, while the actual concentrations reported were 21 ng/L, 116 ng/L, and 2 ng/L at Miyamae Bridge, and 11 ng/L, 56 ng/L, and 0.3 ng/L at Hirakata Bridge, respectively. These estimates show good agreement with the reported values (Söderström et al., 2009; Ghosh et al., 2010b; Azuma et al., 2013), indicating that highly precise concentration estimates are possible with the investigated method.

3.2. Transitional predictions for number of influenza cases during influenza pandemics and concentration level estimates for OS, OC, and ZAN in river water

To simulate transitional changes in the number of flu patients during influenza pandemics, the city of Kyoto, which is an urban area of Kyoto Prefecture with a population of 1.46 million, was chosen for study. Fig. 2 shows the results from the SIR model simulation, in which transitional changes in the number of patients were manipulated with varying infection rates from 25% to 40% (Longini et al., 2004; WHO, 2005; Ministry of Health Labour and Welfare, Japan, 2007) along with the results from a simulation for seasonal influenza with an incidence of 10% (Gordon et al., 2010).

These results showed that as the incidence became higher, the time it takes to reach its peak became shorter, and the number of flu cases during the peak period formed a sharper convex. Ferguson et al. reported that the estimated number of outbreaks during a pandemic flu are 4 to 5 million cases per day in the U.S. and 0.8 to 1.3 million cases per day in the U.K., which account for approximately 1.3–1.6% and 1.3–2.2% of the total populations, respectively (Ferguson et al., 2006). The simulation results from this study, however, estimated 1.9 million outbreaks per day, which is 1.5% of the Japanese population; when considering only Kyoto city, 22,000 outbreaks per day, which is 1.5% of the Kyoto city's population, are estimated to occur. In addition, Ferguson et al. indicated that the total number of infected patients reaches nearly 30% of the population in both the U.S. and U.K. nearly 60 days after the first case of an influenza pandemic (Ferguson et al., 2006); this simulation also predicted that the total number of patients reaches approximately 30%

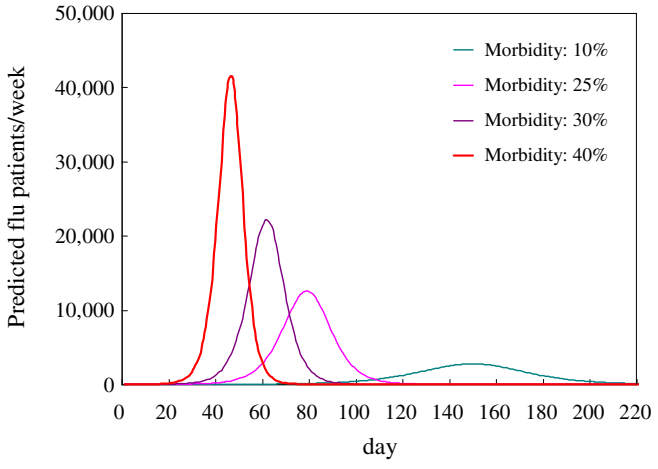

Fig. 2. Number of flu patients/day during a seasonal influenza outbreak and pandemic influenza outbreak predicted by the SIR model in Kyoto city (morbidity rates: 10% for seasonal influenza; 25% for mild pandemic influenza; 30% for moderate pandemic influenza; and 40% for severe pandemic influenza).

of the population in approximately 60 days. Furthermore, R_0 during influenza pandemics in this study were 1.2 to 1.4, which were also similar when compared with the reported values of 1.4 to 2.0 (Ferguson et al., 2006) and 1.3 to 1.7 (Yang et al., 2009; Girard et al., 2010). Thus, the investigated method has been shown to be appropriate for estimating the transitional changes in the number of flu patients during influenza pandemics.

Next, based on the transitional changes in the number of patients obtained from the revised SIR model, we estimated the concentrations for OS, OC, and ZAN at the Miyamae and Hirakata Bridges. Under the scenario in which 25% of the population are infected (R_0, 1.2), the estimated mean values of OS, OC, and ZAN during the peak influenza pandemics were 91 ng/L, 534 ng/L, and 14 ng/L, at Miyamae Bridge, and 54 ng/L, 314 ng/L, and 8 ng/L at Hirakata Bridge, respectively. In the case where approximately 40% of the population is infected (R_0, 1.4), the estimations become 299 ng/L, 1753 ng/L, and 45 ng/L at Miyamae Bridge, and 176 ng/L, 1031 ng/L, and 27 ng/L at Hirakata Bridge, respectively (Table 1). When compared with the greatest values actually measured for OS, OC, and ZAN during seasonal influenza outbreak (OS, 12 ng/L to 20 ng/L; OC, 50 ng/L to 116 ng/L, and ZAN, N.D. to 2 ng/L (Söderström et al., 2009; Ghosh et al., 2010b; Azuma et al., 2012, 2013)), these values were 10 to 50 times more concentrated (Table 1).

The estimated OC concentrations in the river water during influenza pandemics that have been reported between 1 μg/L and 103 μg/L in the U.S. and Europe (Singer et al., 2007, 2008, 2011; Straub, 2009; Ellis, 2010); these values are about one order of magnitude greater than the results produced by this simulation. This discrepancy may be caused by the reported estimates that were obtained without evaluating the correspondence of the predicted values with the measured values, as stated by Leknes et al. (Leknes et al., 2012). Application of a more appropriate model that considers the estimates for chronological transitional changes in influenza outbreak and performs correspondence evaluations against measured values will allow for the estimation of more precise concentrations of OS, OC, and ZAN in river water, as proposed by Singer et al. (Singer et al., 2014).

3.3. Considerations for environmental risk and its reduction measures

The presence of OS, OC, and ZAN in river water can be toxic to aquatic organisms, such as algae, daphnia, and fish; however, it has been reported that these effects are negligible even during periods of high consumption of anti-influenza drugs during large-scale influenza pandemics; both acute and chronic toxic effects occur only when concentrations rise above 1 mg/L (GlaxoSmithKline, 2006; Hutchinson et al., 2009; Straub, 2009; Escher et al., 2010).

Conversely, there is an issue with drug-resistant influenza virus outbreaks originating from wildfowl. Järhult et al. reported that a gene with a mutated coding (H274Y), which is characteristic of an anti-Tamiflu® virus, occurred at a concentration of more than 1 μg/L, when mallards fed on OC-added drinking water in stages for 5 continuous days (Järhult et al., 2011). In addition, the distribution of 50% neuraminidase inhibitor action concentration (IC_{50}) by neuraminidase inhibitor in an in vitro system was used as a validating index with regard to the effectiveness of anti-influenza drugs against influenza virus; these values were determined to be between 43 ng/L and 1500 ng/L (Hurt et al., 2007; Escuret et al., 2008; Centersfor Disease Controland Prevention, USA, 2009; Correia et al., 2010; Okomo-Adhiambo et al., 2010) (Fig. S6).

Although the lower threshold concentration of OC for appearance of anti-influenza drug resistant virus in the water environment is not exactly determined, if around 1 μg/L OC is assumed to be a threshold concentration for the emergence of anti-influenza drug resistant viruses (Chen et al., 2014; Singer et al., 2014), then the risk is small because the reported levels of OC concentrations were generally in the range of several ng/L to 864 ng/L. Thus, the possibility that drug-resistant influenza viruses could originate from wildfowl during seasonal influenza

Table 1
Predicted concentrations of OS, OC, and ZAN, and their measured values (ng/L) during different influenza outbreak scenarios. Each deviation (±50%) was a summed-up value of three deviations due to the revised SIR model (±20%), the removal rate at the STP (±10%; (Azuma et al., 2012)), and the flow rate of the river (±20%; (Azuma et al., 2012)), their measured values (ng/L).

	Infection rate (%)	Classification	R_0	OS (ng/L)		OC (ng/L)		ZAN (ng/L)	
				Hirakata Bridge	Miyamae Bridge	Hirakata Bridge	Miyamae Bridge	Hirakata Bridge	Miyamae Bridge
Predicted values	10%	Seasonal influenza	1.1	12 ± 6	20 ± 10	69 ± 34	117 ± 59	3 ± 2	6 ± 3
	25%	Pandemic influenza (mild)	1.2	54 ± 27	91 ± 46	314 ± 157	534 ± 267	8 ± 4	14 ± 7
	30%	Pandemic influenza (medium)	1.2	94 ± 47	159 ± 80	549 ± 275	934 ± 467	14 ± 7	24 ± 12
	40%	Pandemic influenza (severe)	1.4	176 ± 88	299 ± 150	1031 ± 516	1753 ± 877	27 ± 13	45 ± 23
Measured values	10%	Seasonal influenza	1.1	9–12	13–20	50–56	76–116	N.D.—2.0	N.D.

(N.D.: not detected).

outbreaks in Japan is small (Söderström et al., 2009; Ghosh et al., 2010b; Prasse et al., 2010; Azuma et al., 2012; Chen et al., 2014; Singer et al., 2014). This study, however, revealed that it is possible that OC concentrations can be higher than 1 μg/L only during a large-scale influenza pandemic and when anti-influenza drugs are consumed in large quantities. Additionally, the drug effect of OS is only one-hundredth to one-thousandth that of OC (Williams et al., 1997; Li et al., 1998), and the reported ZAN's IC_{50} for neuraminidase is 68 ng/L to 900 ng/L (Hurt et al., 2007; Escuret et al., 2008; Centers for Disease Control and Prevention, USA, 2009; Okomo-Adhiambo et al., 2010) (Fig. S6). The detected maximum concentration level of ZAN in river water during a seasonal influenza outbreak was 15 ng/L (Azuma et al., 2012), and the estimated maximum level of concentration even during an influenza pandemic is 68 ng/L. Based on these results, we can conclude that the levels of OS and ZAN are less likely to become an environmental risk even during influenza pandemics. Considering OS and ZAN, we determined that they are less likely to become an environmental risk even during influenza pandemics.

Lastly, there is a report that more than 90% of OC, which is the compound of major environmental concern, can be removed when ozonation is applied during sewage treatment process (Ghosh et al., 2010a; Azuma et al., 2012). For this reason, OC reduction measures should be examined for when there is a large-scale influenza pandemic; thus, we tried calculating the effectiveness of two environmental risk-reduction measures: ozonation before discharge in all sewage treatment plants that discharge treated water into the Yodo River Basin, and the temporary doubling of river water flow using the reserves of Lake Biwa and dams in Yodo River system (Japan Water Agency, 2014) while considering the height of the embankment throughout the river. Fig. 3 indicates the estimated OC concentrations during the peak of an influenza outbreak when no reduction efforts were made as well as when these two measures were taken. The results suggest that the OC concentration level in river water can be reduced to the same level (100 to 180 ng/L) as a seasonal influenza outbreak level by applying ozonation during sewage treatment, even when the largest-scale influenza pandemic with an infection rate of 40% occurs. Furthermore, increasing river water was found to have somewhat a positive effect on reducing the OC concentration level in an aquatic environment; its effectiveness was, however, moderate when compared with ozonation. In addition, because there is a limit to discharging reserved water for a long period of time, increasing the river water level should only be considered as a temporary measure during a peak influenza period or as a supplemental measure combined with other measures.

4. Conclusions

In this study, we were able to replicate the transitional changes in the number of flu cases during an influenza outbreak based on the SIR model, which is an infectious disease transmission model. We estimated the concentrations of OS, OC, and ZAN in the river water over time during a seasonal influenza outbreak in the Yodo River Basin in Japan by combining the SIR model and the concentration estimation model for anti-influenza drugs in the river water; we were able to show that the actual concentrations and these estimated levels agreed.

Next, we attempted to estimate the concentrations of OS, OC, and ZAN in the river water by simulating the transitional changes in the number of flu patients during a large-scale influenza pandemic using this model. Under the largest historical influenza pandemic scenario, where nearly 40% of the population was infected (R_0, 1.4), the maximum estimated concentrations attained at the peak of the influenza pandemic for OS, OC, and ZAN in the river water were 264 ng/L to 449 ng/L, 1547 ng/L to 2630 ng/L, and 40 ng/L to 68 ng/L, respectively.

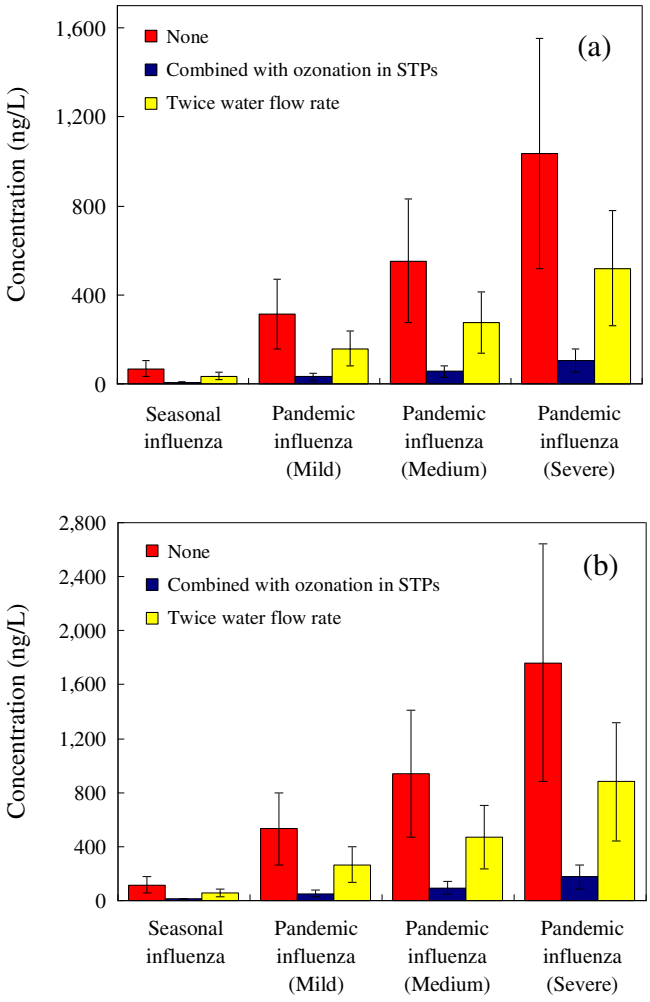

Fig. 3. Estimated OC concentrations during a peak influenza outbreak without reduction efforts, with ozonation, and with doubling the water flow rate, at Hirakata Bridge (a) and Miyamae Bridge (b). Error bars indicate a range between the predicted minimum and maximum values. Annual flow volumes were used in this study (Hirakata Bridge: 13,300,000 m^3/day and Miyamae Bridge: 2,060,000 m^3/day (Azuma et al., 2013)).

These results suggest that it is possible that drug-resistant influenza virus can originate from wildfowl during a large-scale influenza pandemic with increasing concentrations of anti-influenza drugs in river water. However, applying ozonation during sewage treatment at sewage plants was shown to significantly reduce the pollution load of these drugs introduced into the aquatic environment, reducing the impact on the environment regarding a drug-resistant virus outbreak originating from wildfowl. It was also suggested that further environmental risk could be reduced by temporarily doubling the river water flow during influenza pandemics.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2015.03.069.

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