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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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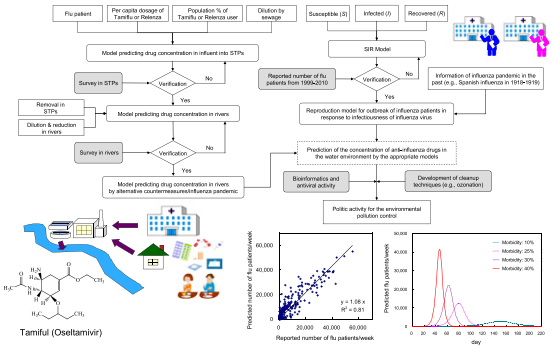
HIGHLIGHTS

- 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