

Research Article

Multi-Agent Simulation of Influenza Outbreaks Based on Small Data to Evaluate the Effect of Control Measures

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ABSTRACT

It is difficult to predict where, when, and who will be affected by any given epidemic. An asymptomatic carrier of influenza can be infectious before the onset of symptoms, which makes it difficult to determine the infection status, such as when, where, and from whom they were infected. In this study, first, the spatiotemporal behavioral history and clinical information of all students at a Japanese boarding school during multiple influenza epidemic waves were collected and recorded as small data. Next, a spatiotemporal mathematical model (SEPIR) based on this data was proposed, and the parameters were calculated. It is confirmed that the infectivity rate should be divided into two phases and types of rooms. Finally, the effectiveness of several infection control measures against influenza outbreaks was evaluated using validated Multi-Agent Simulation (MAS).

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1. Introduction

Influenza (the flu) is one of the greatest epidemics known to humankind and the damage must be minimized. The number of deaths from the flu had been declining since 1970, but it has been gradually increasing again in the 21st century globally and in Japan [1]. School closings due to the flu are also on the rise in Japan this century [2]. Here, it is said that vaccinations have suppressed outbreaks at schools and prevented infections among the elderly and infants in Japan in the 1980s [3]. In other words, suppression of outbreaks at schools could potentially prevent flu epidemics, and it could prevent a nationwide epidemic. It is expected to contribute to reducing social loss.

In Japan, the weekly number of new flu patients is reported by the Ministry of Health, Labor and Welfare, based on data from approximately 5,000 sentinel medical institutions [2]. Each institution can only access information on patients who have visited the institution. It is difficult to grasp the infection status of each patient, such as their behavior, date of infection or recovery, and infection route. Furthermore, it is difficult to obtain individual clinical information and behavioral history, including healthy individuals, within a population. Therefore, it is difficult to analyze causal relationships, such as when, where, and from whom infection occurred, using conventional infectious disease research based on

statistical methods [4]. It is pointed out that epidemiology has neglected efforts to collect information on the contact patterns of populations [5]. Here, boarding schools can provide the missing data. It is important to keep reliable records as much as possible [6]. The flu has many challenges because asymptomatic individuals can be infectious before the onset of symptoms [7].

Flu outbreaks have occurred among Japan Coast Guard Academy (JCGA) undergraduate students since 2017. JCGA is a boarding school, which has classrooms, dormitories and a medical office. There are some training courses and about 200 students were in the undergraduate course at that time. Some of them were absent because of ship training. The students are males and females in their late teens to early twenties. None of the teachers who had some contact with the students, developed similar symptoms.

The first situation occurred in January 2017 at the campus [8]. On January 13th after a three-day holiday, two of 150 students first developed symptoms. Then, 37 developed symptoms within two weeks (situation A). The second situation occurred in January 2019 on a training ship [9]. On January 10th, after winter break, one of 56 first-year students developed symptoms. Then, 18 developed symptoms within two weeks (situation B). Another situation occurred on January 2019 at the campus [9]. On January 9th, after winter break, six of 109 students developed symptoms. Then, 13 developed symptoms within two weeks (situation C). Subsequently, we

classified situations A and B as flu outbreaks. Our medical doctor said that about five students develop symptoms during a typical flu epidemic wave.

In this paper, we collected and recorded daily data on three flu waves from the academic affairs office, student affairs office and medical office at JCGA [8], [9]. We organized it as small data, which is easy to access and focuses on finding causal relationships [10]. Our data is invaluable as it records epidemic information on all members of a closed group. Whereas the applicability of typical models is limited because traditional public health surveillance relies heavily on statistical techniques [4].

2. Mathematical Model

The SIR model is a traditional epidemic model [11]. An individual in a susceptible state "S" can transition to an infectious state "I" by contact with individuals in state "I" at a rate β . An individual in state "I" transitions to a recovered state "R" depending on how long they have been in "I". Exposed state "E" is introduced between "S" and "I" in the SIR model, and an individual in state "S" can transition to an exposed state "E" by contact with individuals in state "I," which is SEIR model for infectious diseases with incubation periods [12]. The incubation period is the exposed period.

At JCGA, because infected students are quarantined in a sick room, patients cannot infect susceptible students. However, flu outbreaks occurred several times. This is because asymptomatic students unknowingly infected healthy students in classrooms or dormitories. We introduced pre-infectious state "P" between "E" and "I," and proposed a spatiotemporal SEPIR model for the flu as shown in Figure 1 [8], [9]. In the incubation period, an exposed student is not yet infectious, but a pre-infectious student is.

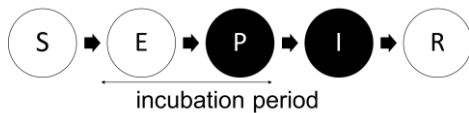


Figure 1 The state transition diagram of a student and incubation period: circle shows state of student. S: susceptible state, E: exposed state, P: pre-infectious state, I: infectious state and R: recovered state. Black circle means that it can affect others.

Similar to former models [11], [12], the difference of the number of "S" students is given by Eq (1) using a mean infectivity rate α (per day). The SEPIR model is a discrete-time model unlike previous research [11], [12], and t represents the day. The subscript k indicates the room, and the SEPIR model is a spatial model, as well. Transition rate σ (per day) is the inverse of the exposed period, and recovery rate γ (per day) is that of the infectious period. The difference of the number of "P" students is given by Eq (3) using transition rate τ (per day). We set transition rate τ (per day) as the inverse of the pre-infectious period. $P_k(t)$ is the number of pre-infectious students in the room. $S_k(t)$ is that of susceptible students, $E_k(t)$ is that of exposed

students, $I_k(t)$ is that of infectious students, and $R_k(t)$ is that of recovered students who have successfully cleared the infection in the room.

$$\Delta S_k = -\alpha S_k(t)P_k(t) - \beta S_k(t)I_k(t) \quad (1)$$

$$\Delta E_k = \alpha S_k(t)P_k(t) + \beta S_k(t)I_k(t) - \sigma E_k(t) \quad (2)$$

$$\Delta P_k = \sigma E_k(t) - \tau P_k(t) \quad (3)$$

$$\Delta I_k = \tau P_k(t) - \gamma I_k(t) \quad (4)$$

$$\Delta R_k = \gamma I_k(t) \quad (5)$$

3. Estimation Parameters

The patient's health condition in situation A is shown in "I" of Table 1 [8]. (The remaining parts will be explained later.) There are 37 infectious students between January 9th and January 26th. Base time is 8:30 am on January 9th. First column (ID) is student identification number. The next 18 columns show the daily state of the students. "I" means infectious and isolated in the sick room. The last columns (ND) is the isolated days of the student. The average infectious period is 3.86 days.

Table 1 The Outbreak of Flu in January 2017

I: Infectious state. Date with under bar means holiday.

ID	D a t e																		ND
	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
1	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	R	4
2	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	R	4
3	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	5
4	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	5
5	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	5
6	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	4
7	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	R	3
8	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	5
9	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
10	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
11	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
12	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
13	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
14	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
15	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
16	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
17	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
18	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
19	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
20	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	3
21	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	3
22	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
23	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
24	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	4
25	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	3
26	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	3
27	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	R	2
28	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	R	4
29	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	R	4
30	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	4
31	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	4
32	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	4
33	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	3
34	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	R	3
35	S	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	R	4
36	S	S	S	S	S	S	S	S	E	P	P	I	I	I	I	R	R	R	3
37	S	S	S	S	S	S	S	S	S	E	P	P	I	I	I	I	I	R	5

3.1. Period of the States

We can easily set the state "R" on the right hand side of "I" in Table 1. We have to set the states "S", "E" and "P" on the left hand side of "I" in Table 1 to calculate the parameters of the equations. We estimate how long it takes to change states. We can calculate back to patients in all rooms because there are not so many students and they are managed by JCGA. Students live according to a daily schedule. On weekdays, students wake up at 6:30 am in the dormitory. Then, they go to classrooms to take classes. They take, at most, four 90-minute classes a day. Then, they exercise and do self-study, and go to sleep at 10:30 pm in the dormitory.

Flu viruses spread by droplet transmission [7]. We focused on closed spaces and analyzed infection channels. The spaces are 35 classrooms, 50 dormitory rooms and 22 study rooms. As for time, we analyzed maximally 17 hours and 15 minutes on a weekday. According to students, it is too cold for students to go out on weekdays in mid-winter. Therefore, we can regard JCGA on weekdays as closed spaces at that time. It was easily determined that the flu outbreak at JCGA originated from two patients. We analyzed the health condition and infection channel of students.

According to the U.S. Centers for Disease Control and Prevention (CDC), the incubation period is between one and four days and the pre-infectious period is one day [7]. The incubation period consists of the exposed and pre-infectious periods. To decide the exposed and incubation period at JCGA, we compare 10 combinations.

Figure 2 shows the infection channel on weekdays, and Figure 3 shows that of weekends. The horizontal axis refers to the combinations of pre-infectious periods (numerator) and incubation period (denominator). And the vertical axis refers to the number of infected students in the room with students in exposed state. It is expected that the longer the incubation period, and the higher the proportion of "P," the higher the probability of identifying the infection channel. Blue bars indicate that students were infected in their own dormitory rooms. In Figure 2, green bars indicate that students were infected in their classrooms on weekdays. The slashed green line bars indicate that students were infected in both their own dormitory rooms and classrooms. Pink and yellow bars indicate that the infection channel is unknown. In Figure 3, orange bars indicate that the infection occurred while outside JCGA on weekends. Yellow bars indicate that the first two patients were infected while outside JCGA on weekends. We can put together dormitory rooms and study rooms by preliminary study.

We found as follows. Contrary to expectations, a longer incubation period is not helpful in explaining infection channels. There are many unknown infection channels, especially when the incubation period is four days. Furthermore, when the incubation period is one or two days, the infection channel of the first patients is unknown in Figure 2, which is assumed to be from while outside

JCGA on holiday (Figure 3). Therefore, a three day incubation period remained as a candidate.

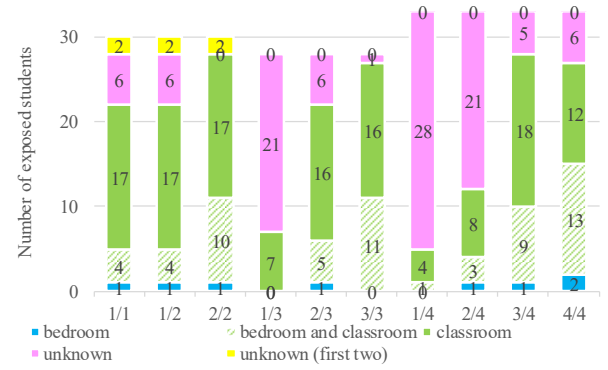


Figure 2 Infection Channels on Weekday

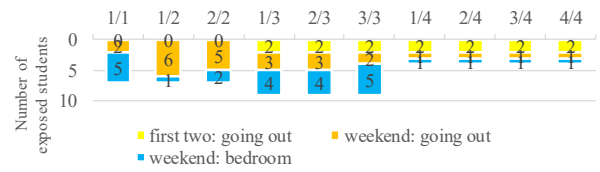


Figure 3 Infection Channels on Weekend

As expected, the number of unknowns decreases as the proportion of "P" increases. Then, combination 3/3 looks the best. The combination means that students are pre-infectious throughout the incubation period. It may be overestimated because we investigated only 72 % of activity time in a day. Therefore, combination 2/3 is plausible. That is, the pre-infectious period is two days, which is longer than that of CDC, and the incubation period is three days.

We could trace 22 infection channels out of 28 students on weekdays, and 31 infection channels out of 37 of all students. And we confirmed 26 campus transmissions from the first two patients. Then, we filled in the state of the student's "S", "E", "P" and "R" in Table 1 [9], [13].

3.2. The Period and Transition Rates

The incubation period is three days and transmission rate σ is 0.333. The pre-infectious period is two days and transition rate τ is 0.5. The average infectious period is about 4 days and recovery rate γ is 0.25. Because infectious students are quarantined in the sick room, we can set $\beta = 0$ at JCGA [8], [9], [13].

According to data, we defined an outbreak as the daily number of new infectious students over 7% of the JCGA community. Therefore, we classified situations A and B as flu outbreaks and situation C as not an outbreak [14].

For flu outbreak situations A and B, we acknowledged that the infectivity rate should be divided into two phases and types of rooms [9], [13]. Focusing on all students' state "P", the infectivity rates α were calculated. Here, we defined the date of onset for the first patient as D-day. The average infectivity rate in classrooms until D-day is 0.041, and thereafter it is 0.002. That of dormitory rooms until D-

day is 0.041 and thereafter it is 0.013. We confirmed that the infectivity rates until D-day are 0.041, and high in both rooms. After D-day, the infectivity rates are smaller than that until D-day, especially in classrooms. Whereas in non-outbreak situation C, the average infectivity rate is 0.0021 in classrooms and 0.0068 in dormitory rooms on all days. They are at the same level as that after D-day.

Table 2 The Average Infectivity Rate of Room's Type

The average infectivity rate	Classrooms		Dormitory Rooms	
	until D-day	after D-day	until D-day	after D-day
	0.041	0.002	0.041	0.013

4. Multi-agent simulation (MAS)

The validity was confirmed by reproducing the flu outbreak using MAS and the parameters [15], [16], [17]. MAS is a virtual experiment involving multiple autonomous entities (agents) [18], [19]. In the MAS, the components are agents, behavior, space, interaction, and time. In this paper, the agent is a student. The effectiveness of several infection control measures was evaluated using the MAS [14]. Basic preventive measures, such as wearing masks, washing hands and better ventilating rooms, for the first five days after winter break is effective.

5. Conclusion

Spatiotemporal behavioral history and clinical information from all students at JCGA during three flu epidemic waves were collected and recorded as small data. Next, a discrete spatiotemporal mathematical model (SEPIR) based on this data for the flu was proposed, and the parameters were calculated. At JCGA, the incubation period was three days, and students can infect others beginning two days before symptoms develop. Infection channels of patients on weekdays and weekends are estimated. It is confirmed that the initial two patients led to 26 cases of infection on campus. It is confirmed that the infectivity rate should be divided into two phases and types of rooms, as well. Finally, we quantitatively evaluated the effectiveness of several infection control measures against flu outbreaks using validated MAS. We confirmed that basic preventive measures for the first five days after winter break are effective.

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