An Agent-Based Model of Infectious Diseases that Incorporates the Role of Immune Cells and Antibodies

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Abstract

An agent-based infection model that takes into account the role of immune cells and antibodies has been constructed, and the effects of various factors on the spread and convergence of infection were analyzed. The resulting data show that the calculated numbers of newly infected, newly recovered, and overall infected individuals were qualitatively consistent with actual phenomena for Severe Acute Respiratory Syndrome Coronavirus 2. The model reveals that an essential factor for the spread of infection is the number of infected persons encountered by a healthy person, whereas the existence of antibodies is not an essential factor influencing the fundamental behavior of the spread and converge of infection. Based on these results, the fundamental mechanism for the spread of infection is that the probability of a healthy person encountering an infected person increases progressively, and the primary mechanism for the convergence of infection spread is that the above probability decreases progressively as the number of recovered people increases. Therefore, to effectively control the spread of infection while minimizing economic deterioration, it is essential to identify infected persons, regulate their behavior, and minimize the probability of healthy persons encountering infected persons.

Keywords: agent-based model, infectious disease, SARS-CoV-2, immune cells, antibodies, pandemic, infection, recovery

1. Introduction

Since the novel coronavirus, i.e., Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first discovered in December 2019 in China, SARS-CoV-2 has spread worldwide, and the number of infections is still increasing in most countries. Although the regulation of social movement has led to the number of infections reaching a low level as of July 10, 2020 [17], many countries are beginning to ease the tight control of social activity to recover the economy despite worries about the emergence of a second wave of this SARS-CoV-2 pandemic.

Many mathematical models for forecasting the emergence of a pandemic were constructed long before the ongoing pandemic began [1-6]. Most of these models, whether classified as deterministic or probabilistic, can be described as system-dynamics models such as the SIR model or SIER model, consisting of a set of equations to be solved simultaneously. However, these equation-based models have the fatal flaw of being unable to describe the complex interactions among heterogeneous agents that are the essential cause of infectious disease propagation. Furthermore, such models do not provide knowledge on the influential factors for recovery as well as the occurrence of second wave of pandemic, because they do not describe the post-infection recovery process from the bottom-up.

Agent-based modeling (ABM) is a modeling method suitable for describing the heterogeneity of the behaviors of agents [7-8]. In ABM, an artificial society is constructed on a computer, and various social phenomena caused by the behavior and interactions of agents are reproduced from the bottom-up. Thus, ABM is an effective way to understand the underlying mechanism and solve economic and social problems [8-11]. ABM has various advantageous features, such as being able to deal with heterogeneity and discrete phenomenon [7]; the essential advantageous characteristic of ABM is that it is a bottom-up modeling method.

Because social phenomena emerge due to the humans' actions and interactions, we can use ABM to construct an artificial society that works in the same principle as the real world. Notably, a model can work in this way only when that model is entirely bottom-up without using any aggregate-variable-related assumptions. Moreover, the type of agents and their behavioral rules and the relevant variables, i.e., the system structure, must be

incorporated as realistic as possible that reflects the micro-level phenomena to reproduce the macro-phenomena [9-11].

Although ABM has also been applied to the problem of disease [12-15], most of the resulting models are not fully bottom-up in that they employed aggregate-variable-related assumptions. In the few cases, the applied ABM was entirely bottom-up regarding the spatial interaction among agents. However, it does not model the post-infection recovery process using a fully bottom-up method, meaning that the infected were assumed to become immune at a certain period and never be infected again [12]. Thus, although models of this type can mimic the spatial interactions among agents that cause infection, they cannot reproduce the specific behaviors that increase or decrease the numbers of newly infected, newly recovered, and total infected persons without using macroscopic assumptions. Moreover, such models cannot predict the emergence of the second wave of a pandemic after easing regulations concerning social movement.

According to statistical data [17], the number of total infected, newly infected, and newly cured persons peaked at different periods [17]. Conventional models cannot explain these features without using macroscopic assumptions, neither the equation-base model nor the ABM model.

According to the medical findings, when a person is infected, the viruses enter the host's body and keep replicating, increasing the number. Regarding the function of innate immune cells and antibodies, it is well known [16] that innate immune cells are the first to attack the virus, followed by antibodies' attack. Typically, antibodies are produced after a certain period, and they join the fight against the virus. The research data also shows that most recovered individuals had a weak antibody response, indicating that the number of recovered individuals with antibodies is small [18].

Based on these medical findings, the fundamental substance that characterize the infectious state is the virus, and the essential factors that characterize the recovery process are immune cells and antibodies. However, there seems almost no epidemic models previously reported that takes into account these micro-factors. Based on this idea, the present research developed an agent-based model that incorporates the role of immune cells and antibodies and the number of viruses, and compared the resulting data with real-world statistical data. The underlying mechanism of infection spread and conversion and the conditions for balancing infection control and promotion of the economy are discussed.

2. The model

2.1 Model outline

This model features that it considers the role of immune cells and antibodies and the number of viruses. On the other hand, the interaction among agents is simplified, assuming random movement of agents. The attribute variables of agents and parameter values are presented in Table 1, where the variables that are defined by a uniform random number are agent-specific variables. The characteristic variables calculated in the model are given in Table2.

In this model, human agent is an only object that moves randomly in the two-dimensional space of 1km^2 every period. The number of human-agent is assumed to be 2000, and their initial positions in the 2-dimensional space are assigned randomly for each agent. The movement distance and the direction are assigned every period by a uniform random number as given in Table 1. One of the individual humans is initially an infected agent, having many viruses, i.e., viral particles, the number of which is an attribute variable. An agent is assumed to meet with another agent to become a neighbor when located within the critical distance which is assumed 5m. The infected human is assumed to release a part of the viruses every period at a predetermined virus-releasing rate in the form of a cough or other means. Thus, any agent who meets the infected neighbor receives a portion of the released viruses at a predetermined virus-absorbing rate, becoming a newly infected agent. A decrease in the virus-absorbing rate corresponds to wearing masks or face shields in the real world. The increasing increment of the number of viruses transferred from the infected to a healthy individual is assumed as given by equation (1).

$$\Delta N^{i}{}_{Infected}(t) = \sum_{j \in neighbors} N^{j}{}_{VP}(t) * Rate^{j}{}_{Release} * Rate^{i}{}_{absorb} \quad (1)$$

where, $\Delta N^{i}{}_{Infected}(t)$: number of viruses of agent i transferred from neighbor agents at the time t

$N_{VP}{}^{j}(t)$: number of viruses of agent j at the time t

$Rate^{j}{}_{Release}$: virus releasing rate of agent j

$Rate^{i}{}_{absorb}$: virus absorbing rate of agent i

If an agent is infected, immune cells attack the viruses at every time step, reducing them at a predetermined virus-attack rate of immune cells or antibodies. The decreasing increment of the number of viruses at the time t is assumed as given by equation (2). Here, virus attack rate takes different values if antibodies are present or not. Antibodies are assumed to emerge that attack the viruses with a much larger rate than that of immune cells, after a predetermined antibody-emerging period, if agent's viral particles exist more than the minimum number. This minimum number of viruses for the antibody emergence is assumed as the product of the number of viruses and the predetermined minimum-virus-count-multiple. The condition for the emergence of antibodies is assumed as given by equation (3).

$$\Delta N^{i}{}_{VP}(t) = N^{i}{}_{VP}(t) * Rate^{i}{}_{attack} \quad (2)$$

where, $\Delta N^{i}{}_{VP}(t)$: Decreasing increment of the number of viruses during the time step t

$Rate^{i}{}_{attack}$ = Virus attack rate of immune cells or antibodies

$$t - t^{i}{}_{infected} > t^{i}{}_{antibody\_emerging} \quad and \quad N^{i}{}_{VP}(t) > N^{i}{}_{VP}(t^{i}{}_{infected}) * Multiple^{i}{}_{antibody\_emergence} \quad (3)$$

where, t : Current time, $t^{i}{}_{infected}$: Time of infection of agent i

$t^{i}{}_{antibody\_emerging}$: Elapsed period for antibody emergence of agent i after infection

$Multiple^{i}{}_{antibody\_emergence}$: Virus count multiple for antibody emergence

The resultant viruses are assumed to multiply, increasing the number, due to viral replication at a predetermined virus replication rate. The virus replication rate represents the rate of increase in the number of viruses per time step, and is assumed constant during the calculation. Thus, the number of viruses is redefined at every time step in the calculation according to equation (4).

$$N^{i}{}_{VP}(t+1) = (1 - Rate^{i}{}_{Release} - Rate^{i}{}_{attack}) * N^{i}{}_{VP}(t) * Rate_{growth} + \Delta N^{i}{}_{Infected}(t) \quad (4)$$

where, $Rate_{Release}$: virus releasing rate of agent i

$Rate_{attack}$: Virus attack rate of immune cells or antibodies of agent i

$Rate_{growth}$: Virus replication rate defined as a constant value

$\Delta N^{i}{}_{Infected}(t)$: Increasing incerment of the number of viruses due to infection

When the number of viruses of an agent becomes smaller than the critical lower limit, it is assumed to be zero as given by equation (5); at this time, the agent state changes from infected to recovered, being classified as newly recovered. Here, the number of viruses is in an arbitrary unit, so that it could be far below 1 in the present model.

$$N^{i}{}_{VP}(t) = 0, \; if \; N^{i}{}_{VP}(t) < N^{i}{}_{\min} \quad (5)$$

where, $N^{i}{}_{\min} : n_{limit} * virus\ releasing\ rate * virus\ absorbing\ rate$

n_{limit} : Critical value for zero viruses assumed as 10^{-9}

The present model does not incorporate agents' death because it requires a massive population, meaning that the calculation time needed becomes too large. Moreover, the death rate is so low compared to the infection rate that it is not an essential factor in the mechanism of infection spread and convergence. Therefore, all the infected agents finally become recovered in this model unless the virus replication rate is assumed too large.

The model is programmed by the author using C++ with object-oriented programing. The fundamental classes used in the model are "Human," which moves randomly, "Germ" which is held by a Human class and responsible for the calculation of virus-related variables, and "Network" which manages the position of Humans and responsible for the calculation of the infection among agents. These classes refer to infection-related variables with each other.

Table 1. Attribute variables of agents and parameter values

Variables	Initial value or definition
Number of agents	2000
Area of network system	1000×1000
Maximum Distance of agent's move	100
Critical distance for infection	5
Initial number of the infected	1
Number of virses hold by the infected initially	5000×100 (arbitrary unit)
Virus replication rate	1.4, 1.6, 1.8, 2.0
Virus attack rate by immune cells	0.3 ± 0.1 uniform random number
Virus attack rate by antibodies	0.5 ± 0.1 uniform random number
Virus-count multiple for antibody emergence	0.5 ± 0.2
Elapsed period after infection for antibody emergence	7 ± 2 uniform random number
Minimum-virus-count multiple for zero viruses	0.001*0.001*0.001 (arbitrary unit)
Virus releasing rate	0.1 ± 0.05 uniform random number
Virus absorbing rate	0.1 ± 0.05 uniform random number
Position (x,y) in the 2 dimentional space	defined at every step
Distance of agent's move	[0,maximum distance] uniform random number
Direction of agent's move	$[0,2\pi]$ uniform random number
Agent as an object in the neighbour	defined at every step
Number of virses	calculated at every step

Table 2. Characteristic variables calculated in the model

Variables related to individual's attribute	Variables related to the state of the network system
Number of viruses	Average number of neighbours per capita
Position in the 2 dimentioanal space	Number of the infected(% per capita)
Agents of nearest neighbour(Object)	Number of the newly infected(% per capita)
Number of viruses contaminated by infection	Number of the newly recovered(% per capita)
Infection-related state variables	Accumulated number of the infected(% per capita)
Uninfected, Infected	Accumulated number of the recovered(% per capita)
Infected with antibody	Number of the recovered with antibody(% per capita)
Infected without antibody	Number of the recovered without antibody(% per capita)
Recovered with antibody	Number of the infected with antibody(% capita)
Recovered without antibody	Number of the infected without antibody(% per capita)

The calculation is processed according to the following steps. The flowchart of the calculation is presented in Figure 1.

a) Define parameter values.
b) Create various class object and set initial values of variables.
c) Repeat following steps until reaching the maximum time step.
   c-1) For each agent, redefine the agent's position, define the neighbor agent, calculate the change in the number of viruses, and print out agent's attribute variables.
   The agent's attribute variables include the number of viruses transferred from infected agents at the time of new infection, the number of viruses decreased due to the role of immune cells or antibodies, the number of viruses increased by the virus replication, various state variables.
   c-2) Calculate aggregate variables such as the number of infected agents, etc., and print out the results.

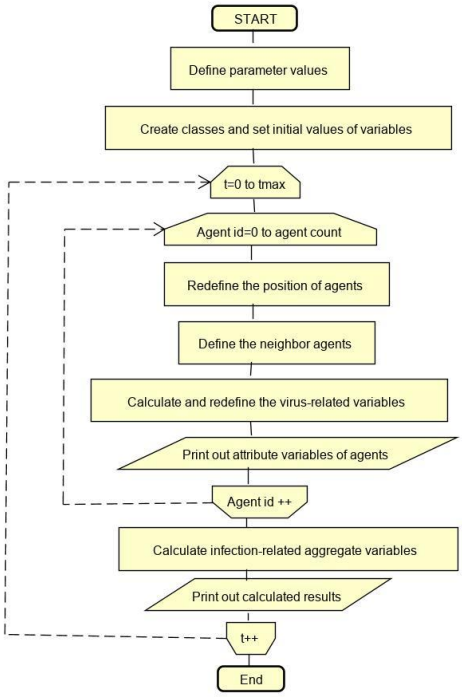

Figure 1. The flowchart of the calculation

3. Experimental conditions

3.1 Analysis items at each time step

At each time step, the numbers of the following were calculated: infected agents (% per capita), newly infected agents (% per capita), newly recovered agents with or without antibodies (% per capita), human agents who meet another human agent (per capita), and the infected and uninfected neighbors of each agent (per capita). Also, the calculated results were compared with the statistical data available in the real world.

3.2 Experimental conditions

The influence of the following factors on the abovementioned variables was analyzed: 1) virus replication rate, 2) maximum traveling distance 3) virus-absorbing rate (accounting for mask use), and 4) regulations and mitigations of agent movement that includes the temporal regulation of traveling distance with or without reducing the virus-absorbing rat, and 5) existence of antibodies.

4. Calculated results

4.1 Fundamental behavior during infection and recovery

4.1.1 Behavior of the number of viruses of each agent during infection spread and convergence

This model features that we can calculate the number of viruses of each agent at each time step. The aggregate variables, such as the number of infected agents, etc., are evaluated at each time step based on this value, as explained in the previous section. Figure 2 shows an example of the change in each agent's number of viruses in the beginning stage of infection spread. This example is when the virus-replication rate and the maximum traveling distance are assumed to be 1.8 and 100, respectively. Figure 1 shows how infections propagate from agent to agent in this artificial system. This example of calculated results show that Agent 1 is the only infected agent initially, and Agent 13 is infected by Agent 1 at the time of 4. The next agent who is infected by Agent 1 is Agent 155 at the time of 25. However, before Agent 155 is infected, Agent 13 infects Agent 1373 at the time of 6, and infection propagates from Agent 1373 to Agent 1019, and from Agent 1019 to Agent 1911. In this way, this model thus allows individual tracking of the details of the infection process. The same is true for the recovery process.

Note that, in Figure 2, the slope of the change in the number of viruses shows positive or negative just after the infection. Here the slope in the number of viruses depends on the relative magnitude relationship between the virus replication rate and the immune attack rate. If the effect of replication is larger than that of immune cells, the slop becomes positive, and vice versa. Moreover, note that, after some infection period, the slopes of all agents become negative, and their magnitudes become more extensive due to the emergence of antibodies. The slope's magnitude is different for each agent due to the agent-specific value of the antibody attack rate.

During the infection and recovery, an agent could be infected multiple times. Figure 3 shows such an example. Note that, as seen in Agent 1556 in Figure 3, the decreasing speed in the number of viruses may change during the decline. This change results due to the emergence of antibodies. In Agent 613, there is no speed change during the decrease in the number of viruses, indicating that the agent is recovered before the emergence of antibodies. Whether antibodies emerge or not depends on the number of viruses at the time of infection, the agent-specific value of the antibody-emerging period, and immune-cells' virus attack rate.

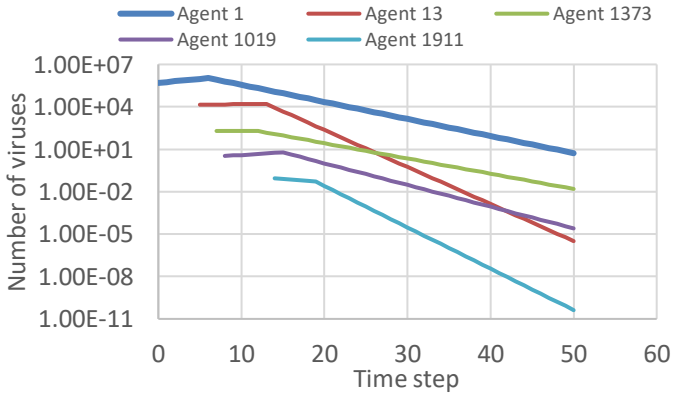

Figure 2. Change in the number of viruses of agent, showing the procedure of infection spread in the beginning stage of infection spread (Virus replication rate =1.8).

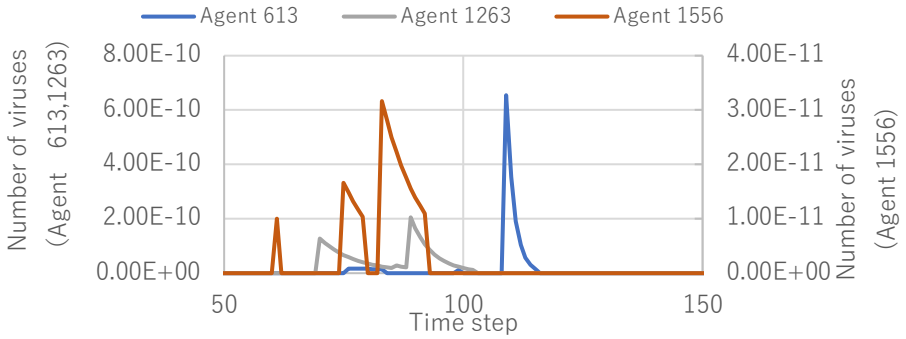

Figure 3. Examples of cases where agents are infected multiple times. Calculation condition is the same as Figure 1.

Figures 4 and 5 show the behavior of the number of viruses during infection spread and convergence. The number of viruses of each agent at the time of infection decreases during infection spread and convergence, as shown in Figure 4. This tendency results because of the effects of the virus releasing rate and virus absorbing rate. Namely, when an infection occurs, a healthy person receives a portion of viral particles released by the infected person due to a cough or other means. And the emitted viral particles are the portion of the viruses that the infected person holds. Thus, the number of viruses at the time of infection decreases during the propagation process of infection because viral particles transferred from the infected to a healthy person are only a portion of viruses that the infected person holds.

Not that as the number of viruses at the time of infection decreases, the time required for recovery becomes small, as shown in Figure 5, indicating that the time necessary to recover an infected person becomes shorter with time in the process of infection spread and convergence.

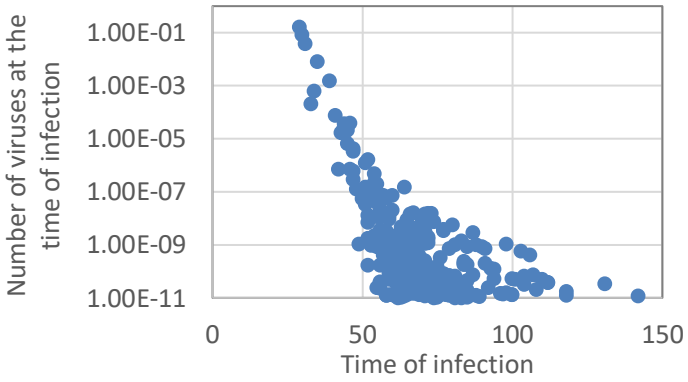

Figure 4. Number of viruses at the time of infection as a function of time during infection spread and convergence (virus replication rate =1.6).

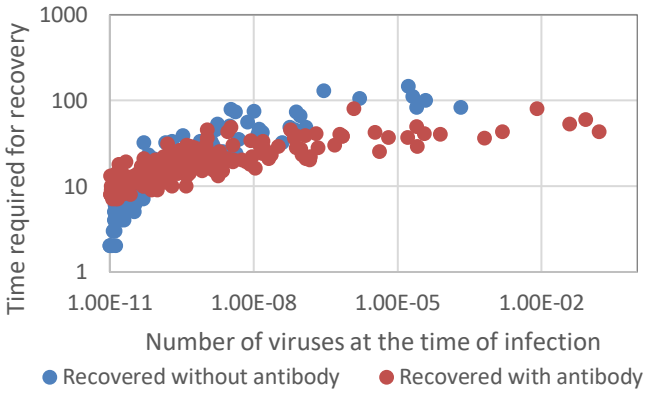

Figure 5. Time required for recovery as a function of the number of viruses at the time of infection (virus replication rate=1.6).

4.1.2 Effect of virus replication rate on the numbers of infected and recovered agents

This section describes the calculated numbers of infected and recovered agents in the case without any countermeasures against disease, where the maximum distance of movement, the virus-absorbing rate, and the virus-attack rates of immune cells and antibodies is each assumed constant.

Figure 6 shows the changes in the number of infected agents when the virus replication rate is changed from 1.4 to 2.0. The number of infected agents is represented as the percentage of the total population. When the virus replication rate is between 1.4 and 1.8, the number of infected agents increases, peaks, and decreases, ending the pandemic. These are the cases where the virus replication rate is not too large compared with the virus attack rate of immune cells or antibodies. These are the cases where the virus replication rate is not too large compared with the virus attack rate of immune cells or antibodies. In contrast, when the virus replication rate is too large such as 2.0, the entire population is eventually infected, and the pandemic does not end. When the virus replication rate is too low compared with the virus attack rate, the infection scale becomes too small to be called a pandemic. In the present model, the cases where the virus replication rate is between 1.4 and 1.8 corresponds to the issues observed in the real world; thus, the model reproduces the pandemic process's fundamental behavior without introducing any macroscopic assumptions.

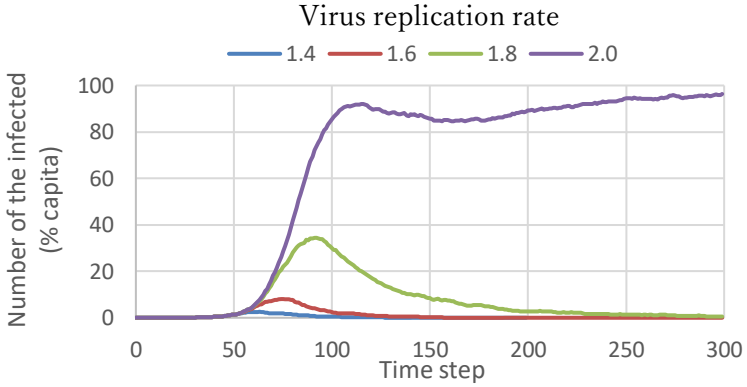

Figure 6. Effect of the virus replication rate on the number of infected agents.

We can also examine the numbers of newly infected and newly recovered agents. The number of newly infected agents, which was initially one, increases drastically, peaks, and decreases, a trend stemming from agent

interactions (Fig. 7). A similar increase and decrease appear in the number of recovered agents because of the innate immune cells and antibodies (Fig. 8).

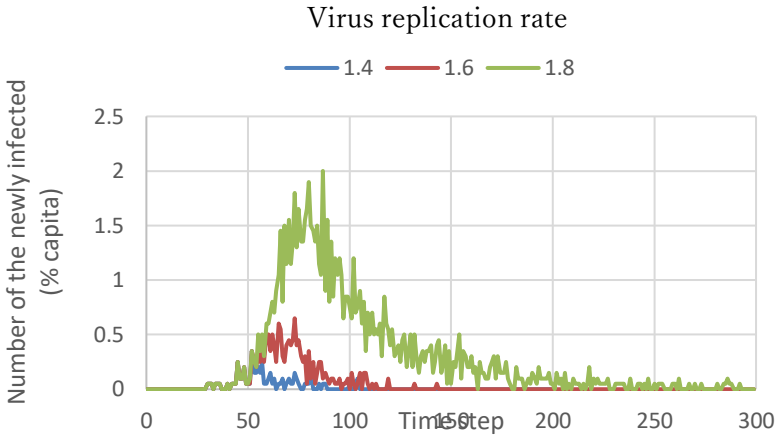

Figure 7. Effect of virus replication rate on the number of newly infected agents.

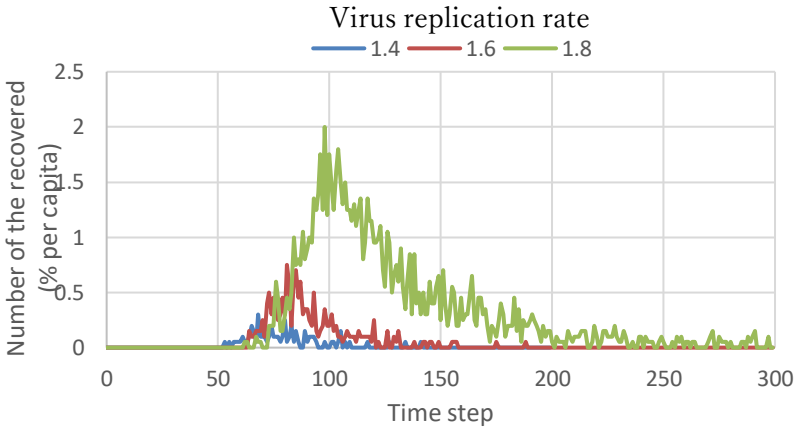

Figure 8. Effect of virus replication rate on the number of newly recovered agents.

4.1.3 The relationship between newly infected, newly recovered, and total infected agents

Figure 9 shows the numbers of newly infected, newly recovered, and total infected agents as a function of the time step. Note that the total number of infected agents peaks at the period between the peaks for the numbers of newly infected and recovered agents. More precisely, the total number of infected agents reaches its maximum at the point where the number of newly infected agents equals the number of newly recovered agents (Fig. 10). This fact is evident from the definition expression of the total number of infected agents, as shown in Equation (6). Namely, when the total number of infected agents reaches its maximum, its value at the current term equals that of the previous period. Since the present model is assumed to neglect the death rate, this condition is satisfied when the number of newly infected agents equals the number of recovered agents, as seen in Equation (6).

$$N_{infected}^{\ t+1} = N_{infected}^{\ t} + N_{newly\ infected}^{\ t} - N_{newly\ recovered}^{\ t} - N_{newly\ dead}^{\ t} \quad (6)$$

where, $N_{infected}$: *Number of the infected*

$N_{newly\ infected}$: *Number of the newly infected*

$N_{Newly\ dead}$: *Number of the newly dead*

t : *period*

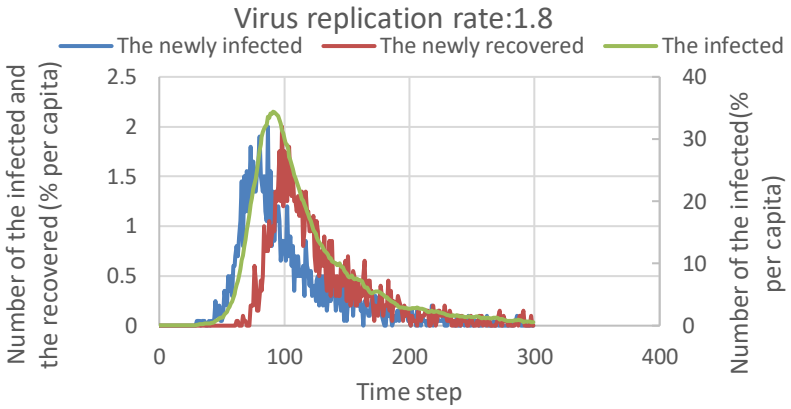

Figure 9. Changes in the numbers of newly infected, newly recovered, and total infected agents.

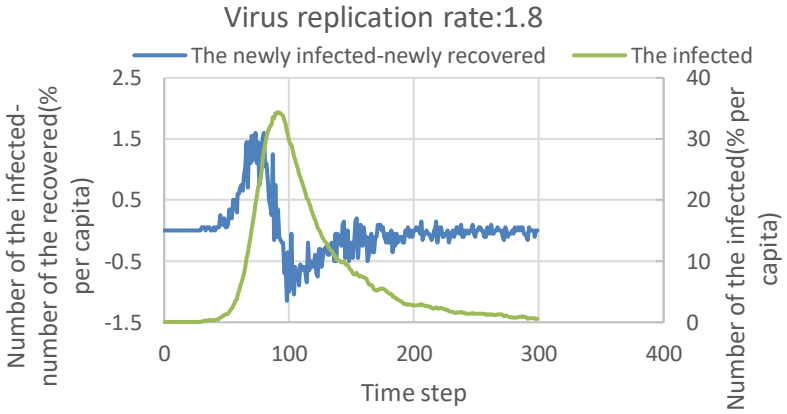

Figure 10. Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents.

4.1.4 The ratio of the recovered agents with antibodies to the total number of recovered agents

Because the present model neglects the existence of death, all infected agents eventually recover. Whether the infected agents recover with antibodies or not depends on the virus replication rate. In the case of low virus replication rates, such as 1.4, $^2/_3$ of the infected agents recover without antibodies (Fig. 11). Although the ratio of the number of recovered with antibody to the total recovered people increases with increasing the virus replication rate as shown in Figure 12, it is evident that all infected people will recover regardless of the emergence of antibodies. This result indicates that whether the people who recover with antibodies make up most of the population is not a crucial factor for the end of the pandemic.

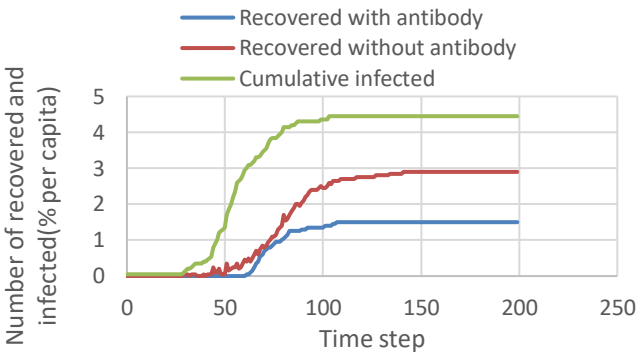

Figure 11. Changes in the numbers of recovered agents with and without antibodies and the cumulative number of infected agents (virus replication rate: 1.4).

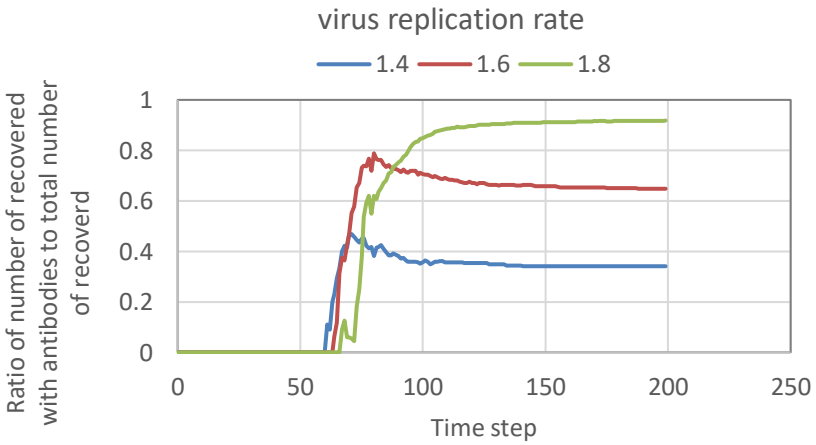

Figure 12. Effect of virus replication rate on the ratio of the number of recovered agents with antibodies to the total number of recovered agents.

4.1.5 Effect of the virus replication rate on the number of infected neighbors

In the present model, agents who exists within a distance range of 5 m are called neighbors. Neighbors who are infected are called infected neighbors.

Figure 13 demonstrate the effect of the virus replication rate on the average number of infected neighbors. Note that this pattern is very close to those of the infected and newly infected agents shown in Figures 6 and 7. There exists a close relationship between the number of infected agents and the number of infected neighbors as shown in Figure 14. The number of infected agents increases with the number of infected neighbors as shown in Figure 15. The source of scattering in Figure 15 is considered to be the scattering of the number of viruses at the time of infection. These results indicate that the leading cause of infection spread is a healthy person encountering an infected person, the repetition of which increases the probability of other healthy persons meeting an infected person, causing a progressive increase in the number of infected agents.

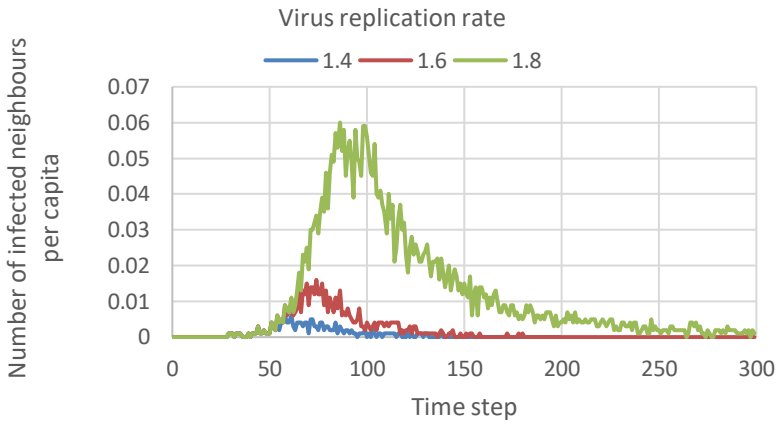

Figure 13. Effect of virus replication rate on the average number of infected neighbors.

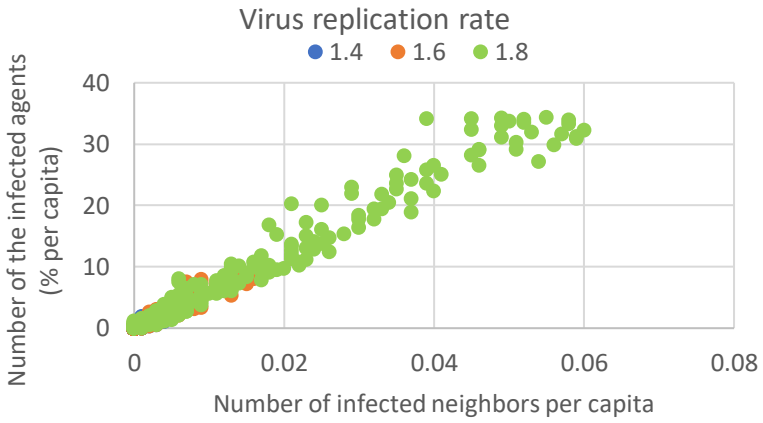

Figure 14. Relationship between the number of infected agents and the average number of infected neighbors.

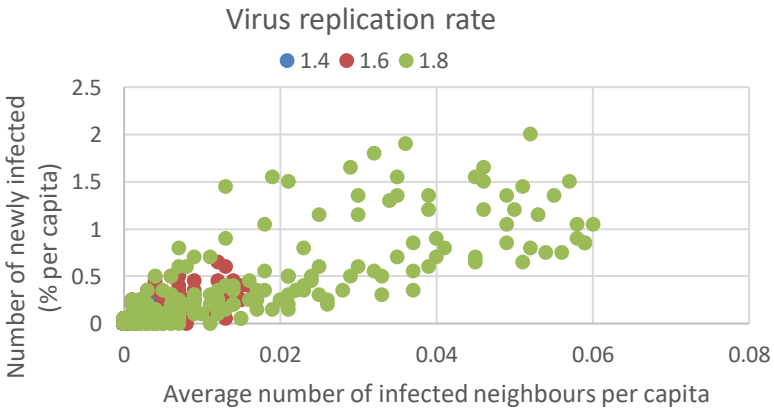

Figure 15. Relationship between the number of newly infected agents and the average number of infected neighbors.

4.1.6 Effect of maximum traveling distance on the number of infected agents

Because the present model assumes the movement concerning distance and direction is random, the probability of an uninfected agent meeting an infected agent depends on the maximum traveling distance. The calculated results presented in the previous sections correspond to cases where the maximum traveling distance is set as 100 m. How the estimated numbers of various groups are affected by doubling the maximum traveling distance can also be examined.

Figures 16 and 17 show the effect of the maximum traveling distance on the numbers of total infected and newly infected agents, respectively. Note that both factors became much more significant by doubling the maximum traveling distance. The reason for this tendency is that, as shown in Figure 18, as the maximum traveling distance increases, the average number of infected neighbors increases, i.e., an uninfected agent can meet with an infected neighbor more often.

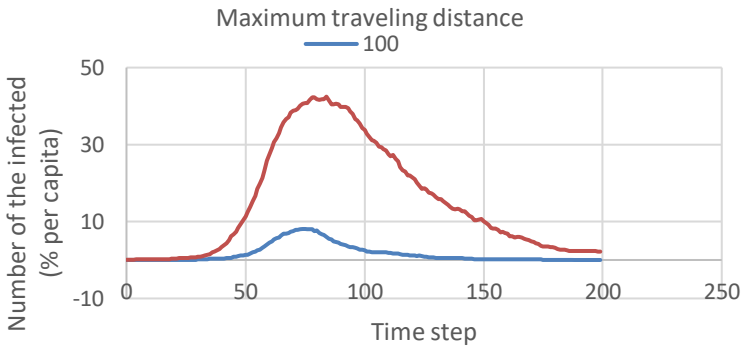

Figure 16. Effect of the maximum traveling distance on the total number of infected agents (virus multiplication rate: 1.6).

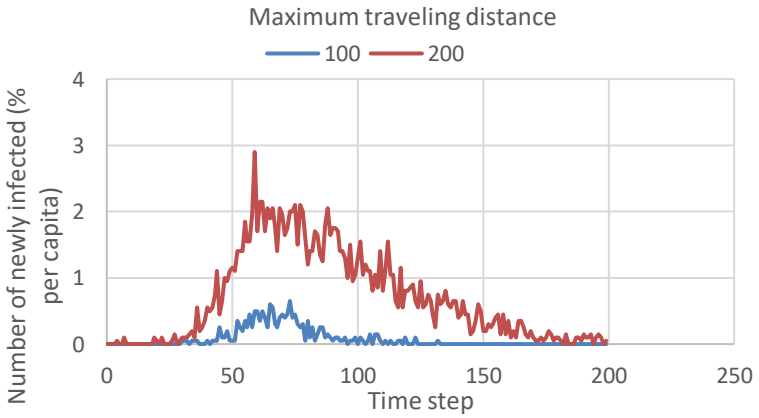

Figure 17. Effect of the maximum traveling distance on the number of newly infected agents (virus multiplication rate: 1.6).

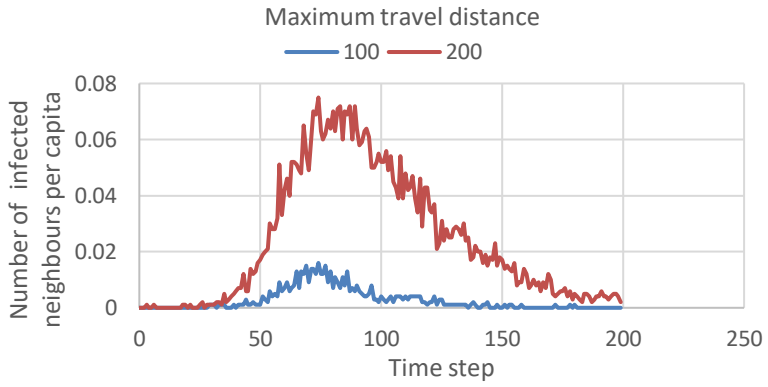

Figure 18. Effect of the maximum traveling distance on the average number of infected neighbors (virus multiplication rate: 1.6).

4.1.7 Effect of virus-absorbing rate on the number of infected agents

Figure 19 shows the effect of the virus-absorbing rate on the number of infected agents; the number of infected agents drastically decreases as the virus-absorbing rate decreases. Thus, wearing masks or engaging in infection prevention measures may be effective for decreasing the viral particles at the time of infection.

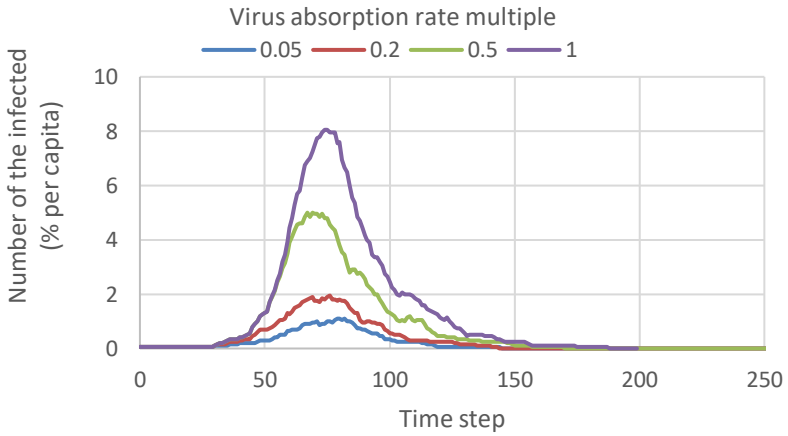

Figure 19. Effect of the virus-absorbing rate on the number of infected agents.

4.2 Comparison of the calculated results with real-world data

Figures 20 and 21 show the changes in the numbers of newly infected and recovered people and in the number of currently infected people, respectively, observed in Japan for the SARS-CoV-2 pandemic [17]. Note that the number of newly infected persons peaked around April 15, the number of newly recovered persons peaked around May 10, and both indices were almost the same around April 30. Additionally, the number of infected persons peaked around April 30.

Thus, the period at which the number of infected persons peaks coincides with the period at which the number of newly infected persons and the number of newly recovered persons are almost the same. This trend matches the calculated results shown in Figures 9 and 10. Thus, the model adequately reproduces the fundamental behavior of the numbers of infected and recovered persons.

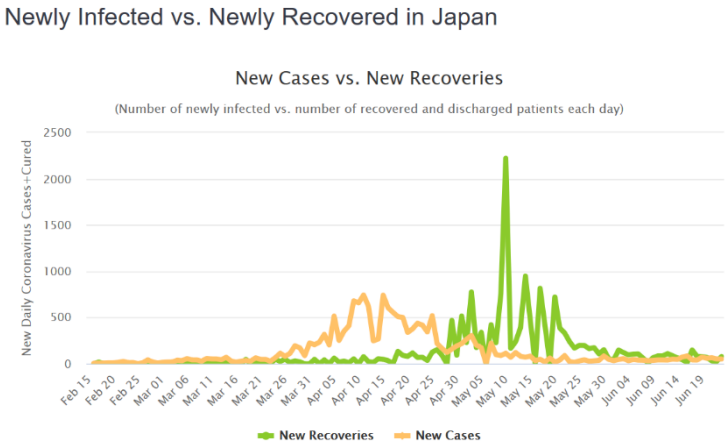

Figure 20. Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020.[17)]

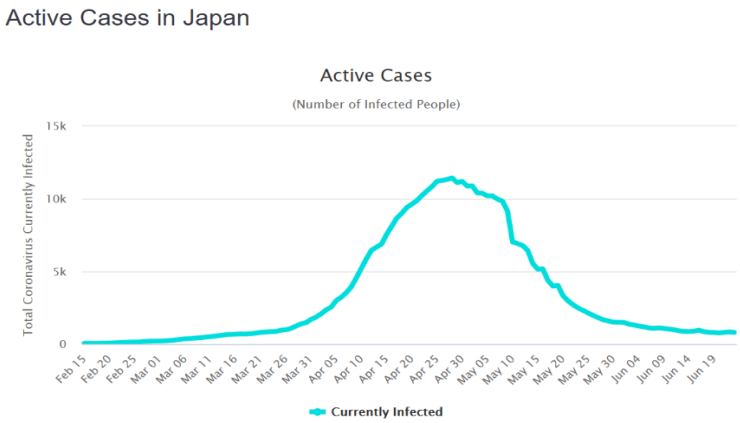

Figure 21. Change in the number of currently infected people in Japan as of June 20, 2020[17)].

4.3 Regulation and mitigation of movement and the effect of the virus-absorbing rate

4.3.1 Effect of regulating and mitigating movement

Figure 22 shows the changes in the number of infected agents under the base condition and the experimental conditions. In the experimental conditions, the maximum traveling distance is decreased by 0.2 times or 0.1 times during the period between t=50 and t=100 and is returned to the original value for the period after t=100. Notably, when the maximum traveling distance is decreased by 0.2 times, the peak value of the number of newly infected agents greatly decreases, whereas it increases again after the end of the restriction, i.e., a second wave of the pandemic arises. In contrast, when the maximum traveling distance is decreased by 0.1 times, i.e., when the regulation is applied thoroughly, the emergence of a second wave of the pandemic is not remarkable.

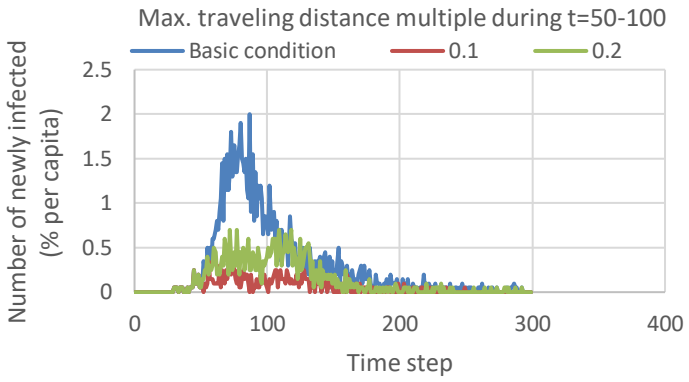

Figure 22. Effect of temporary regulation of traveling distance and its release on the number of newly infected agents (virus replication rate: 1.8).

Similar behavior is observed in the average number of infected neighbors and the total number of infected agents, as shown in Figures 23 and 24, respectively. Namely, the emergence of a second wave of the pandemic is remarkable in the case of loose regulation, whereas it is not impressive in the case of strict control. The reason for this is that, in the case of strict regulation, the number of infected agents just before releasing the rule is small. Moreover, the number of viruses of infected persons is also small resulting in faster recovery, as suggested by Figures 4 and 5. Therefore the probability of meeting with an infected agent becomes low in the case of strict regulation.

The number of recovered agents with antibodies is smaller in the case of strict regulation (Fig. 25), indicating that the increase in the number of recovered agents with antibodies is not an influential factor for preventing the emergence of a second wave of the pandemic.

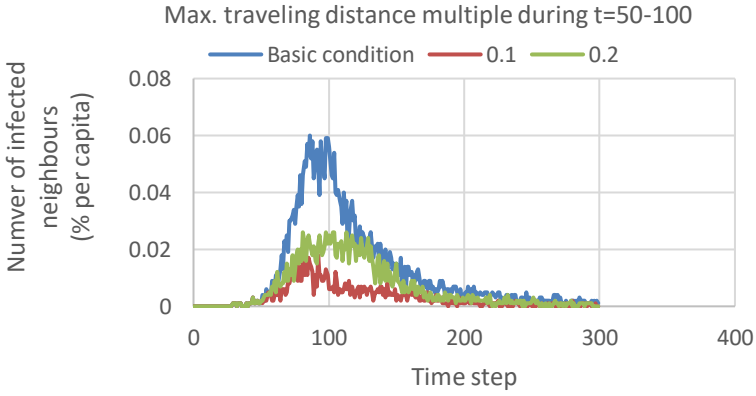

Figure 23. Effect of temporary regulation of traveling distance and its release on the number of infected neighbors (virus-increasing rate: 1.8).

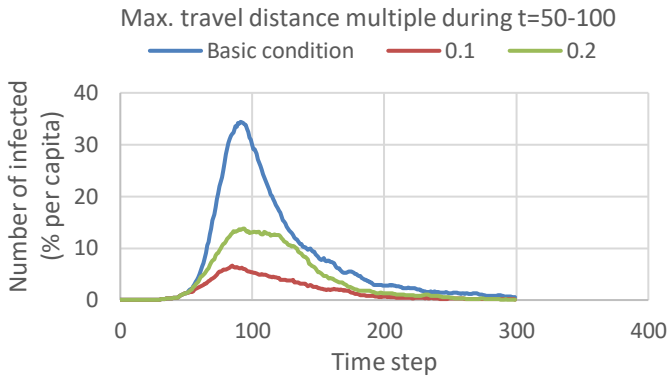

Figure 24. Effect of temporary regulation of traveling distance and its release on the total number of infected agents (virus multiplication rate: 1.8).

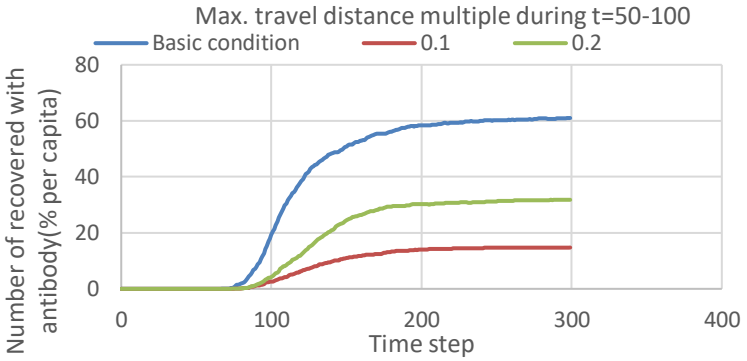

Figure 25. Effect of temporary regulation of traveling distance and its release on the number of recovered agents with antibodies (virus replication rate: 1.8).

4.3.2 Effect of the virus-absorbing rate on infection behavior during the regulation and mitigation of movement

This section describes the effect of the virus-absorbing rate on infection behavior during the regulation and mitigation of movement. Figure 26 shows the number of newly infected agents for different patterns of decreasing the virus-absorbing rate. Here, the maximum traveling distance is decreased by 0.2 times during only certain periods. There are three periods: t<50, t=50–100, and t>100. The virus-absorbing rate is set for each period, and the notations "1-1-1," "1-0.2-1," and "1-0.2-0.2" in Figure 26 each represent a set of multiples for each period. For example, the notation "1-0.2-0.2" represents a pattern in which the virus-absorbing rate is decreased by 0.2 times in the second and third periods.

In the case of the 1-1-1 pattern, a second wave of the pandemic arises in the period after t=100 where regulation is released (Fig. 26). In the case of the 1-0.2-1 pattern, the emergence of a second wave of the pandemic is not remarkable, but the number of newly infected agents increases slightly in the period after t=100. In contrast, in the case of the 1-0.2-0.2 pattern, a second wave of the pandemic does not arise, indicating that strict prevention measures against infection are quite effective for preventing the emergence of a second wave of the pandemic. This tendency is more clearly observed in the total number of infected agents (Fig. 27).

A similar trend is also seen in the average number of infected neighbors (Fig. 28). This result indicates that the effect of the virus-absorbing rate on the number of newly infected agents is as follows. The decrease in the virus-absorbing rate decreases the number of infected persons' viruses at the time of infection, which

increases the number of newly recovered agents due to the increase in the recovery speed, as suggested by Figure 5, thus decreasing the probability of a healthy agent meeting with an infected agent.

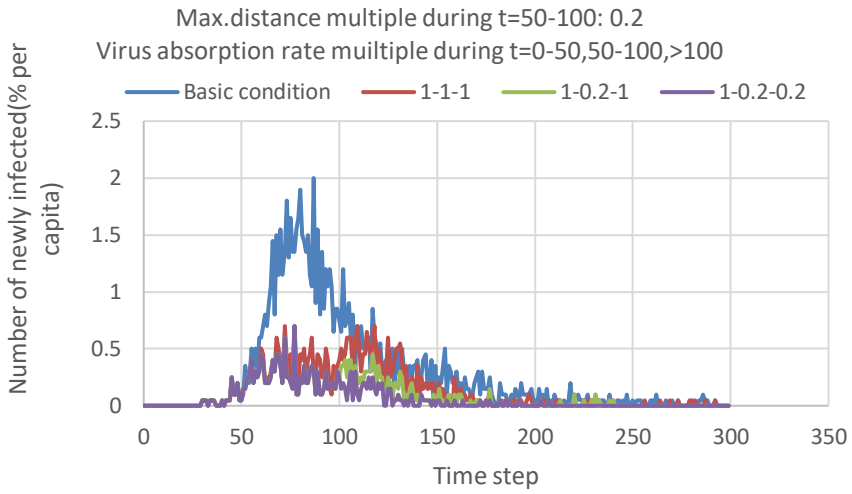

Figure 26. Effect of the virus-absorbing rate on the number of newly infected agents when movement regulation is applied.

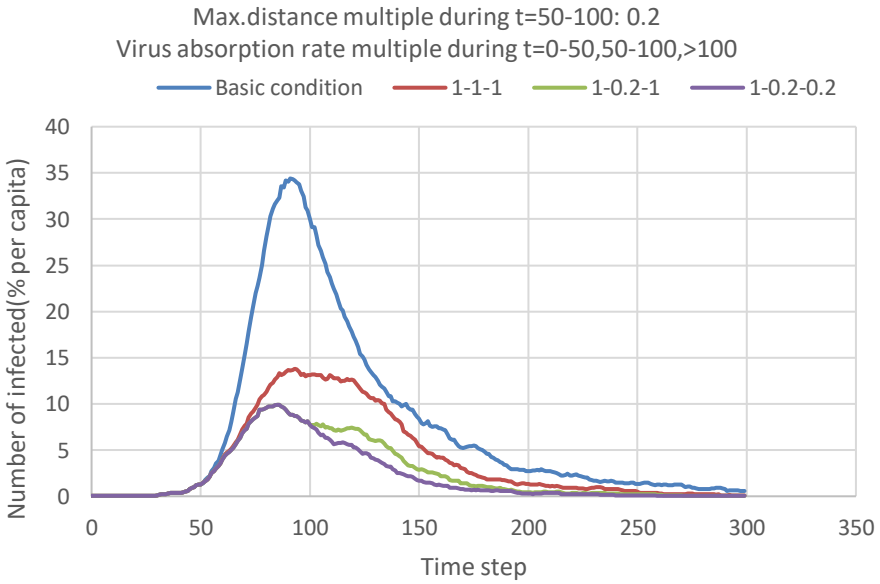

Figure 27. Effect of the virus-absorbing rate on the number of infected agents when movement regulation is applied.

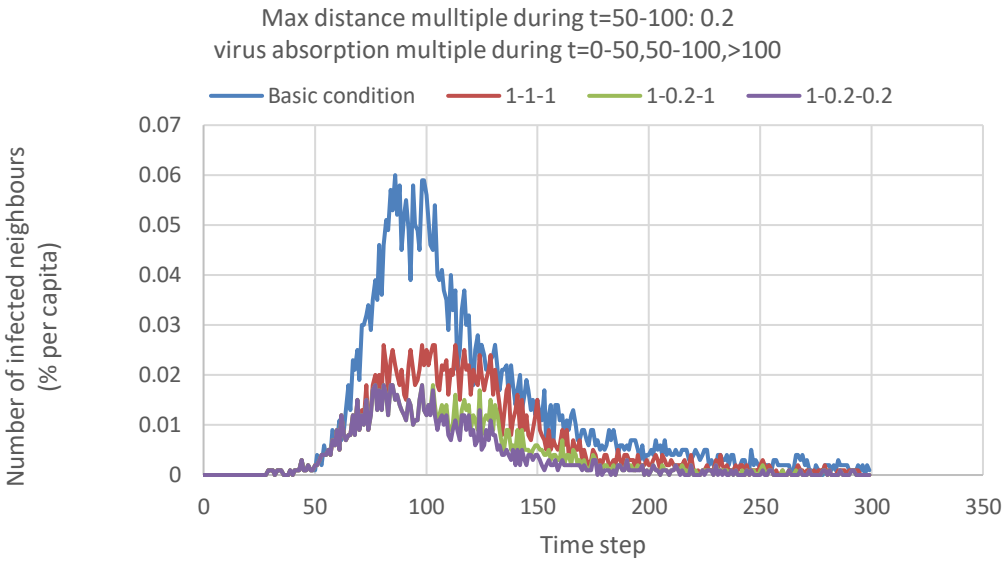

Figure 28. Effect of the virus-absorbing rate on the average number of infected neighbors when movement regulation is applied.

4.4 Infection behavior when antibodies do not exist

Figure 29 shows the infection and recovery trends when antibodies do not exist. Notably, the numbers of newly infected, newly recovered, and total infected agents exhibit patterns similar to those shown in Figure 9, which represents the case with antibodies. This result indicates that the existence of antibodies is not an essential factor in the mechanism of the fundamental behavior of increasing and decreasing the number of infected agents.

However, in the case without antibodies, the virus replication rate that is necessary to reproduce the fundamental behavior of infection and recovery is 1.3 in Figure 29, which is significantly lower than that in the case with antibodies. This result indicates that antibodies play a significant role in attaining stable recovery after infection. Therefore, although antibodies are not essential for the fundamental mechanism of infection and recovery, the role of antibodies might be indispensable for the stable end of the pandemic.

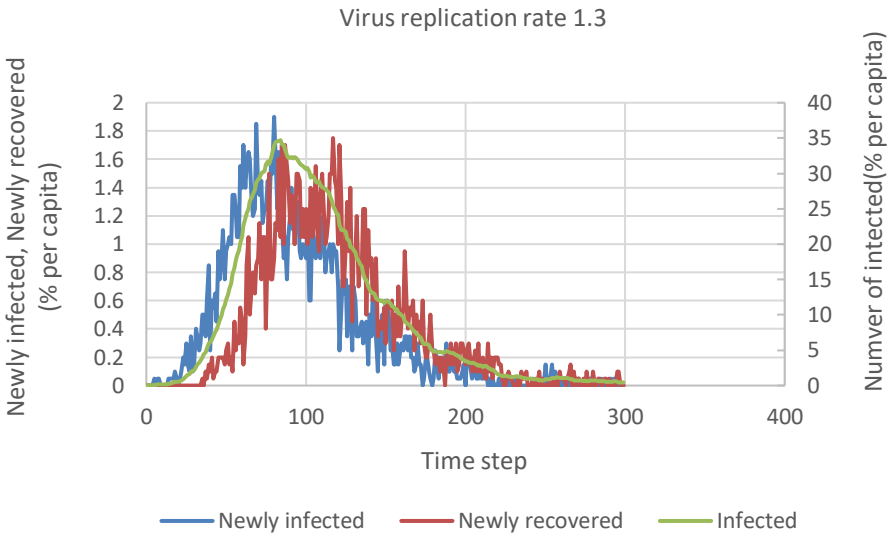

Figure 29. An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case without antibodies. The pattern of the start and end of the pandemic is similar to that in the case with antibodies, shown in Figure 9.

5. Discussion

5.1 Fundamental mechanisms of infection spread and convergence

The essential factors concerning the fundamental mechanism of infection spread and convergence are the numbers of newly infected, newly recovered, and total infected persons. These factors are related to each other. Namely, the time step at which the number of infected agents peaks coincides with the point at which the number of newly infected agents equals the number of newly recovered agents as explained in Figures 9 and 10. This pattern is consistent between the cases with and without antibodies. Furthermore, the pattern of the average number of infected neighbors is very similar to that of the number of infected and newly infected agents, as shown in Figures 6,7 and 13, and there is a positive correlation between both indices, as shown in Figures 14 and 15.

These findings indicate that the fundamental mechanisms of infection and convergence are as follows. Even in the case where there is initially only one infected person, if the infected and uninfected persons move around, they inevitably meet within a few meters at some point, causing uninfected persons to become infected. The possible infection routes include splash infection and contact infection. Either way, if a healthy person meets with an infected person in a close area, some infectious viruses will be expelled from the infected person in the form of a cough or forceful exhalation and transferred to the body of the healthy person, causing an infection. Thus, if the total number of infected persons doubles, the probability for a healthy person to meet an infected person also doubles, and the number of infected persons increases progressively. During the spread of infection, persons who are infected early may become recovered, and the number of recovered persons increases over time. The increase in the number of newly recovered persons decreases the probability that a healthy person will meet an infected person, causing the rate of increase in the number of new infections to slow down. At some point, the number of newly infected persons peaks, then decreases as the number of recovered persons increases.

In summary, the fundamental mechanism of infection spread is the progressive increase in the probability of a healthy person meeting with infected people. The mechanism of convergence is that this probability decreases during the infection process as a result of an increase in the number of recovered people.

Notably, the existence of antibodies was found not to be essential for this fundamental mechanism. However, the existence of antibodies may effectively increase the number of recovered persons, thereby decreasing the probability of a healthy person encountering an infected person. Thus, the presence of antibodies has the function of suppressing the spread of infection and stabilizing the convergence of infection.

5.2 A proposed strategy for controlling the pandemic while saving the economy

Restricting the movement of people is an effective measure to control the spread of infection. However, movement restrictions cause economic activity to stagnate, thus weakening the economy. To control the spread of infection while minimizing economic deterioration, it is essential to minimize the probability that healthy people, who are the majority, will encounter infected people, who are the minority.

Therefore, most fundamental strategy to control the spread of infection while minimizing the deterioration of the economy is to identify the infected persons and isolate them from the healthy people until the infected persons recover. Thus, the following measures are proposed as effective ways of both preventing economic deterioration and controlling infection spread. To reflect the current situation of the SARS-CoV-2 pandemic, it is assumed here that a licensed vaccine is not yet available.

1) To establish PCR test system in the society, so that anyone who wants can take PCR test at any time in any convenient places. Measurement of body temperature is also considered effective, as the fever is considered a sign of immune system fighting against viruses.
2) Self-identification by thermometry for self-controlling the movement at the individual level. If many individuals self-regulate the behavior in the society, it may reduce the social probability of healthy person encountering the infected person, thus reducing the number of newly infected people.
3) Preventive measures in dense places. Commercial establishments should measure the body temperatures of customers at the entrance and refuse entry to anyone with a high body temperature because they might have an infection. The critical temperature for refusing entry could be around 37.5 degree, but its absolute value does not have to be taken seriously, because, in any cases, this measure will reduce the probability of healthy person encountering the infected person, thereby working effectively to control the infection spread.
4) Wearing masks or face shields at the dense places. However, society should not force the people to do this uniformly, because, the need depends on individual and location.
5) Public grasp of the number of newly infected, newly recovered, and total infected persons. These values should be updated daily and shared through public announcements quickly, ideally on the same day.

6. Conclusions

An agent-based infection model that incorporates the roles of immune cells, antibodies, and the viral particles was constructed. Using this model, the effect of various factors on the spread and convergence of infection was analyzed, and the calculated results were compared with real-world data. The obtained results are summarized as follows.

1) The patterns of the calculated numbers of newly infected, newly recovered, and total infected agents were qualitatively consistent with the actual phenomena.
2) This feature of the patterns emerges even in the case where antibodies are entirely not present.
3) The number of viruses at the time of infection decreases over time, and the time required for recovery decreases accordingly.
4) These results indicate that the fundamental mechanism for the spread of infection is a progressive increase in the probability of a healthy person encountering an infected person and that the primary mechanism for convergence of the infection spread is a progressive decrease in the above probability as the number of recovered persons increases. The existence of antibodies is not a fundamental cause of the pandemic convergence, but it makes convergence stable by increasing the recovery speed.
5) This model also reproduced the re-increase in the number of infected persons (second wave) after the temporally regulation of peoples' movement, when regulation is not strict. Strict regulation of peoples' movement and reducing the virus-absorbing rate, such as by wearing a mask or face shield, effectively suppress the pandemic and the appearance of a second wave. This tendency arises because these factors reduce the number of viruses at the time of infection, thus increasing the recovery speed.

6) To control the spread of infection while minimizing economic deterioration, it is essential to identify infected persons, limit the behavior of infected persons only, and minimize the probability that healthy persons will encounter infected persons.

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