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

Shigeaki Ogibayashi

Abstract This paper constructed an agent-based infection model that focused on the recovering process modeling and obtained the following results. The mechanism of pandemic convergence is that the probability of a healthy person's encountering an infected person decreases progressively as the number of recovered people increases and the total number of viruses in the system decreases due to immunity. The existence of antibodies promotes recovery but is not an essential factor for pandemic convergence. By assuming the effect of immunity being proportional to the number of viruses rather than assuming a constant value, the model well reproduced the actual trend of the number of infected and recovered persons. This result suggests that the medically well-known fact that fever associated with infection enhances immunity is an essential requirement for pandemic convergence. Identifying and isolating infected persons is critical to overcome the pandemic and minimize economic deterioration, especially at the border of the system, such as airports. Individual persons recognizing the state of infection by self-monitoring body temperature is also adequate for the pandemic convergence.

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 [1], 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.

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Many mathematical models for forecasting the emergence of a pandemic were constructed long before the ongoing pandemic began [2–7]. Most of these models are the type of system-dynamics models such as the SIR model or SIER model, consisting of a set of equations to be solved simultaneously. The infection and recovery process is modeled by only introducing a set of parameter variables representing the probability of a healthy person's infection and an infected person's recovery. 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 factors influencing recovery or the occurrence of a second wave of the 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 [8, 9]. In ABM, we construct an artificial society on a computer that mimics the real world, aiming to reproduce various social phenomena caused by the behaviors and interactions of agents from the bottom-up. Thus, ABM is an effective way to understand the underlying mechanism and solve economic and social problems [9–12]. ABM has various advantageous features, such as being able to deal with heterogeneity and discrete phenomenon [8]; the essential advantageous characteristic of ABM is that it is a bottom-up modeling method.

Because social phenomena emerge due to humans' actions and interactions, we can use ABM to construct an artificial society that works according to the same principles 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 types of agents and their behavioral rules and the relevant variables, i.e., the system structure, must be as realistic as possible to reflect micro-level phenomena and thereby reproduce the macro-phenomena [10–12].

Although ABM has also been applied to diseases [13–16], most of the resulting models are not fully bottom-up in that they employed aggregate-variable-related assumptions. In a few cases where the applied ABM was entirely bottom-up regarding the spatial interaction among agents, the post-infection recovery process was not modeled from the bottom-up in that infected agents were assumed to become immune at a specific period after infection and never be infected again [13]. 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 [1], the number of total infected, newly infected, and newly cured persons peaked at different periods [1]. 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 replicate repeatedly, increasing the number of viruses. Regarding the function of innate immune cells and antibodies, it is well known [17] that innate

immune cells are the first to attack the virus, followed by antibodies. Typically, antibodies are produced after a certain period of time, and they join the fight against the virus.

Based on these medical findings, the fundamental factor that characterizes the infectious state is the virus, and the essential factors that characterize the recovery process are immune cells and antibodies. However, few previously reported epidemic models take these micro-factors into account. Based on this, 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 for the spread of infection and convergence, and the conditions for balancing infection control and promotion of the economy, are discussed.

2 The Model

2.1 Model Outline

This model considers the role of immune cells and antibodies and the number of viruses. The interactions among agents are simplified, assuming random movement of agents. The behavior of viruses, immune cells, and antibodies is modeled as faithfully as possible based on the medical knowledge available in the literature [17, 18], taking into account the heterogeneity of agents.

In this model, the human agent is the only object that moves randomly in the two-dimensional space of 1 km^2 every period. The number of human agents 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 the infected agent, possessing 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 to be 5 m. The infected human is assumed to release some 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 Eq. (1).

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

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	100,200
Critical distance for infection	5
Initial number of the infected	1
Number of viruses 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 uniform random number
Elapsed period after infection for antibody emergence	7 ± 2 uniform random number
Minimum number of viruses, below which number of viruses is assumed zero	10e-9 (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 two dimensional space	Defined at every step
Distance of agent's move	[0, maximum distance] uniform random number
Direction of agent's move	[0, 2π] uniform random number
Agent in the neighbor	Defined at every step
Number of viruses of each agent	Calculated at every step

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

$N^{j}_{VP}(t)$: *Number of viruses of agent j at the time t*

$Rate^{j}_{\text{Release}}$: *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 their numbers at a predetermined virus-attack rate of immune cells or antibodies. The

decreasing increment of the number of viruses at time t is assumed to be proportional to the number of viruses, as given by Eq. (2). Here, the virus-attack rate is assumed to be a larger value if antibodies are present. Antibodies are assumed to emerge that attack the viruses at a greater rate than that of immune cells, after a predetermined antibody-emerging period, if the agent's viral particles exceed the minimum number. This minimum number of viruses required for antibody emergence is assumed to be the product of the number of viruses and the predetermined minimum-virus-count-multiple. The conditions required for the emergence of antibodies is assumed, as given by Eq. (3).

For comparison, an additional series of experiments in which the right side of Eq. (2) is assumed to be a constant value, was also conducted to better understand the mechanism by which immune cells or antibodies reduce the number of viruses and indispensable factors for the pandemic convergence.

$$\Delta N^i_{VP}(t) = N^i_{VP}(t) * Rate^i_{attack} \tag{2}$$

$$\begin{aligned} where,\ \Delta N^i_{VP}(t) &: \text{Decreasing } increment\ of\ the\ number\ of\ viruses\ during\ the\ time\ step\ t \\ Rate^i_{attack} &= Virus\ attack\ rate\ of\ immune\ cells\ or\ antibodies \end{aligned}$$

$$t - t^i_{\text{infected}} > t^i_{antibody\_emerging}\ and\ N^i_{VP}(t) > N^i_{VP}(t^i_{\text{infected}}) * Multiple^i_{antibody\_emergence} \tag{3}$$

$$\begin{aligned} where,\ t &: Current\ time\ t^i_{\text{infected}} : Time\ of\ \text{infection}\ of\ agent\ i \\ t^i_{antibody\_emerging} &: Elapsed\ period\ for\ antibody\ emergence\ of\ agent\ i\ after\ \text{infection} \\ Multiple^i_{antibody\_emergence} &: \text{Virus}\ count\ multiple\ for\ antibody\ emergence \end{aligned}$$

The resultant viruses are assumed to multiply, increasing in 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 to be constant during the calculation. Thus, the number of viruses is redefined at every time step in the calculation according to Eq. (4).

$$N^i_{VP}(t+1) = (1 - Rate^i_{\text{Release}} - Rate^i_{attack}) * N^i_{VP}(t) * Rate_{growth} + \Delta N^i_{\text{Infected}}(t) \tag{4}$$

where, $Rate_{\text{Release}}$: *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 Eq. (5); at this time, the agent state changes from infected to recovered, being classified as newly recovered. Here, the number of viruses is an arbitrary unit, so it could be below 1 in the present model.

$$N^i_{VP}(t) = 0, \ if \ N^i_{VP}(t) < N^i_{\min} \tag{5}$$

where, $N^i_{\min}$: $n_{\text{limit}} * Virus$ releasing *rate* $*$ *Virus absorbing rate*

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

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 present model does not incorporate agent death because it requires a massive population, meaning that the calculation time needed becomes too large. Moreover, the death rate is so low compared with 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 is responsible for the calculation of infection among agents. These classes refer to infection-related variables among each other.

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

(a) Define parameter values.
(b) Create various class objects and set initial values for the variables.
(c) Repeat the following steps until the maximum time step is reached.

(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 the 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 decrease in the number of viruses due to the role of immune cells or antibodies, the increase in the number of viruses due to virus replication, various state variables.

(c-2) Calculate aggregate variables, such as the numbers of infected agent and recovered agents, and print out the results.

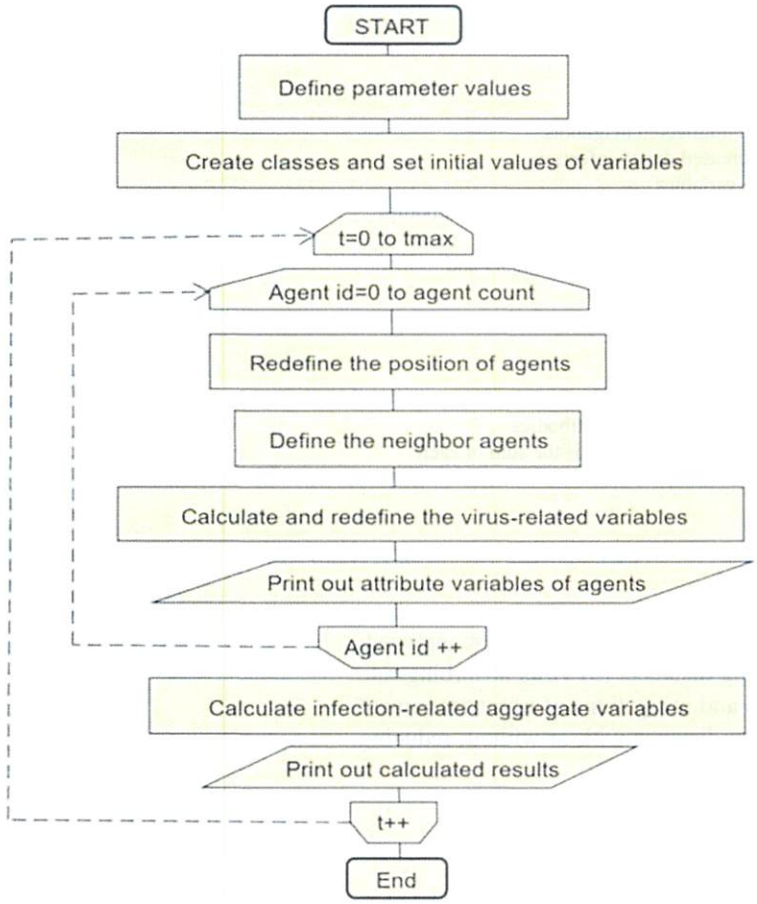

Fig. 1 The flowchart of the calculation

3 Experimental Conditions

3.1 Analysis Items at Each Time Step

The characteristic variables calculated at every time step are divided into agent's attributes variables and state variables of the system and given in Table 2.

The former variables include agents as objects located in the neighbors responsible for the mutual infection and determined based on the distance among agents in the two-dimensional space. The latter variables include the numbers of infected agents, newly infected agents, newly recovered agents with or without antibodies. The time changes of the calculated state variables were compared with the statistical data available in the real world.

Table 2 Characteristic variables calculated at every time step

1. *Agent's attributes variables*
Number of viruses
Position in the two-dimensional space
Agents as objects located in the neighbor
Number of infected or uninfected neighbors
Number of viruses increased due to infection
Infection-related state variables
Uninfected, Infected and recovered with or without antibodies
2. *State variables of the network system*
Average numbers of neighbors, infected neighbors and uninfected neighbors
Number of infected agents
Number of newly infected agents
Number of newly recovered agents
Number of recovered agents with antibodies
Number of recovered agents without antibodies
Number of viruses in the system which is the sum of each agent's viruses

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 include the temporal regulation of traveling distance with or without reducing the virus-absorbing rate, 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 Possessed by Each Agent During Infection Spread and Convergence

This model can calculate the number of viruses possessed by each agent at each time step. The aggregate variables, such as the numbers of infected agents and recovered agents, 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 first stage of infection spread. In this example, 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 shows that Agent 1 is the only infected agent initially, and Agent 13 is infected by Agent 1 at time step 4. The next agent who is infected by

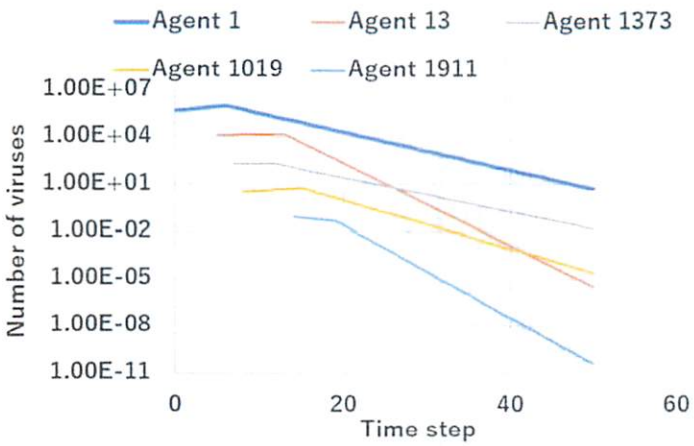

Fig. 2 Changes in the number of viruses of agents who are sequentially infected during the initial stage of infection spreads (Infection spread sequence: Agent 1 → 13 → 1373 → 1019 → 1911, Virus replication rate = 1.8)

Agent 1 is Agent 155 at time step 25. However, before Agent 155 is infected, Agent 13 infects Agent 1373 at time step 6, and infection propagates from Agent 1373 to Agent 1019, and from Agent 1019 to Agent 1911. In this way, this model allows individual tracking of the details of the infection process. The same is true for the recovery process.

Note that, in Fig. 2, the slope of the change in the number of viruses appears positive or negative just after the infection. Here the slope in the number of viruses depends on the relative magnitude of the relationship between the virus replication rate and the immune attack rate. If the effect of replication is larger than that of immune cells, the slope 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. Thus, the number of viruses possessed by each infected agent decreases with time, at least after the antibody emergence.

During infection and recovery, an agent could be infected multiple times. Figure 3 shows such an example. Note that, as seen in Agent 1556 in Fig. 3, the rate of propagation of viruses may change over time, as seen by a decrease in the number of viruses, 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 has 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 the immune-cells' virus attack rate.

Figures 4 and 5 show the trends in the number of viruses during infection spread and convergence. The number of viruses possessed by each agent at the time of infection decreases during infection spread and convergence, as shown in Fig. 4.

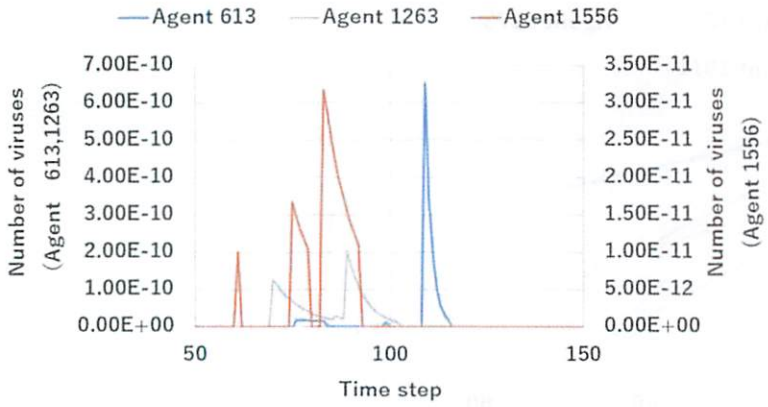

Fig. 3 Examples of cases where agents are infected multiple times. The calculation conditions are the same as in Fig. 1

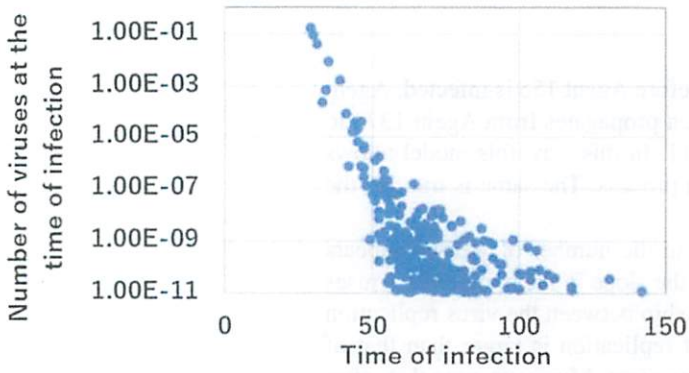

Fig. 4 Number of viruses at the time of infection as a function of time during infection spread and convergence (virus replication rate = 1.6)

This trend reflects the effects of the virus-releasing rate, the virus-absorbing rate, the virus attack rate of immune cells or antibodies and the virus-replication rate. Namely, when an infection occurs, a healthy person receives a portion of the viral particles released by the infected person due to a cough or by other means, and the emitted viral particles are a portion of the viruses possessed by the infected person which decreases with time if the effect of the virus attack rate of immune cells or antibodies is larger than the effect of virus-replication rate. Thus, the number of viruses at the time of infection decreases during the propagation process because viral particles transferred from an infected to a healthy person are only a portion of the viruses held by that infected person which decreases with time due to the effect of immunity. It is noted that total number of viruses in the system also decreases with time due to the effect of immunity.

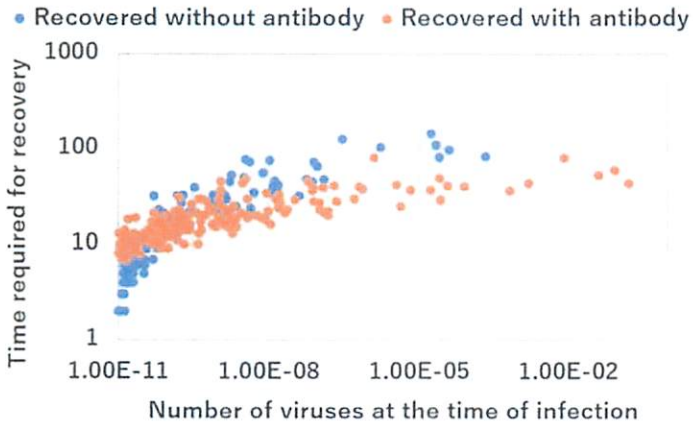

Fig. 5 Time required for recovery as a function of the number of viruses at the time of infection (virus replication rate = 1.6)

Note that, as the number of viruses at the time of infection decreases, the time required for recovery becomes shorter, as shown in Fig. 5. This result indicates that the time necessary for an infected person to recover becomes faster with time as the number of viruses at the time of infection decreases during the process of infection spread and convergence.

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, then decreases, ending the pandemic. In such cases, the virus replication rate is not too large compared with the virus attack rate of immune cells or antibodies. By 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 correspond to situations observed in the real world; thus, the model reproduces the pandemic process's fundamental behavior without introducing any macroscopic assumptions.

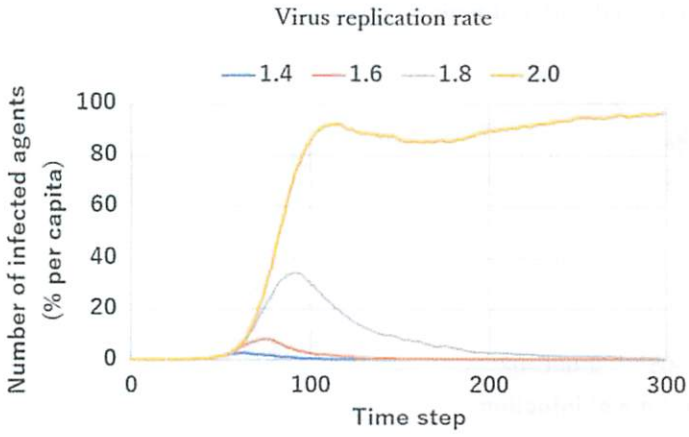

Fig. 6 Effect of the virus replication rate on the number of infected agents

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, then decreases, a trend stemming from agent interactions (Fig. 7).

A similar trend of increase and decrease appears in the number of recovered agents because of the activity of innate immune cells and antibodies (Fig. 8).

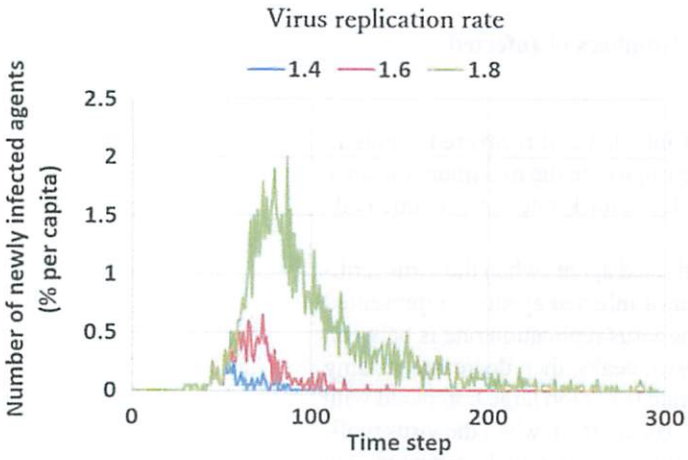

Fig. 7 Effect of virus replication rate on the number of newly infected agents

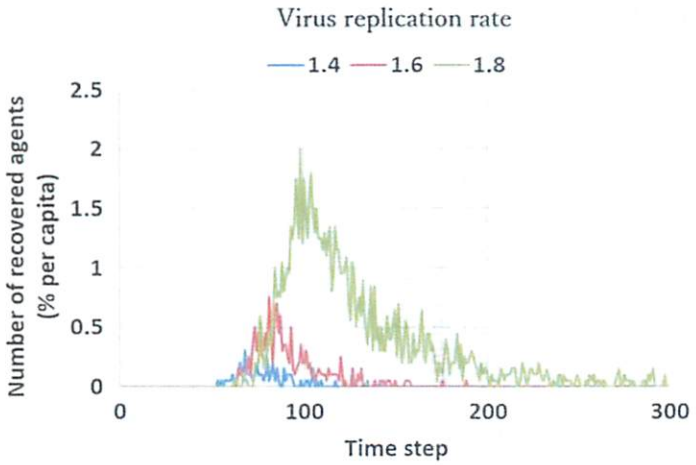

Fig. 8 Effect of virus replication rate on the number of newly recovered agents

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 time. 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

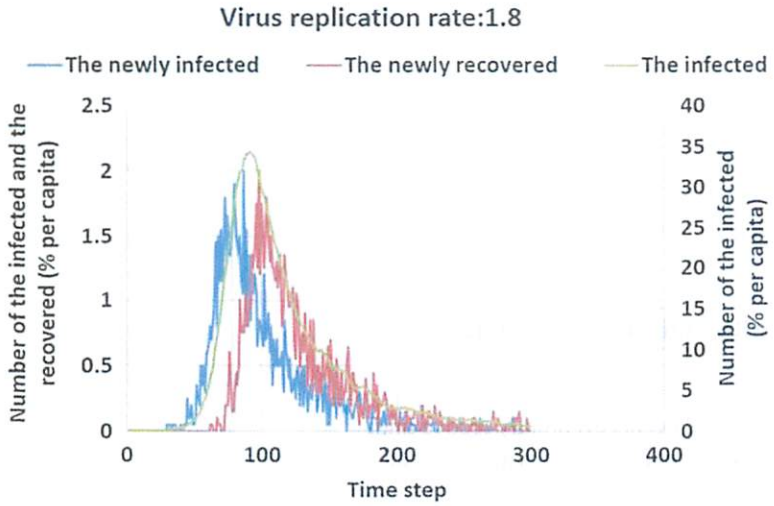

Fig. 9 Changes in the numbers of newly infected, newly recovered, and total infected agents

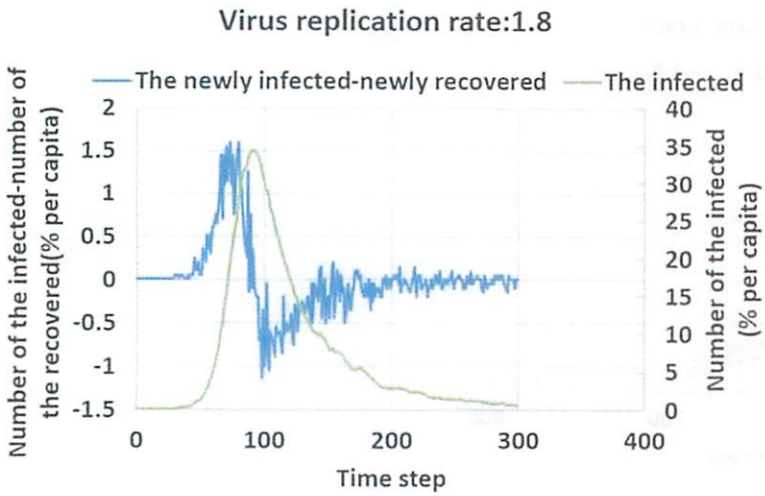

Fig. 10 Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents

agents (Fig. 10). This fact is evident from the defined expression of the total number of infected agents, as shown in Eq. (6). Namely, when the total number of infected agents reaches its maximum, its value at the current term equals that of the previous period. Because 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 Eq. (6).

$$N_{\text{infected}}^{t+1} = N_{\text{infected}}^{t} + N_{\text{newly infected}}^{t} - N_{newly\ \text{recovered}}^{t} - N_{newly\ dead}^{t} \tag{6}$$

$$where,\ N_{\text{infected}} : Number\ of\ the\ \text{infected}$$
$$N_{\text{newly infected}} : Number\ of\ the\ newly\ \text{infected}$$
$$N_{Newly\ dead} : Number\ of\ the\ newly\ dead$$
$$t : period$$

4.1.4 The Ratio of the Recovered Agents with Antibodies to the Total Number of Recovered Agents

Because the present model neglects death, all infected agents eventually recove until the pandemic convergence. Whether the infected agents recover with antibodies depends on the virus replication rate and agent-specific virus attack rate. As shown in Fig. 11, in the case of low virus replication rates, such as 1.4, two-thirds of the

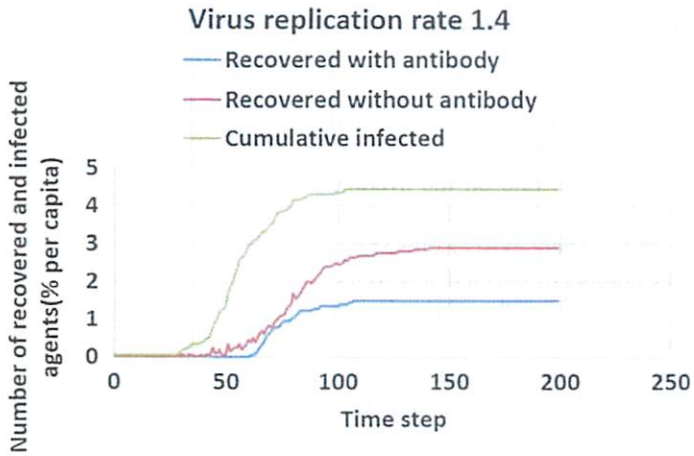

Fig. 11 Changes in the numbers of recovered agents with and without antibodies and the cumulative number of infected agents (virus replication rate: 1.4)

infected agents recover without antibodies. In contrast, with the replication rate being 1.8, more than 90% of recovered agents hold antibodies as shown in Fig. 12. In any case, all infected people recover regardless of the emergence of antibodies. This result indicates that whether those who recover with antibodies constitute most of the population is not a crucial factor in determining the end of the pandemic.

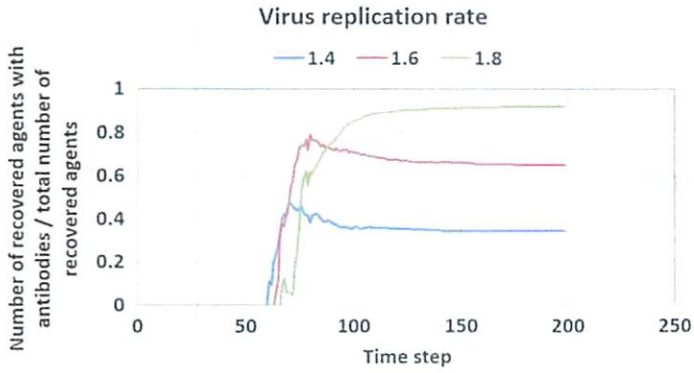

Fig. 12 Effect of virus replication rate on the ratio of the number of recovered agents with antibodies to the total number of recovered agents

4.1.5 Effect of the Virus Replication Rate on the Number of Infected Neighbors

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

Figure 13 demonstrates 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 Figs. 6 and 7. There exists a close relationship between the number of infected agents and the number of infected neighbors, as shown in Fig. 14. The number of infected agents increases with the number of infected neighbors, as shown in Fig. 15. The source of scattering in Fig. 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

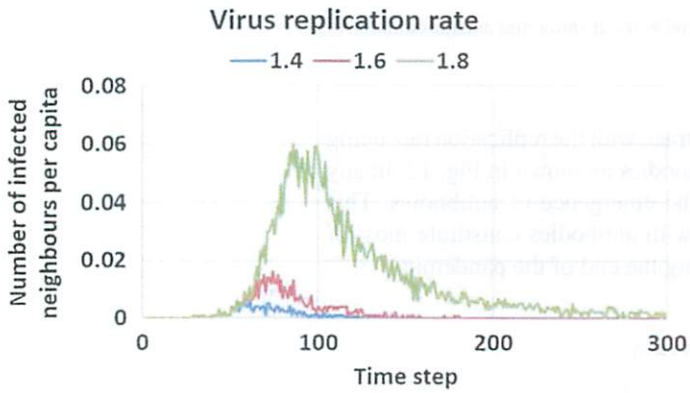

Fig. 13 Effect of the virus replication rate on the average number of infected neighbors

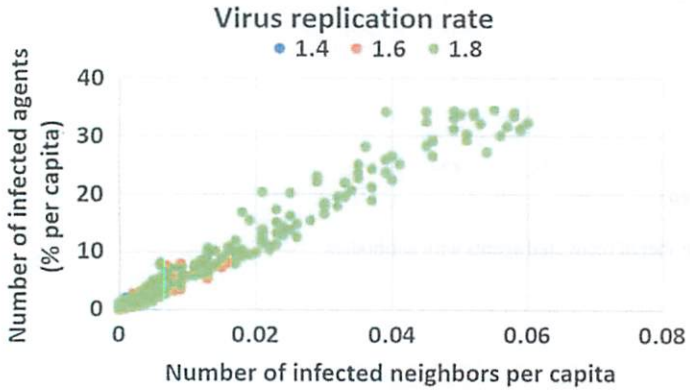

Fig. 14 Relationship between the number of infected agents and the average number of infected neighbors

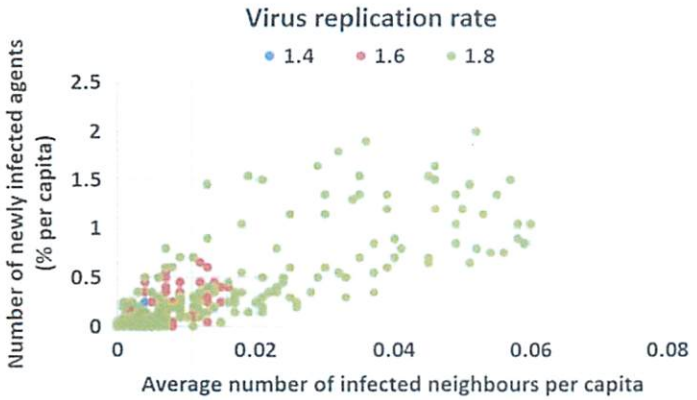

Fig. 15 Relationship between the number of newly infected agents and the average number of infected neighbors

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.

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 Fig. 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.

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 number of viral particles at the time of infection.

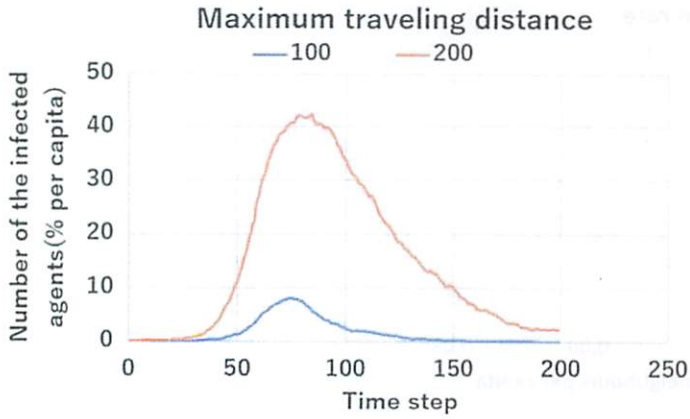

Fig. 16 Effect of the maximum traveling distance on the total number of infected agents (virus replication rate: 1.6)

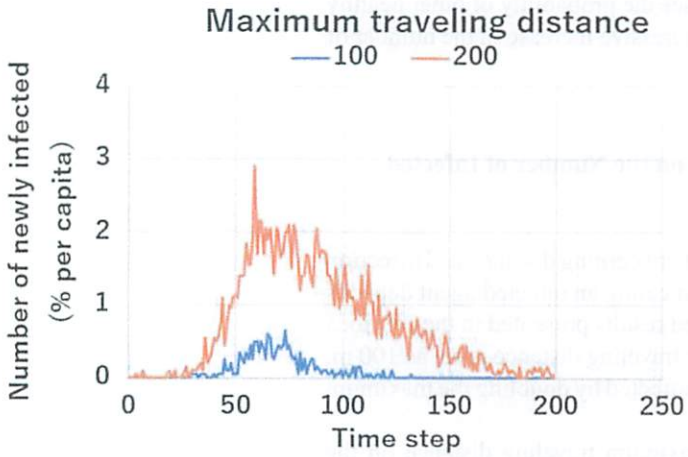

Fig. 17 Effect of the maximum traveling distance on the number of newly infected agents (virus replication rate: 1.6)

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 [1]. 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.

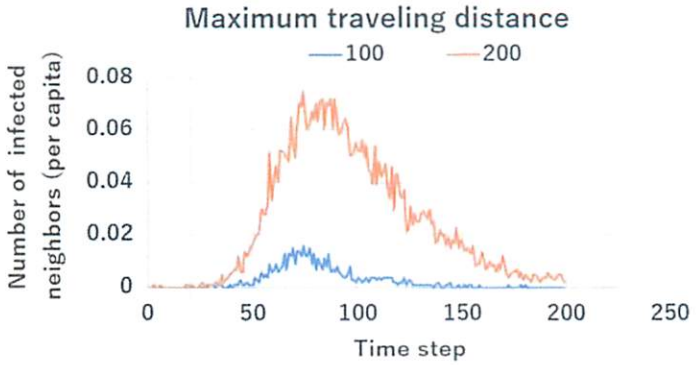

Fig. 18 Effect of the maximum traveling distance on the average number of infected neighbors (virus replication rate: 1.6)

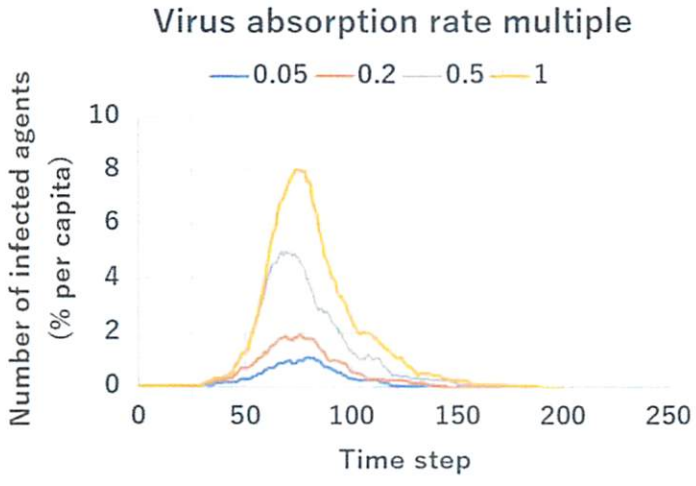

Fig. 19 Effect of the virus-absorbing rate on the number of infected agents

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 Figs. 9 and 10. Thus, the model adequately reproduces the fundamental behavior of the numbers of infected and recovered persons.

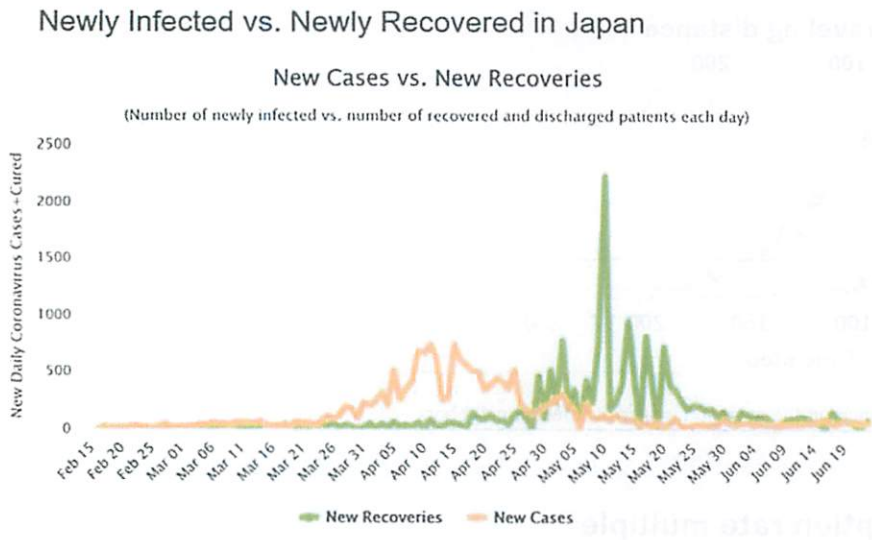

Fig. 20 Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020 [17]

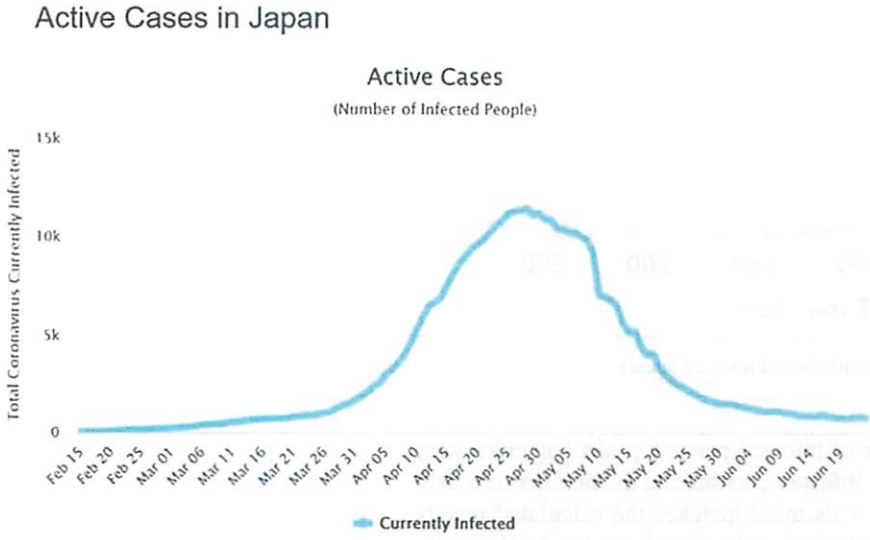

Fig. 21 Change in the number of currently infected people in Japan as of June 20, 2020 [17]

4.3 *Regulation and Mitigation of Movement and the Effect of the Virus-Absorbing Rate*

In this section, the effect of various factors on the emergence of re-increase in the number of infected persons, referred to here as the second wave, is analyzed. The re-increase in the number of infected persons after the complete convergence of the pandemic, a real second wave, does not occur because the total number of viruses in the system becomes almost zero after the convergence of the pandemic, as seen in Fig. 4.

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 number of newly infected agents once decreases and then 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 strictly, the emergence of a second wave of the pandemic is not remarkable.

Similar behavior is observed in the average number of infected neighbors and the total number of infected agents, as shown in Figs. 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 regulations, the number of infected agents just before

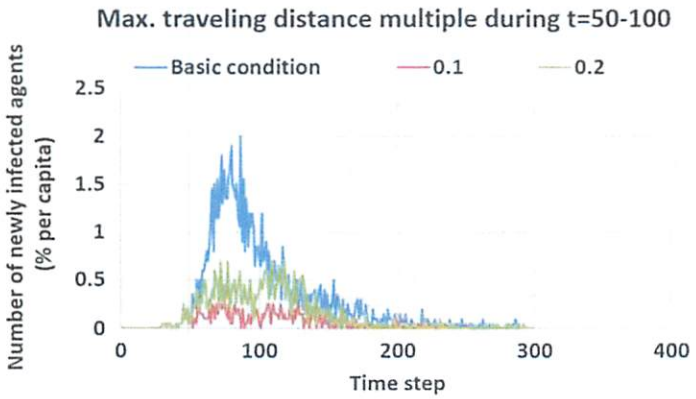

Fig. 22 Effect of temporary regulation of traveling distance and its release on the number of newly infected agents (virus replication rate: 1.8)

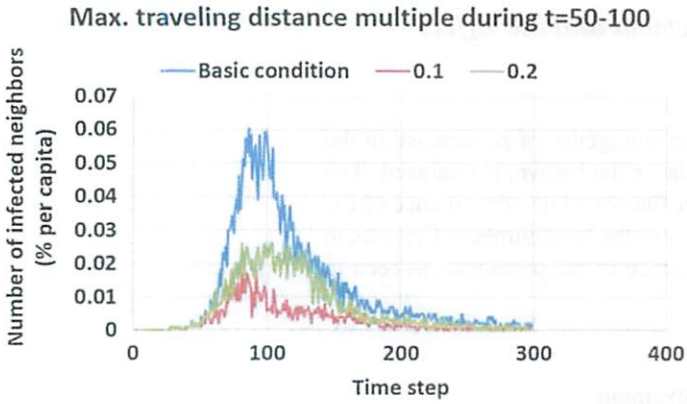

Fig. 23 Effect of temporary regulation of traveling distance and its release on the number of infected neighbors (virus replication rate: 1.8)

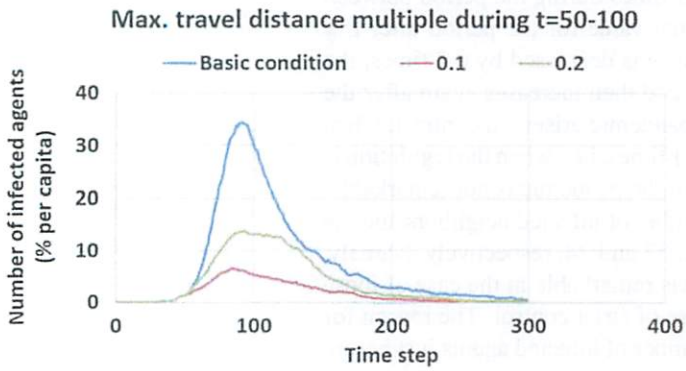

Fig. 24 Effect of temporary regulation of traveling distance and its easing on the total number of infected agents (virus replication rate: 1.8)

releasing the regulations is small. Moreover, the number of viruses in infected persons is also small resulting in faster recovery, as suggested by Figs. 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 emergence of antibodies is not responsible for preventing a second wave of the pandemic because more people may recover without antibodies in the case of strict regulation.

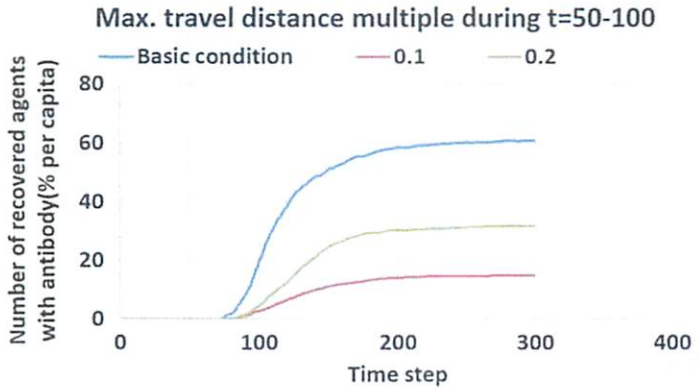

Fig. 25 Effect of temporary regulation of traveling distance and its easing on the number of recovered agents with antibodies (virus replication rate:1.8)

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 Fig. 26 each represent a set of multiples for each period. For example, the notation

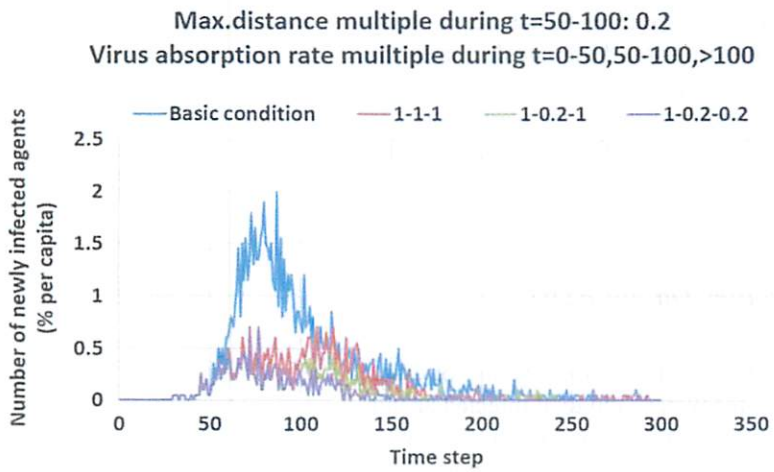

Fig. 26 Effect of the virus-absorbing rate on the number of newly infected agents when movement regulation is applied (virus replication rate: 1.8)

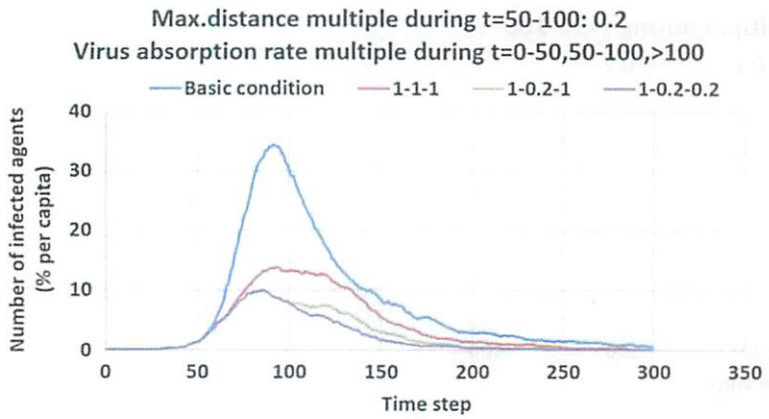

Fig. 27 Effect of the virus-absorbing rate on the number of infected agents when movement regulation is applied (virus replication rate: 1.8)

"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 Fig. 5, thus decreasing the probability of a healthy agent meeting with an infected agent.

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 Fig. 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.

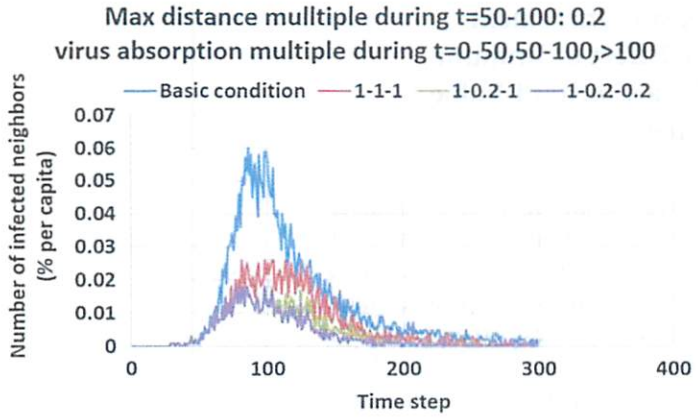

Fig. 28 Effect of the virus-absorbing rate on the average number of infected neighbors when movement regulation is applied (virus replication rate: 1.8)

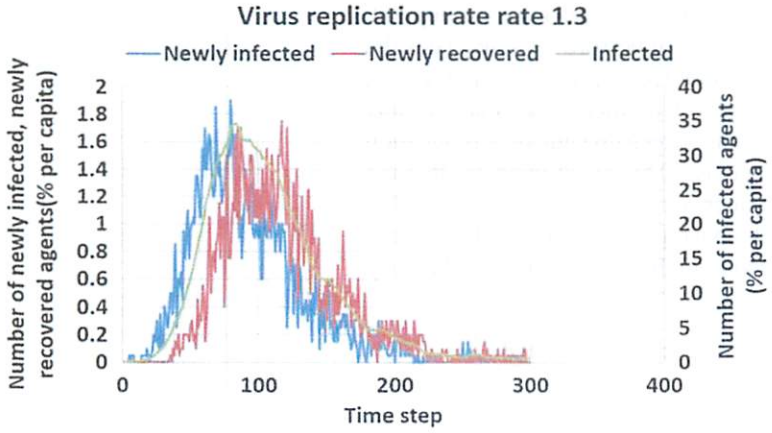

Fig. 29 An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case without antibodies

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 Fig. 29, which is significantly lower than that in the case with antibodies, indicating that antibodies play a significant role in attaining stable recovery after infection. In other words, if the virus replication rate is large such as 1.8, as is the case in Fig. 9, the pandemic does not converge in the case without antibodies. In contrast, if the virus replication rate is as small as 1.3, the pandemic does not occur in the case of existing antibodies. 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 under the given rate of virus replication.

5 Infection Behavior When the Decreasing Increment of the Number of Viruses Due to the Effect of Immune Cells or Antibodies is Assumed to Be a Constant Value Not Depending on the Number of Viruses

The calculation shown above assumes that the decreasing increment of the number of viruses each period due to the effect of immunity is proportional to the number of viruses as given in Eq. (2). A series of experiments was additionally conducted that assumed that the decreasing increment of the number of viruses each period, which is referred to as the virus-attack-count, is a constant value. In these experiments, the constant value and the virus replication rate were widely changed. An example of the calculated results for the number of newly infected persons, newly recovered persons, and the number of currently infected persons is shown in Fig. 30. Here, the constant value for the virus-attack count is assumed to be 200 for immune cells and 500 for antibodies. The virus replication rate is assumed to be 1.2. This combination of the virus-attack count and virus replication rate corresponds to the condition where infected agents are more likely to recover due to the immunity under this assumption.

As shown in Fig. 30, the number of newly recovered persons never exceeds the number of newly infected persons, and the number of infected persons never reduces, meaning that the pandemic never converges. The reason for this trend is that, in many infected people, virus elimination by immunity cannot keep up with virus replication and thus the number of viruses continues to increase. This result indicates that the model structure in which the effect of immunity increases with an increasing number of viruses is indispensable for reproducing the convergence of the pandemic. It is considered that the factors that realize this structure in the human body are the body

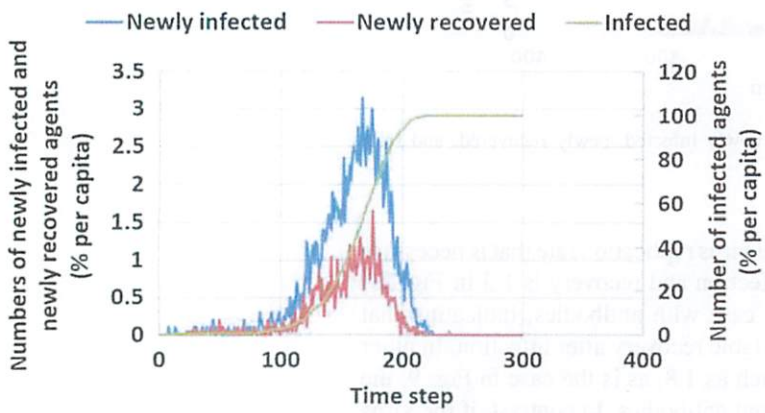

Fig. 30 An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case where the decreasing increment of the number of viruses due to immunity is assumed to be a constant value

temperature rise due to infection and the formation of antibodies, which let us discuss in the next section.

6 Discussion

6.1 Fundamental Mechanisms of Infection Spread and Convergence

The essential factors that characterize the 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 Figs. 9 and 10. After this point, the number of newly recovered agents exceeds the number of newly infected agents, resulting in a decrease in the number of infected agents and the convergence of the pandemic. The present model successfully reproduces these features in the case where immunity effect is assumed to be proportional to the number of viruses as given in Eq. (2). It is also notable that these trends consistently emerge irrespective of the existence of antibodies, indicating that the existence of antibodies is not an essential factor for the convergence of the pandemic. Furthermore, the pattern of the average number of infected neighbors is highly similar to that of the number of infected and newly infected agents, as shown in Figs. 6, 7, and 13, and there is a positive correlation between both indices, as shown in Figs. 14 and 15.

By contrast, if the model assumes that the immunity effect, namely the decreasing increment of the number of viruses each period, is constant, the number of newly recovered agents never exceeds the number of newly infected agents, and the model fails to reproduce the convergence of the pandemic as explained in Fig. 30.This result indicates that the model structure in which immunity effect increases with increasing number of viruses is indispensable for reproducing the pandemic convergence.

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 airborne infection, splash infection and contact infection. Either way, if a healthy person meets with an infected person in close proximity, infectious viruses will be expelled from the infected person in the form of a cough or forceful exhalation, or by breathing, and will be 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 recover, 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, which is indispensable for the convergence of the pandemic.

It is also noted that in the case of assuming that the immunity effect is constant and does not depend on the number of viruses, the number of recovered persons never exceeds the number of infected as shown in Fig. 30. This result indicates that the model structure in which immunity effect increases with increasing number of viruses is indispensable for reproducing the pandemic convergence. The factors that realize this structure in the human body are considered the body temperature rise due to infection and the emergence of antibodies. According to the literature [18], the immunity effect increases five-fold in response to a 1 °C increase in body temperature. It is also well known [17] that innate immune cells are the first to attack the viruses, and if necessary, antibodies emerge after a specific time, and they join the fight against the viruses. Thus, if an individual is infected, resulting in an increase in the number of viruses in the body, the body temperature will rise, which increases the immunity effect due to innate immune cells. In many cases, people will recover due to this effect of innate immune cells. For people with repeated infection or weak immunity, this effect of innate immune cells is not enough to keep up with the virus replication and antibodies will emerge and join the fight against viruses. Therefore, it can be said that humans have a mechanism for increasing immunity by increasing body temperature and producing antibodies if necessary, when the number of viruses in the body becomes large due to infection and replication of viruses. Thanks to this mechanism, we can understand that humans will recover due to the immunity effect in most cases unless repeated infections. For this reason, it is considered that monitoring body temperature might be an effective measure to identify individuals' state of being infected.

In summary, the fundamental mechanism of infection spread is the progressive increase in the probability of a healthy person meeting an infected person. 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. Moreover, the body temperature rise due to an infection that increases the immunity effect is considered to play an essential role in human recovery and the convergence of the pandemic.

Notably, the existence of antibodies was found not to be essential for this fundamental mechanism. However, the emergence of antibodies may increase the effect of immunity with an increasing number of viruses, thereby increasing the number of recovered persons and promoting the recovery. The emergence of antibodies may be an indispensable factor for the convergence of the pandemic in the case of the virus whose replication rate is significant.

It is also notable that, once the pandemic ultimately converges in a system, an additional pandemic, namely, a second wave, never occurs unless infected people outside of the system newly enter into the system because the total number of viruses in a closed system decreases during the pandemic process due to the effect of immunity as shown in Fig. 4. This fact indicates that identifying and isolating infected persons

at national borders, such as at airports, is vital in preventing the promotion of the pandemic and in aiding its convergence.

6.2 *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, the most fundamental strategy to control the spread of infection while minimizing the economy's deterioration is identifying the infected persons and isolating them from healthy people or exclusively regulating their movement. It is not necessary to control the movement of all people. Identifying infected persons can be done by monitoring body temperature in addition to PCR tests. Thus, the following measures are proposed as effective ways of both preventing economic deterioration and controlling infection spread. The following methods are also adequate for the vaccinated person because the effect of the vaccine is not to prevent infection but to promote recovery.

1. Identifying infected persons and regulate their social movement as completely as possible. This measure is particularly essential at national borders, such as airports to prevent infected individuals from entering domestic regions. Identification of infected persons can be made not only by a PCR test but also by measuring body temperature, which is much easier to apply for all people. Establishing a PCR test system in society is also preferable so that anyone who wants to take a PCR test can, at any time, in a convenient location.
2. Preventive measures in densely-populated places, such as identifying infected people, ventilation of the area, and sterilizing at the entrance. Particularly essential is that 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 degrees, but irrespective of the absolute value, this measure will reduce the probability of a healthy person encountering an infected person, thereby working to effectively control the spread of infection.
3. Individual persons recognizing the state of infection by self-monitoring body temperature for self-controlling social movement. Suppose many infected individuals self-regulate their behavior in society based on monitoring body temperature. In that case, it may greatly reduce the social probability of a healthy person encountering an infected person, thus reducing the number of newly infected people.

4. Wearing masks or face shields in densely-populated places because it reduces the viruses emitted from an infected person and absorbed by a healthy person. However, society should not force people to do this uniformly, because the need depends on individuals and the location.

7 Conclusions

An agent-based infection model that incorporates the roles of immune cells, antibodies, and 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. Present model well reproduced the qualitative feature of the chronological patterns in the numbers of newly infected, newly recovered, and total infected agents observed in the actual world, when immunity effect is assumed proportional to the number of viruses.
2. 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 pandemic 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 pandemic convergence, but it stabilizes convergence by increasing the recovery speed when virus replication rate is large.
3. The model structure in which the immunity effect increases with an increasing number of viruses is indispensable for reproducing the pandemic convergence. The temperature rise caused by infection and the emergence of antibodies realize this structure in the human body, indicating that these factors are indispensable for an individual's recovery and the pandemic convergence of society.
4. This model also reproduced the re-increase in the number of infected persons (i.e., second wave) after the mitigation of temporary regulation of peoples' movement, which is observed when activity limitation and wearing masks or face shields are not strict. However, once the pandemic ultimately converges, the second wave never occurs unless infected people outside of the system newly enter into the system because the total number of viruses in the closed system decreases during the pandemic due to immunity.
5. To control the spread of infection while minimizing economic deterioration, it is essential to identify infected persons, limit the behavior of these infected persons only, and minimize the probability that healthy persons will encounter infected persons. The identification and isolation of infected individuals are especially essential at national borders, such as at airports.
6. Monitoring body temperature is considered effective in identifying a person's state of being infected, where the higher the temperature, the larger the number of viruses the person might hold. Commercial establishments should apply this

measure at the entrance, including refusing entry of infected persons. As an Individual measure, self-monitoring body temperature for self-controlling social movement is also considered adequate for the pandemic convergence.

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