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

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1. Introduction

1）Although coronavirus pandemic has ended, various new sources of pandemics are emerging, necessitating effective countermeasures.

2) Many infection models, such as system dynamic model(e.g., SIR model) have been developed to understand infection disease dynamics. However, these models have failed to accurately reproduce key features of pandemic phenomena.

3) Agent-based modeling (ABM) is a promising methodology. However, previously developed model have focused solely on the infection process Consequently, they have also failed to reproduce the real characteristics of pandemics.

In this study, I have developed an agent-based model that accounts for both infection and recovery processes, incorporating the roles of immune cells and antibodies.

This results indicate that this model well reproduces detailed features of pandemic phenomena and enhances our understanding of the causal mechanisms and effective countermeasures.

Mechanism Oriented Agent-Based-Modeling(ABM)

ABM is a bottom-up modeling approach in which an artificial society is constructed on a computer and causal mechanism of a given phenomenon can be elucidated thorough a series of computer experiments.

I have proposed a new validation method for agent-based modeling, which I refer to as mechanism-oriented agent-based modeling.

The principle of this methodology is as follows:

■ All social phenomena ,including pandemics, emerge as a result of heterogeneous human behaviors of various types and interactions.

■ Since ABM is a bottom-up modeling approach, phenomena within the artificial society could , in principle, emerge under the same mechanism as in a real world, where the set of behavioral rules is the cause of the phenomenon.

■ By systematically changing the behavioral rules, and observing if the qualitative feature of the emerged phenomenon is the same as that of real world, we can determine an indispensable set of behavioral rules for accurately reproducing the phenomenon through a series of systematic computer experiments.

■ Then , we can elucidate the causal mechanism of the phenomenon by analyzing the reason why those factors are indispensable.

This procedure is scientifically rigorous without depending on the modeler’s ad hoc factors.

2. The ABM model of present research

The ABM model of present study focuses on recovery processes, where behavioral rules relevant to the immunity response are assumed based on the well known medical knowledge.

【Main assumptions】

1. Initial Setup: 2000 agents are initially randomly placed in a two-dimensional space, with one agent initially assumed to be infected having a large number of viruses. Agents move randomly within a defined critical distance limit.
2. Neighbor Definition: Two agents are considered neighbors if they are within the critical distance limit.
3. Virus Exchange: Neighboring agents exchange viruses, infecting others or being infected.,
4. Virus Transmission: Among neighboring agents, viruses are released from an infected agent , with a portion being absorbed by the neighboring agents., The extent of virus transmission depends on the viruses release rate and absorbtion rate.
5. Immune response: When infected, innate immune cells first attack the viruses and if their effect is insufficient to counter virus replication, antibodies emerges depending on the agent-specific delay time after infection and the agent-specific threshold of virus count required for antibodies emrgence.

5. The number of viruses in agent (i) at time (t+1) is the sum of the following terms, which are divided into four , each of which is assumed to be proportional to the number of viruses at time (t):

1) Replication:

An increase in the number of viruses due to replication, where the replication rate is assumed to be constant.

$$\Delta N^i{}_{replicate} = r_{replicate} N^i(t)$$

2) Release from the body:

A decrease due to their release from the body via coughing, etc., where the release rate is an agent-specific constant defined by a uniform random number.

$$\Delta N^i{}_{released} = -r_{released} N^i(t)$$

3) Immune response:

A decrease due to attacks by immune cells and antibodies, where the attack rates of immune cells and antibodies are agent-specific constants defined by uniform random numbers.

The attack rate of antibodies is greater than that of immune cells.

$$\Delta N^i{}_{atack} = -r_{attack} N^i(t),$$

$$r_{attack} = r_{attack\_immune\_cells} \ or \ r_{attack\_antibodies}, \quad r_{attack\_immune\_cells} < r_{attack\_antibodies}$$

4) New infection:

An increase in the number of viruses due to new infections via absorption of viruses released by infected neighboring agents. This increase is assumed to be proportional to the product of the release rate and the absorption rate, where the absorption rate is an agent-specific constant defined by a uniform random number.

$$\Delta N^i{}_{infected} = \sum_{j \in neighbor} r_{absorbed} r_{released} N^j(t)$$

Attribute variables shown in red are agent-specific uniform random numbers

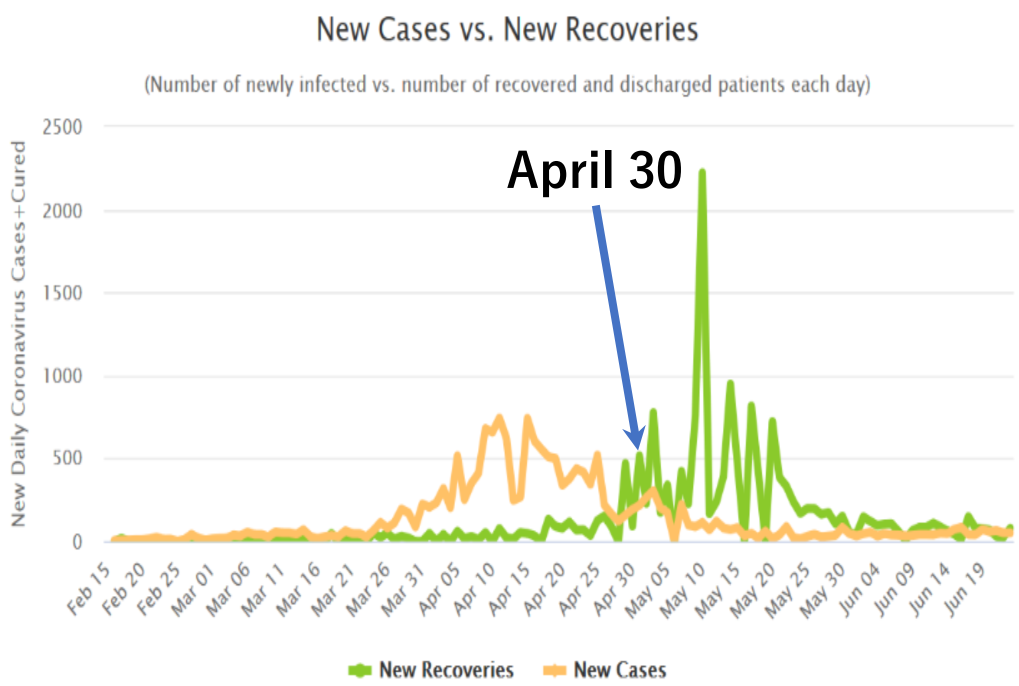
Table Attribute variables of agents and parameter values.

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
Elapsed period after infection for antibody emergence	7±2 uniform random number
Virus-count multiple for antibody emergence	0.5±0.2 uniform random number
Minimum-virus-count multiple for zero viruses	10^{-9}
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 for each agent
Distance of agent's move	[0, maximum distance] uniform random number
Direction of agent's move	[0, 2π] uniform random number
Agent as an object in the neighbour	defined at every step for each agent
Number of virses	calculated at every step for each agent
Infection-related state variables	calculated at every step for each agent

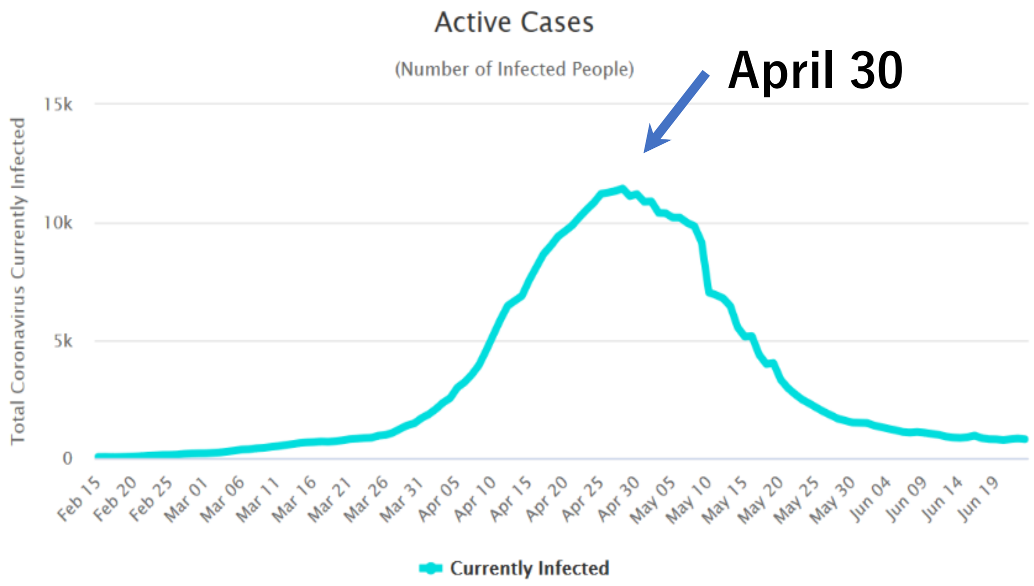
4. Actual feature of the pandemic phenomenon that should be reproduced by the model.

1. The number of newly recovered agents exceeds the number of infected agents, at some point, at which total number of infected agents shows its peak value.

Newly Infected vs. Newly Recovered in Japan



Active Cases in Japan



2. A regulation of the movement of people and wearing masks are effective for quick convergence of the pandemic.
3. Despite of historically encountering multiple times of severe pandemics, due to the viral particles of various replication rate, human being survived without been perished.

5.1 Fundamental behavior during infection and recovery.

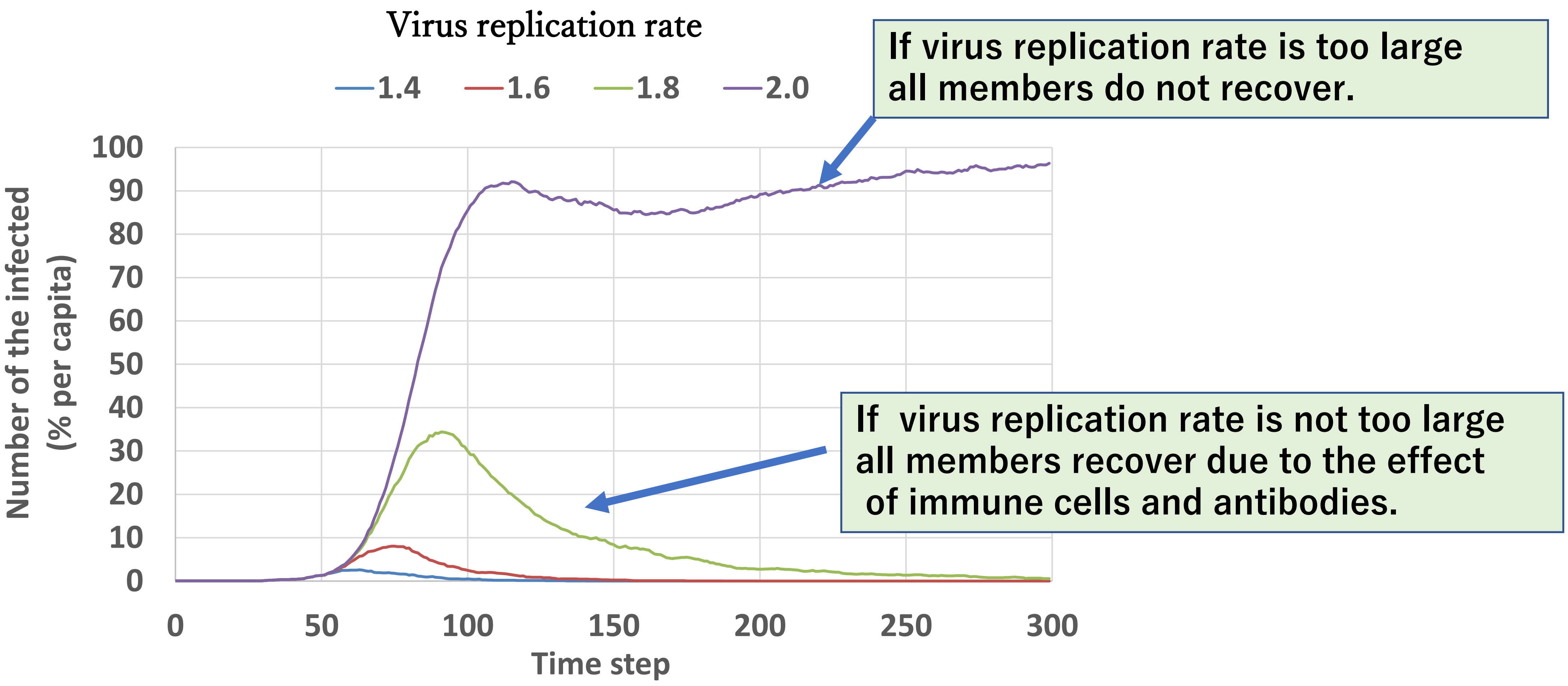


Fig. Effect of the virus replication rate on the number of infected agents.

Relationship between the pattern of the change in the number of newly infected, newly recovered and currently infected agents.

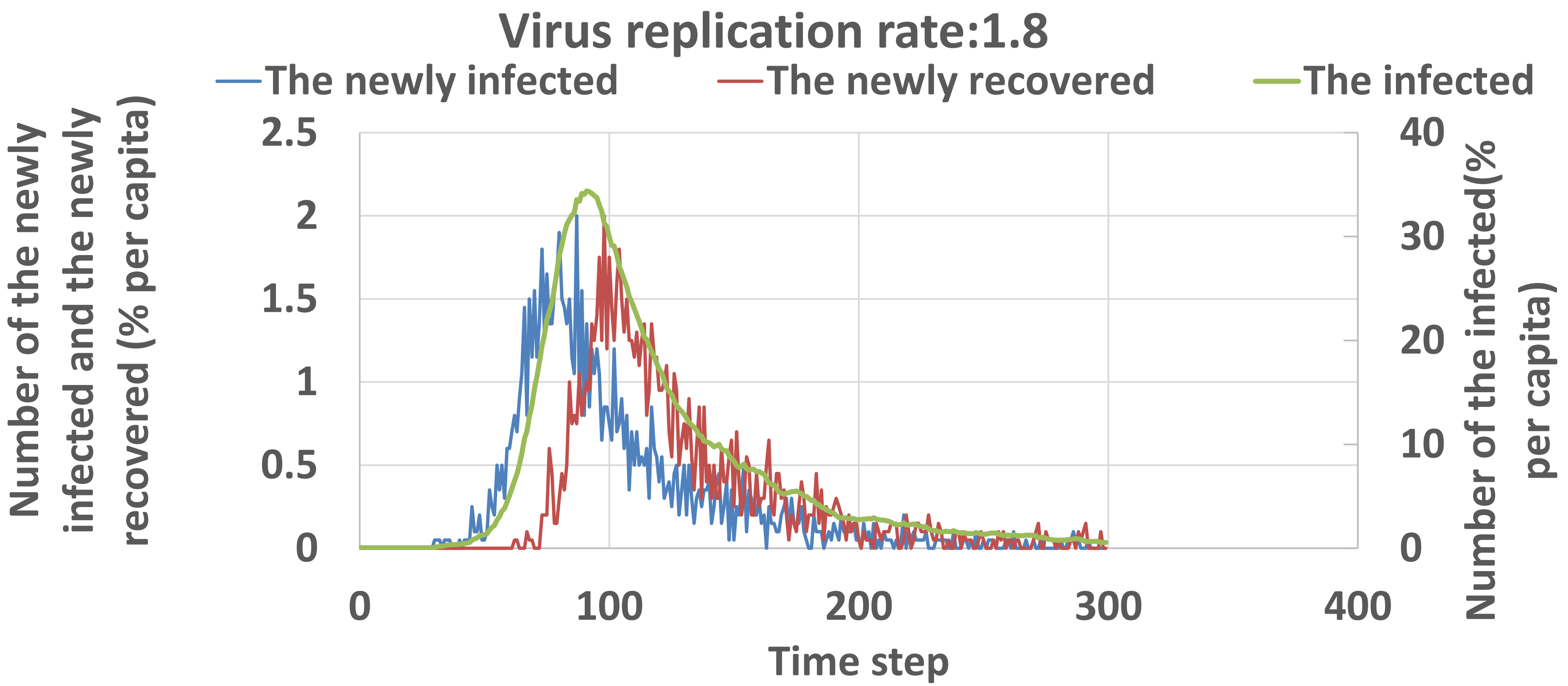


Fig. Changes in the numbers of newly infected, newly recovered, and total infected agents.

Number of total infected agent peaks
when the number of newly infected equals the number of recovered.

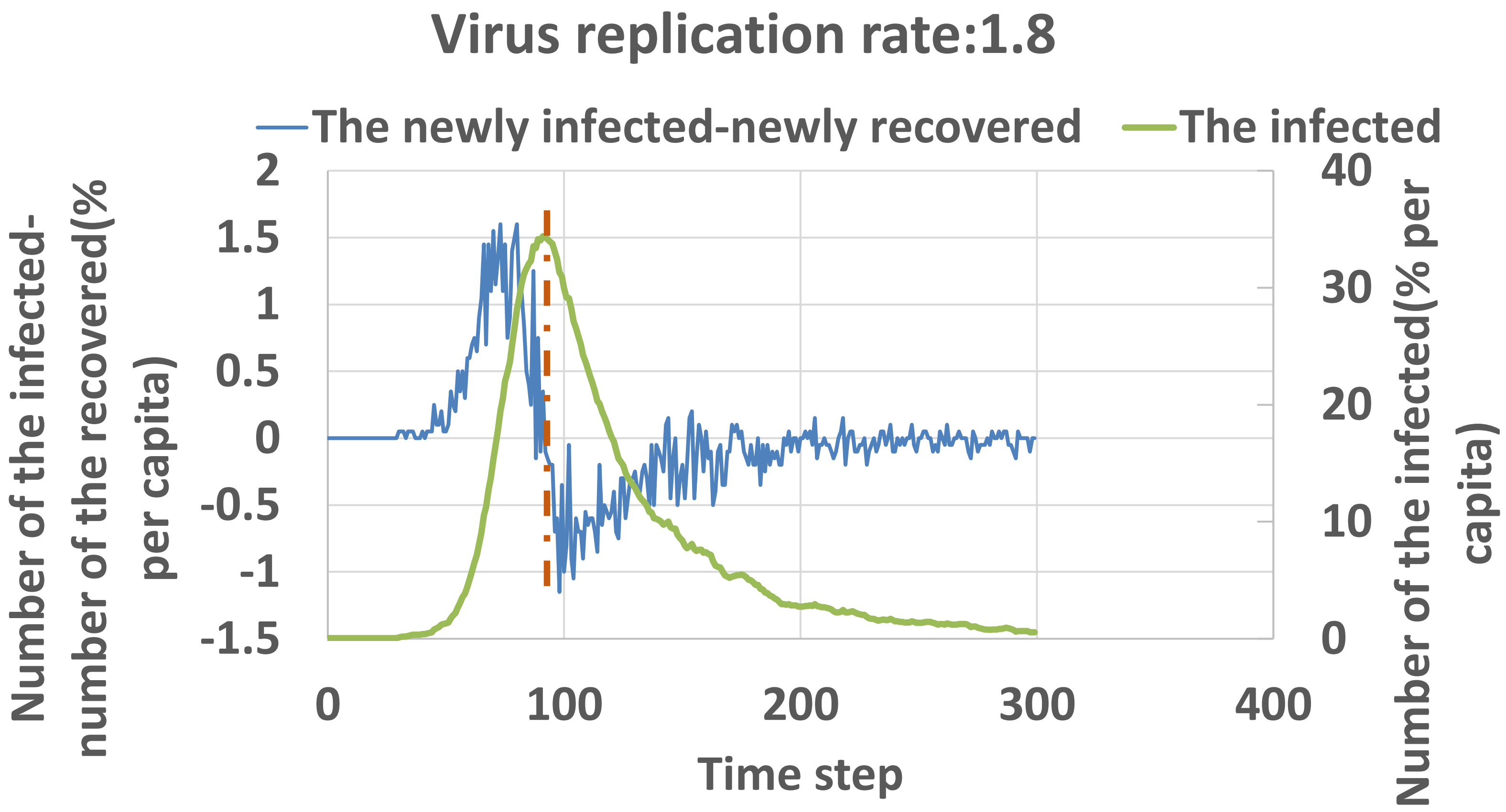
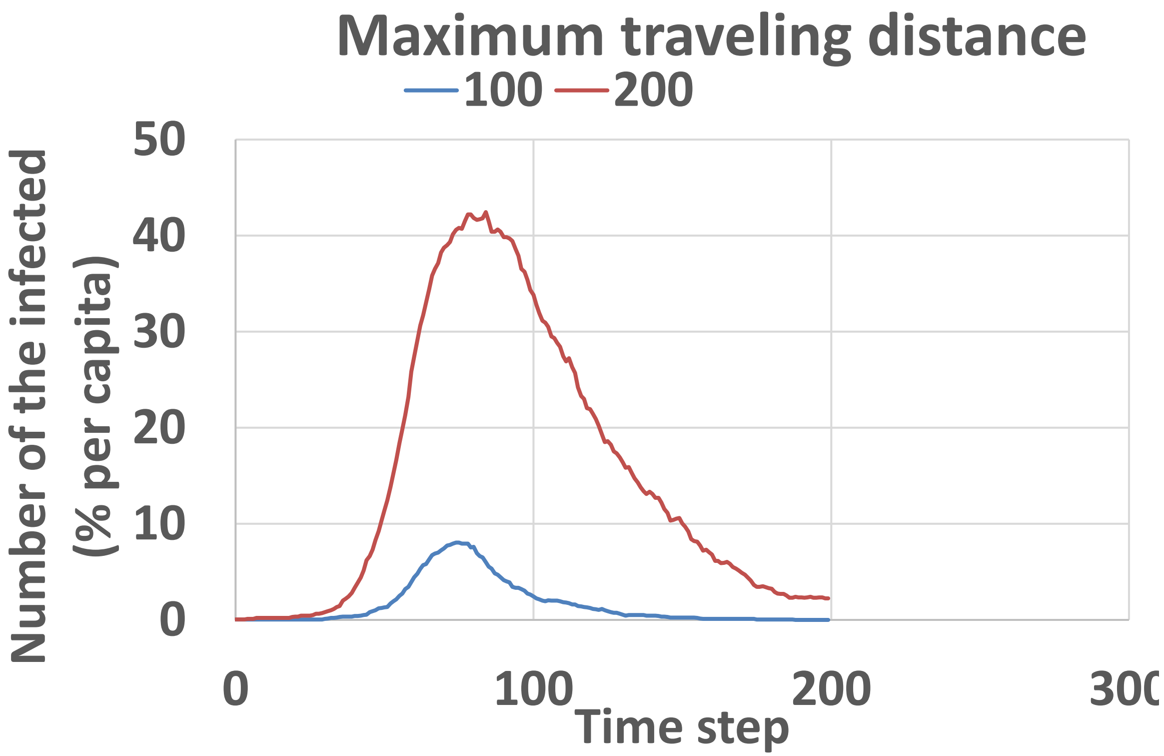
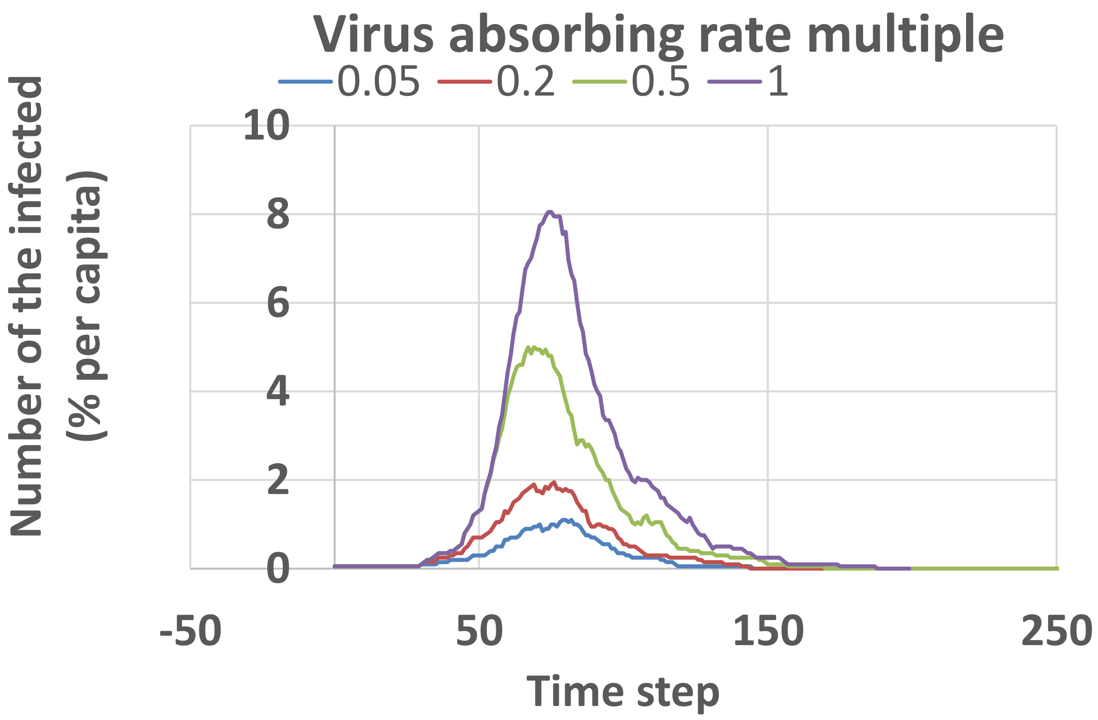


Fig. Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents.

5.2 Effect of the regulation of movement and wearing a mask.



Effect of the regulation of movement.



Effect of wearing a mask.

5.3 Mechanism of the pandemic convergence.

In this model, we can track every detail of infection propagation as well as changes in the number of viruses within each agent.

Infection Propagation		Number of Viruses at infection
Agent 1	at t=0	10^5
Agent 13	at t=4	10^4
Agent 1373	at t=6	10^2
Agent 1019	at t=7	10^1
Agent 1911	at t=13	10^{-1}
Agent 155	at t=25	

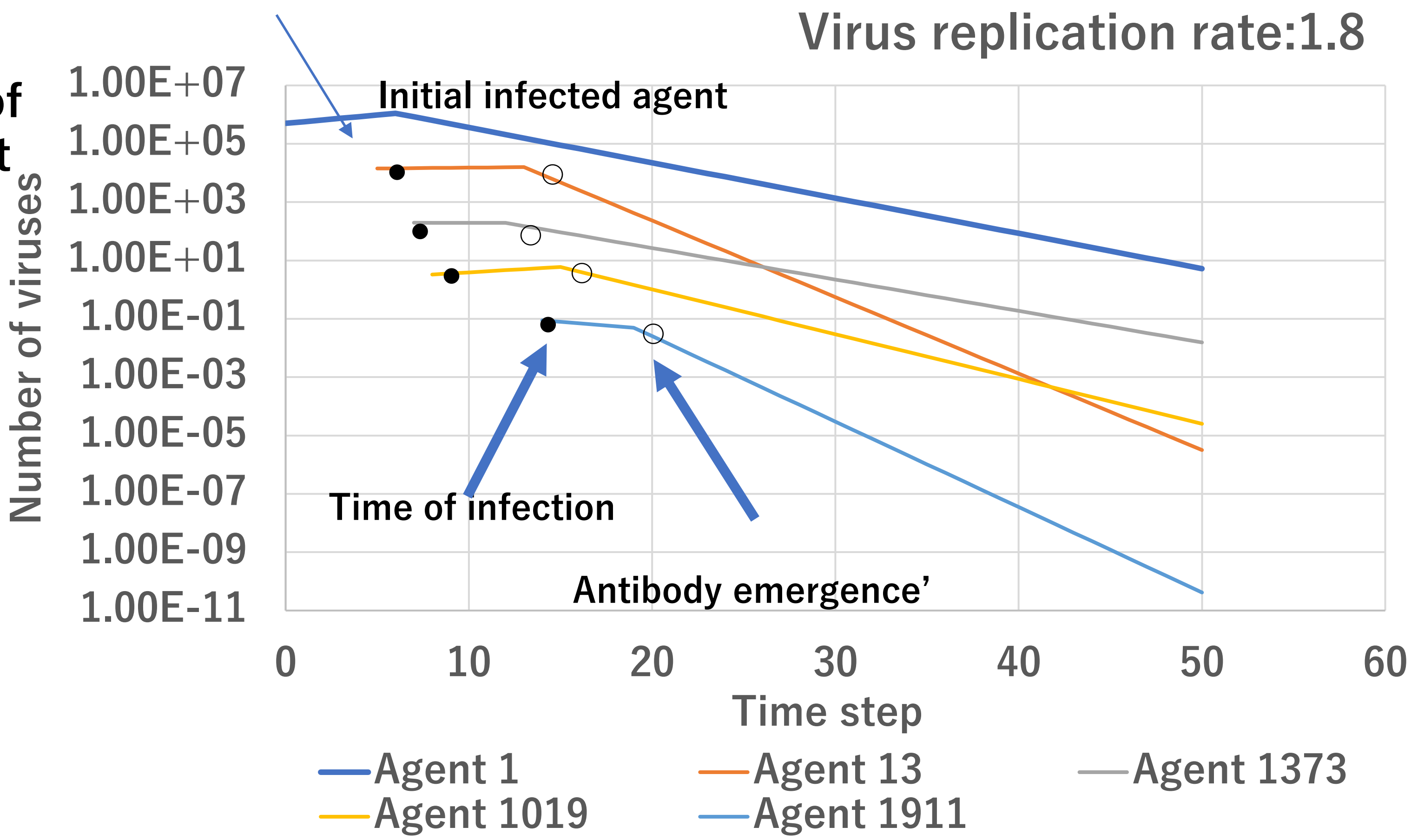
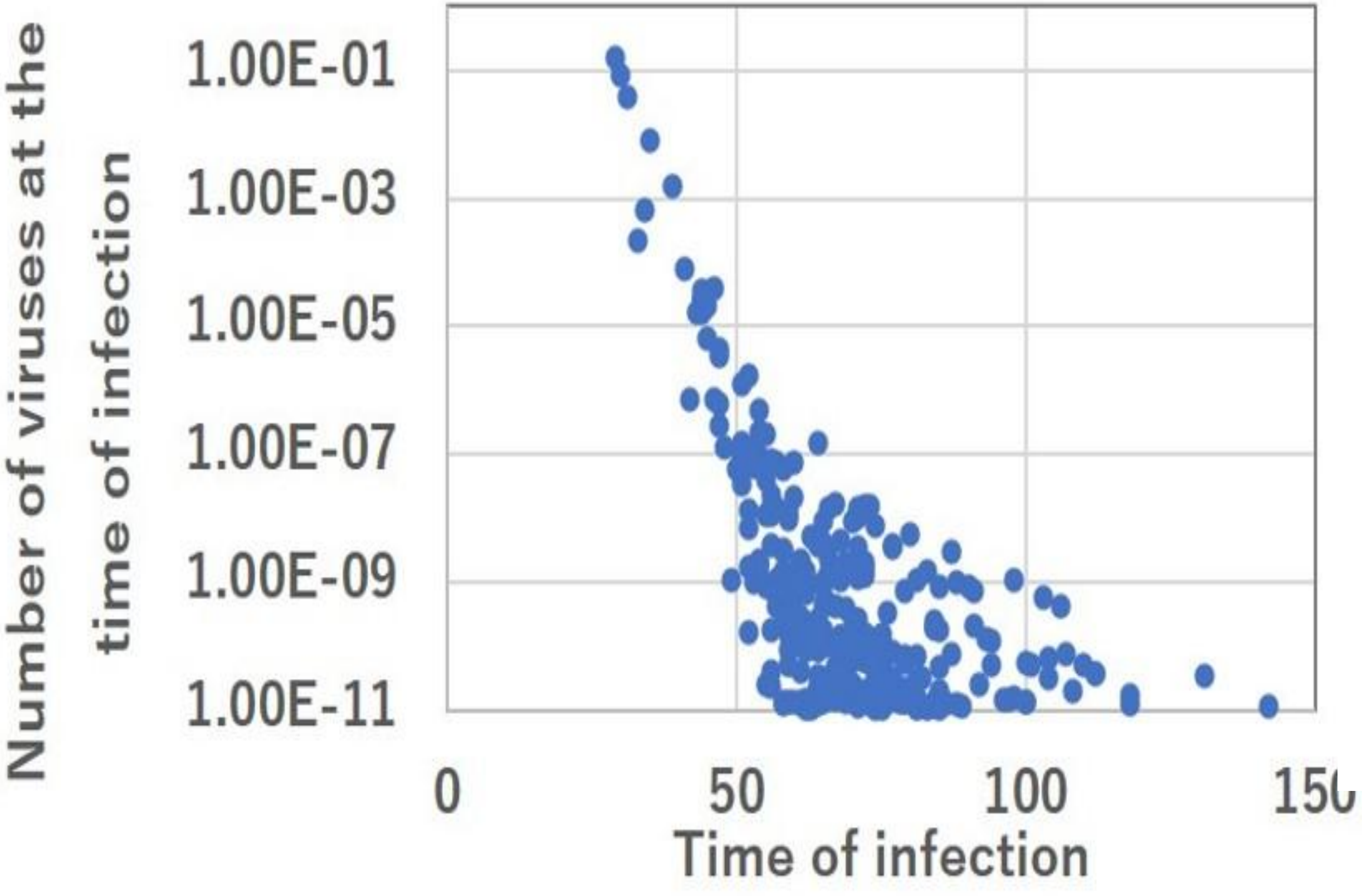
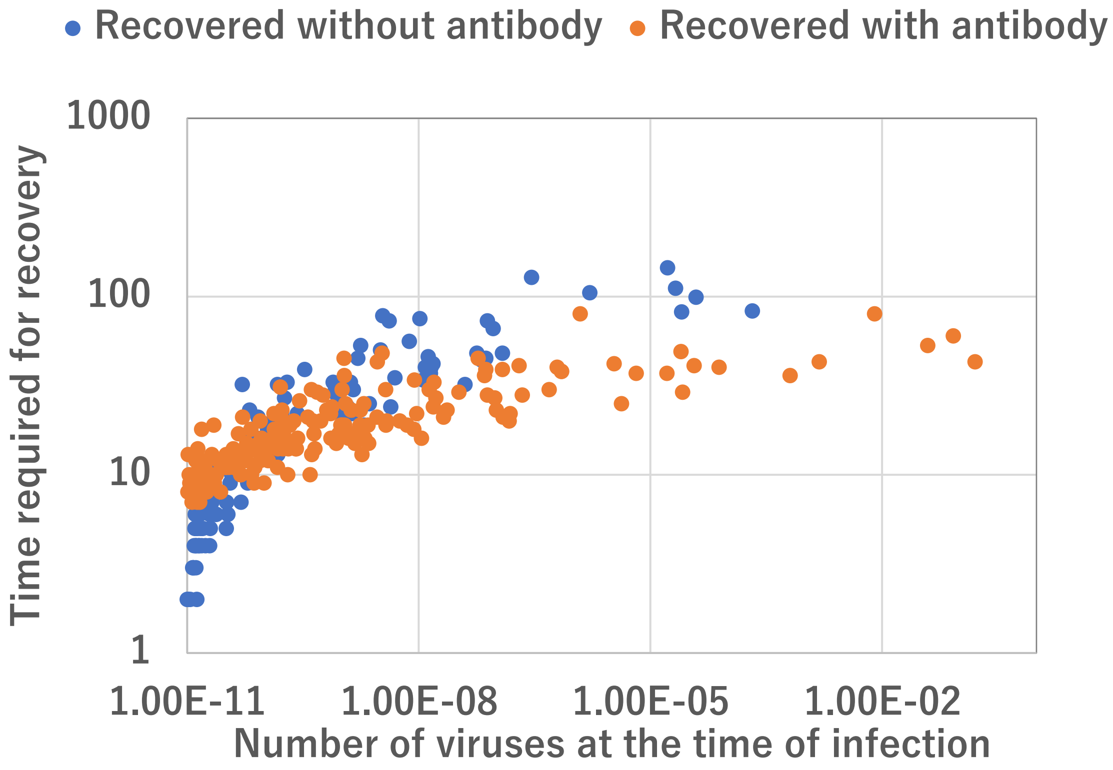


Fig. Change in the number of viruses of each agent during the beginning of infection spread.

Mechanism of the pandemic emergence and convergence.

At the initial stage, the number of infected individuals rapidly increases due to transmission chains. As the virus count within the system decreases and the amount of virus entering the body upon infection sharply declines, recovery is more likely to surge, leading to the pandemic convergence.



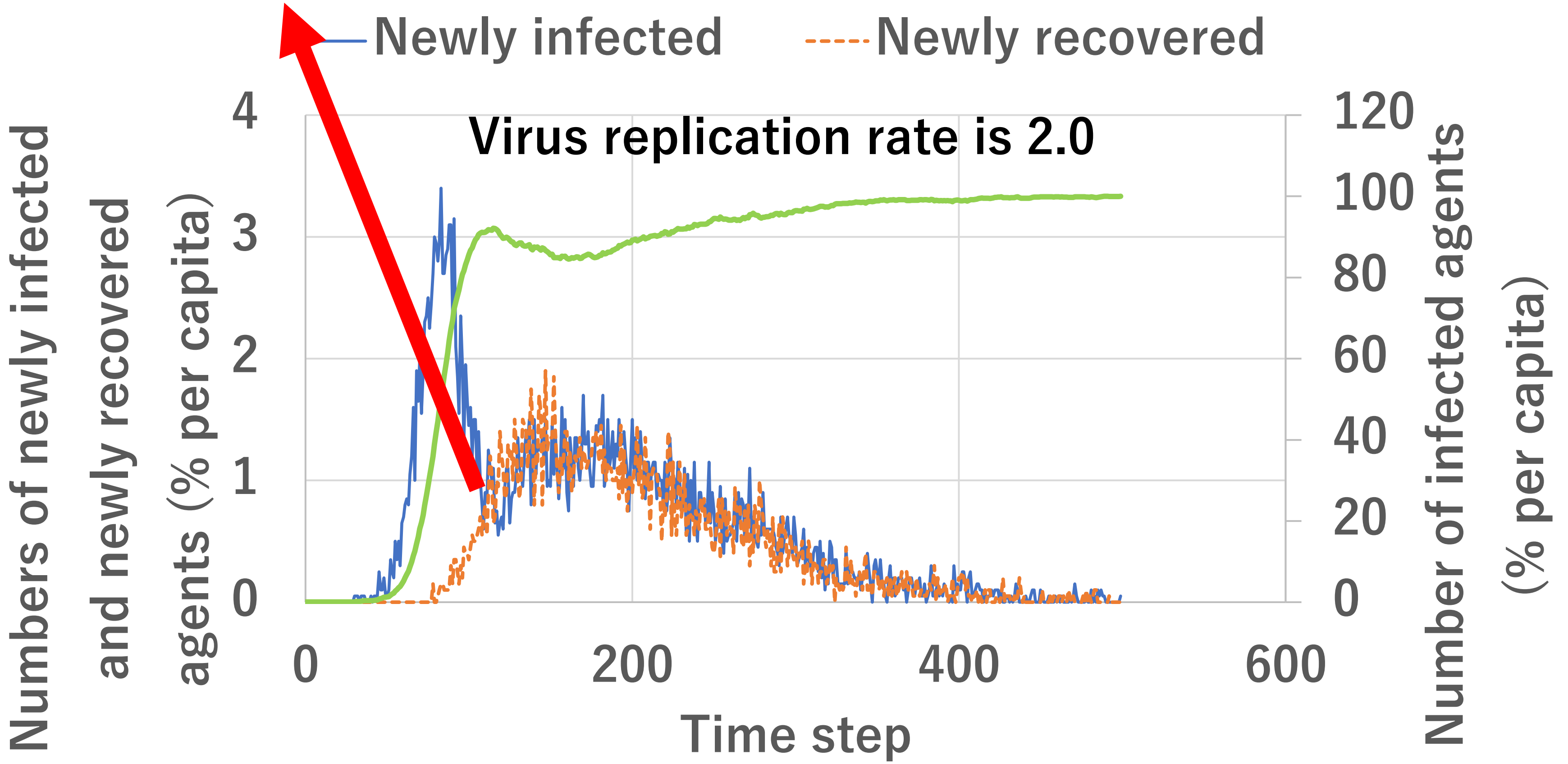


5.4 Mechanism behind a pandemic that does not converge. What happens?

When an agent with weak immunity is infected, the number of viruses increases, indefinitely, leasing to a resurgence of viruses within the system.

The proposed countermeasure is to isolate severely infected individuals.

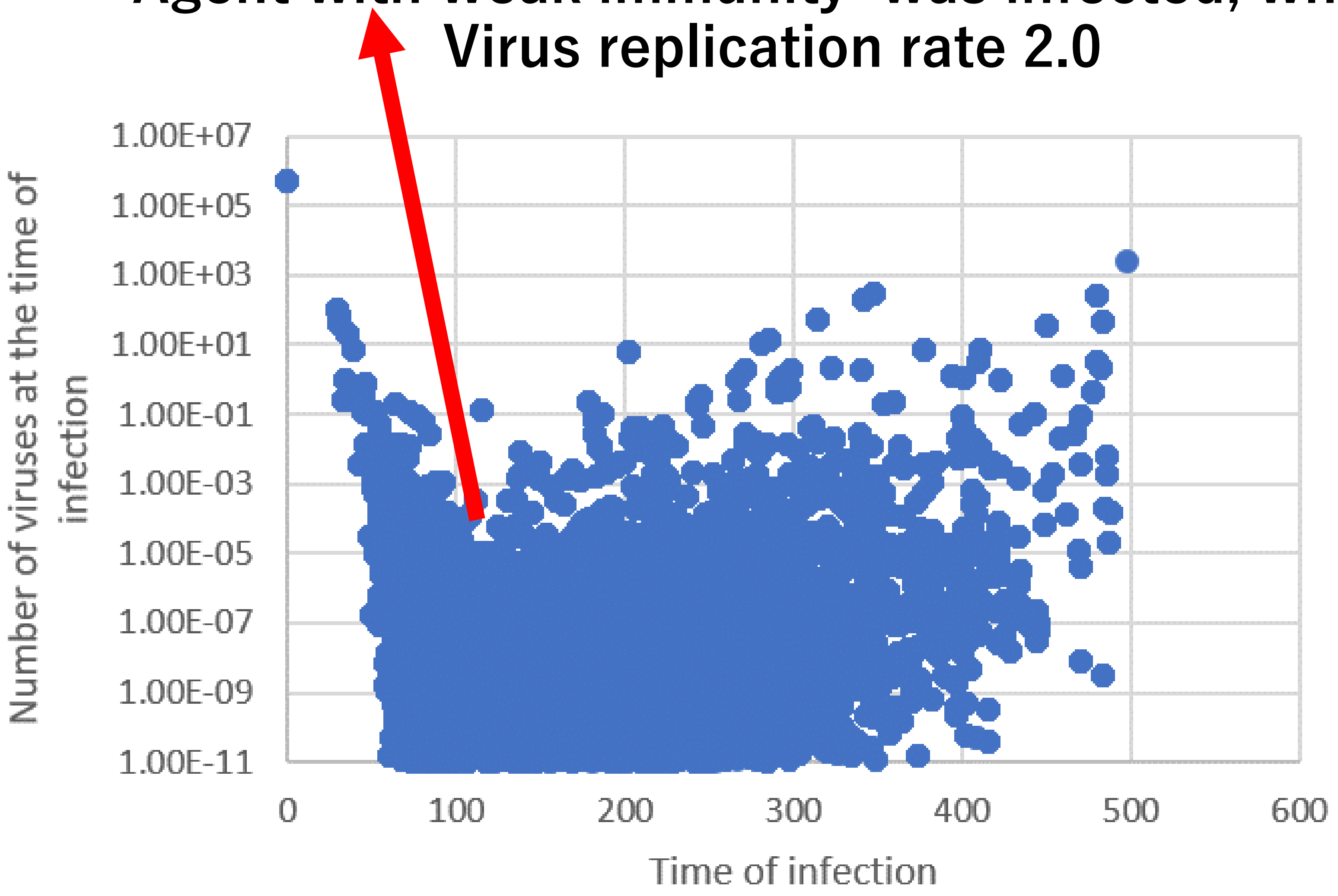
Agent with weak immunity was infected, who is agent 71.



Virus replication rate 2.0

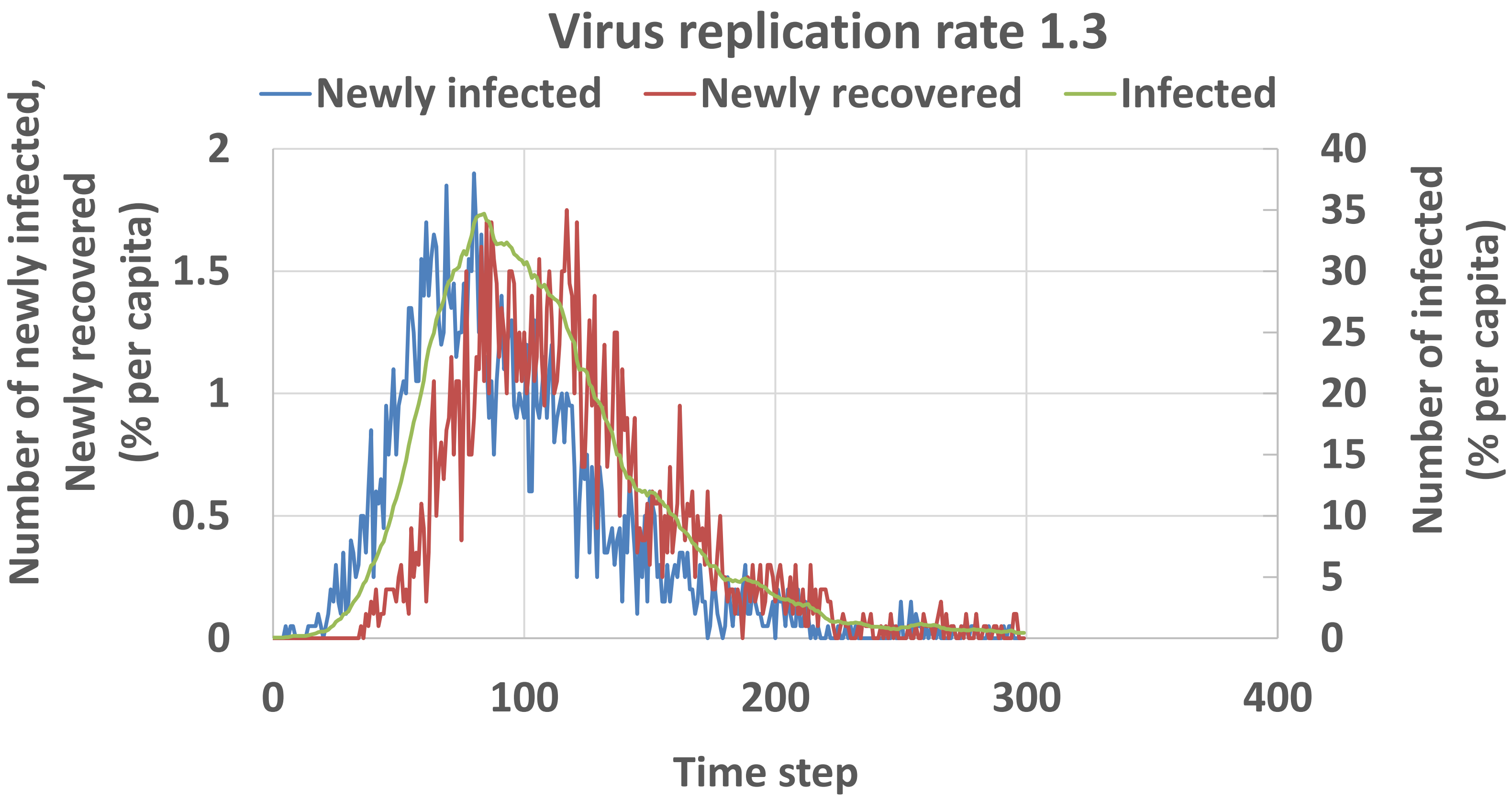
Resurgence of viruses following the infection of an agent with weak immunity.

Agent with weak immunity was infected, who is agent 71.
Virus replication rate 2.0



3.5 Effect of antibodies on the pandemic behavior.

Without antibodies, the upper limit of the virus replication rate for pandemic convergence becomes much smaller, from 1.8 to 1.3, but fundamental pattern of the pandemic is unchanged, indicating that antibodies are not essential factor for the pandemic convergence.



Calculated result in the case without antibodies.

3.6 Effect of the role of fever on the pandemic behavior

Without the effect of fever, a pandemic either does not occur or does not subside depending on the virus replication rate, making stable convergence across various rates unexplainable

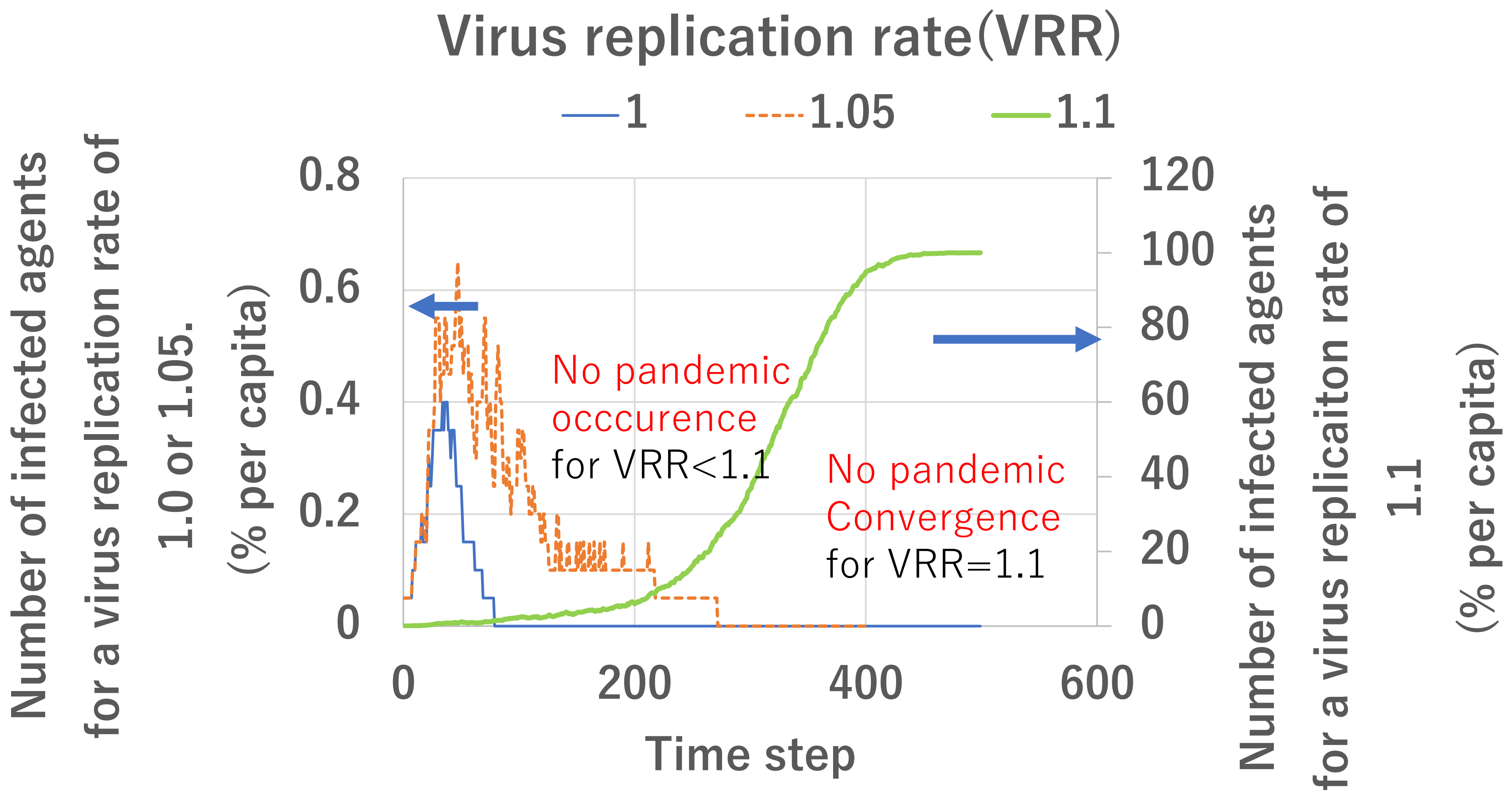


Fig. The behavior of the pandemic when the role of fever is not present.

6. Conclusions

1) **An agent-based infection model incorporating the roles of immune cells and antibodies was constructed and aggregate phenomena were analyzed based on the behavior of viral particles during the infection and recovery processes.**

2) **The calculated trend in the number of infected shows good agreement with the actual data. Effect of movement restriction and wearing a mask is also reproduced**

3) **The most essential factor for accurately reproducing the characteristics of pandemic phenomena is the role of fever, rather than antibodies. Based on this finding, an effective individual level countermeasure is self-monitoring body temperature to recognize his state of infection at an early stage, followed by self-restriction of movement if necessary . If a large number of individuals adopt this measure, it will contribute to the rapid containment of the pandemic.**

4) **I have proposed a new methodology for elucidating the causal mechanisms behind the emergence of social and economic phenomena using ABM and this research is an example of such an approach. I believe this methodology can be also applied to biological systems, as many phenomena emerge from bottom-up interactions.**

3. Experimental conditions.

1. Basic condition, only changing the virus replication rate.

2. Experiments changing parameter values.
   1) Regulation of agent's movement
      during the whole period of time or temporary during the time 50-100.
      ,changing maximum moving distance.
   2) Regulation of wearing masks
      during the whole period of time or temporary during the time 50-100.
      , changing the virus-release rate and virus-absorb rate
   3) Temporary regulation in both the moving distance and wearing masks.

3. Experiments changing behavioral rules for immune cells and antibodies.
   1) With or without antibodies emergence.
   2) With or without the effect of fever.
      In the present study, the former corresponds to the condition ,where the viruses release rate by immunity is proportional to the number of viruses and the latter corresponds to the condition where it is constant without depending on the number of viruses.

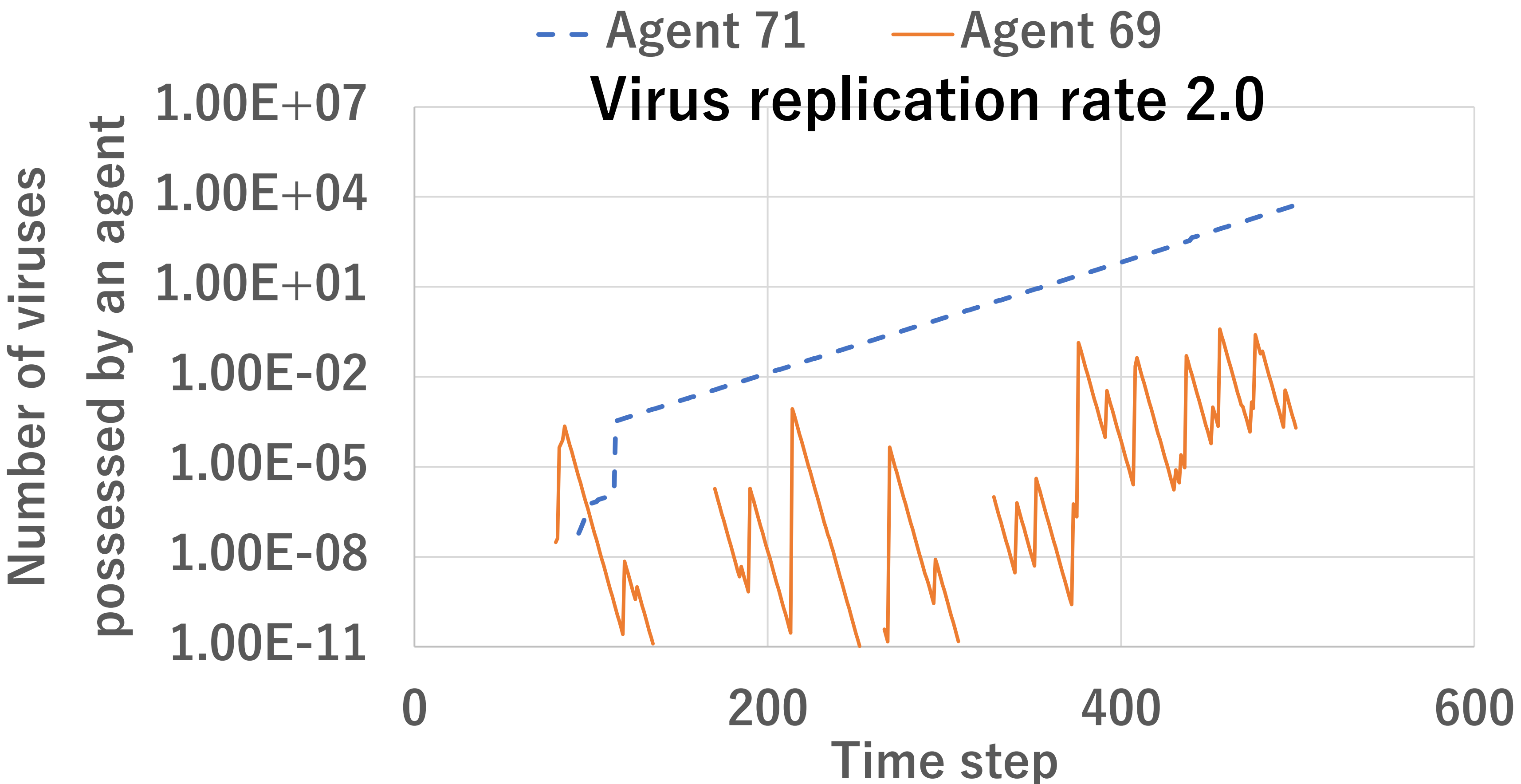
Change in the virus count of agents with weak immunity and normal immunity.

Agent71(Weak immunity) : Infected at t=92, and at t=113.

The number of viruses increases indefinitely due to viral replication.

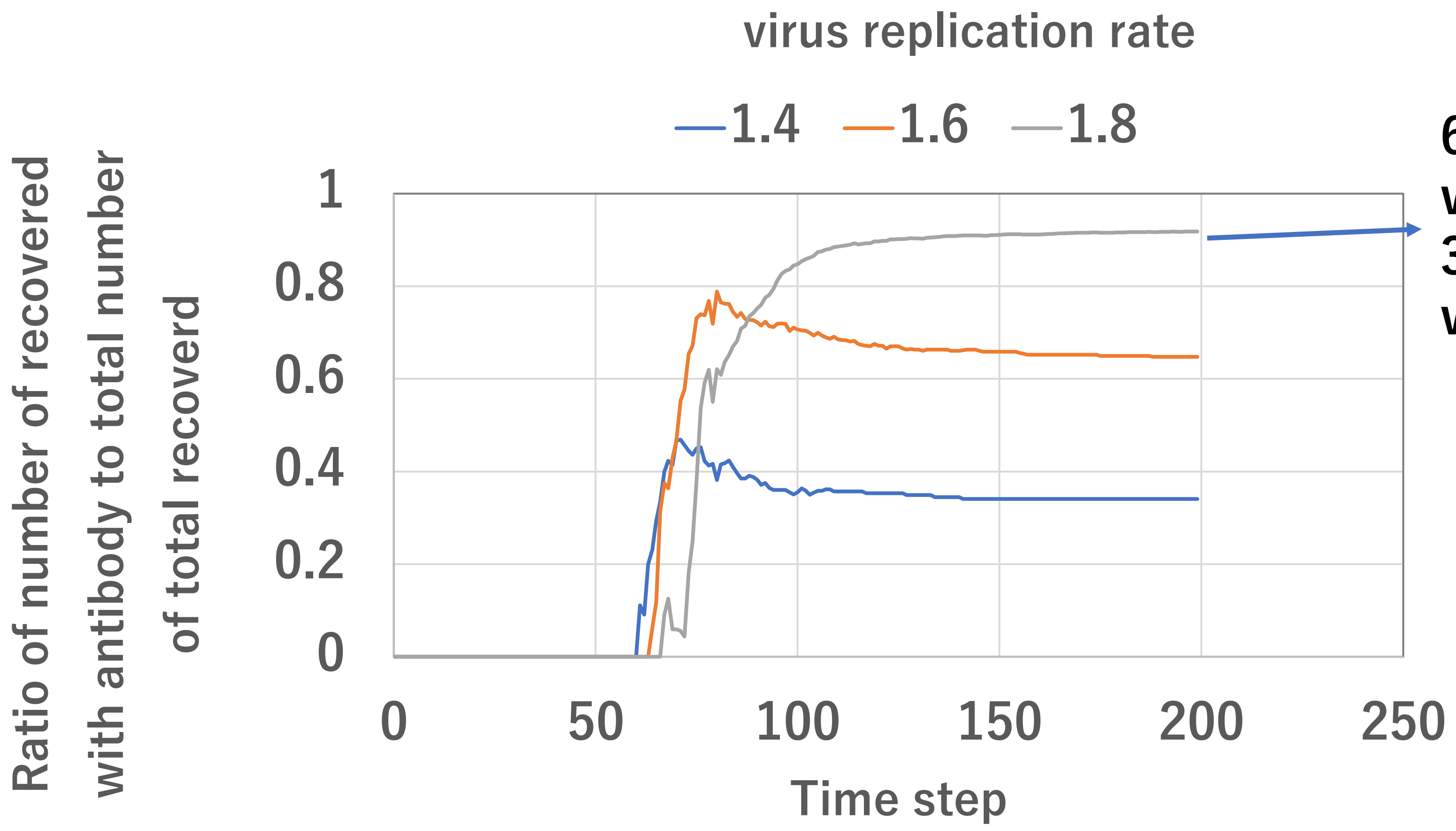
Agent 69(Normal agent) : Infected multiple times.

The number of viruses increases due to the rising viral count in the system, which is caused by the agent with weak immunity.



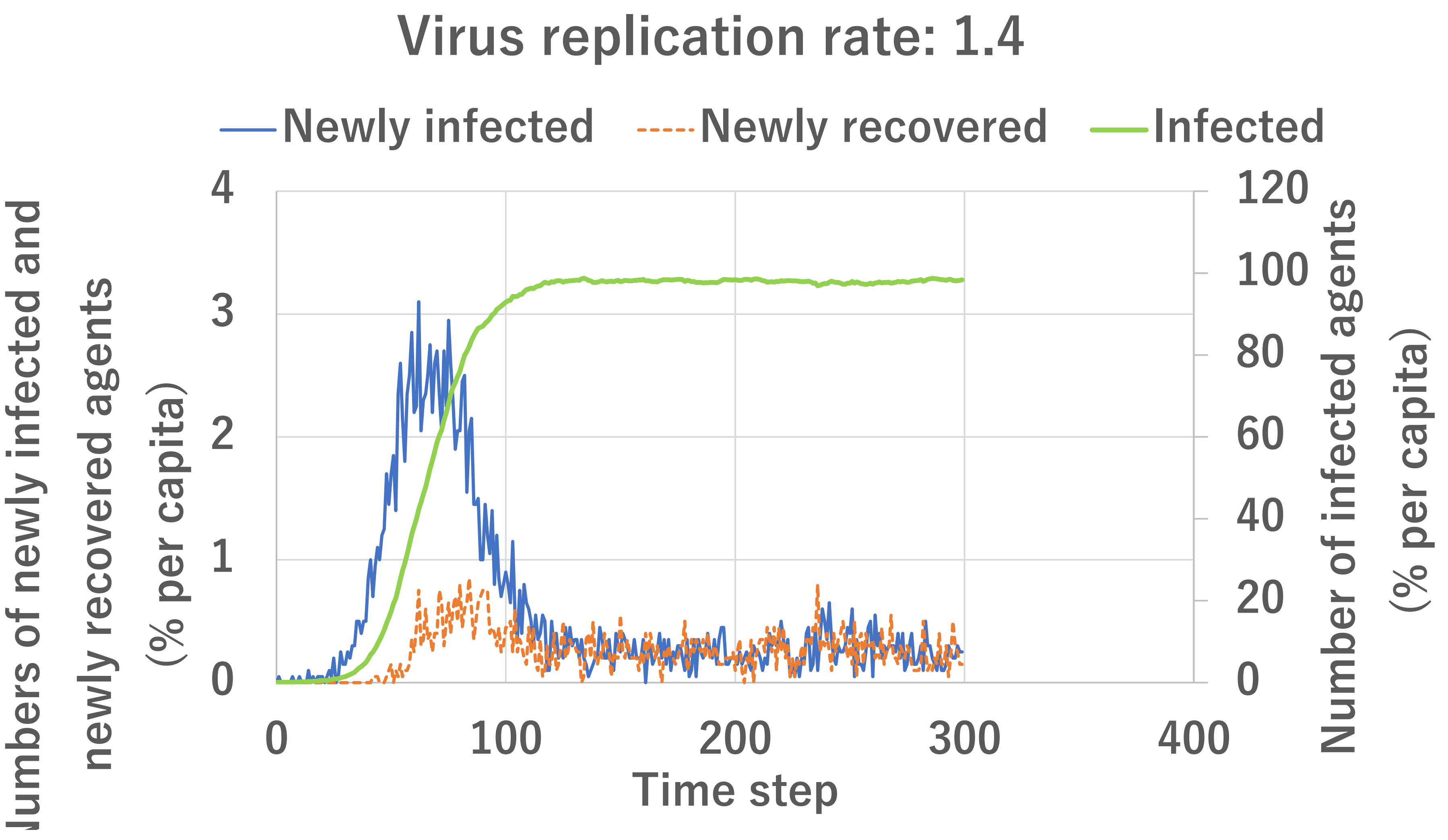
The ratio of the number of recovered agents with antibodies.

The number of agents who are recovered with antibodies increases with increasing virus replication rate.



65% recovered with antibodies. 35% recovered without antibodies.

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



Virus replication rate: 1.4
Newly infected
Newly recovered
Infected
4
3
2
1
0
120
100
80
60
40
20
0
0
100
200
300
400
Time step
umbers of newly infected and
newly recovered agents
(% per capita)
Number of infected agents
(% per capita)

3.3 Temporal regulation of movement followed by temporal mitigation

- It decreases the peak value of the number of infected agents.
- Resultant second wage is not remarkable,
  if the new infected person does not enter into the system from outside.

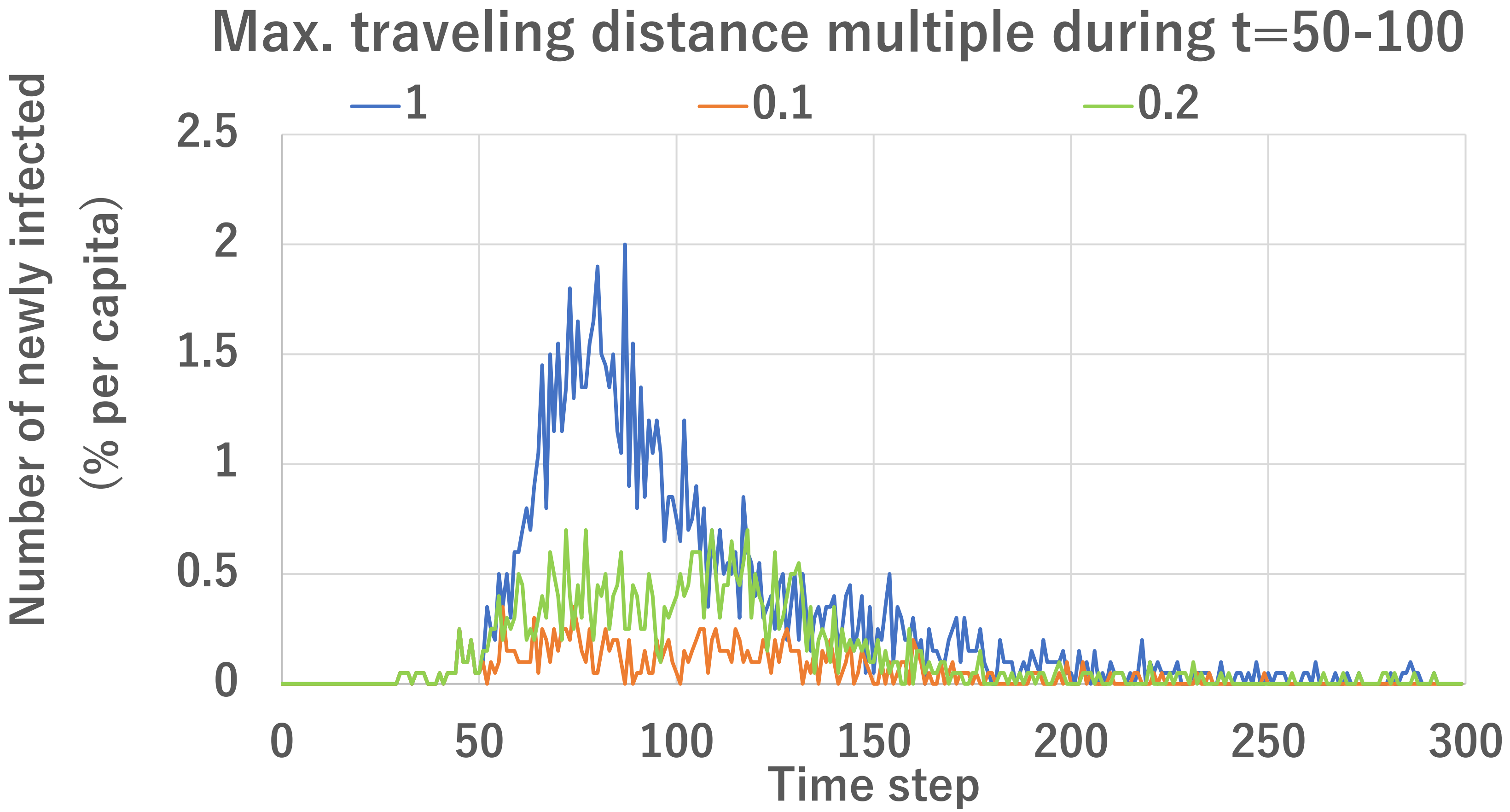


Fig. Effect of temporary regulation of traveling distance and its release on the number of infected neighbors (virus growth rate: 1.8).

3.2.2 Effect of virus absorbing rate on the infection behavior during the regulation and mitigation of movement.

Decreasing the virus absorbing rate by wearing masks is effective for preventing the second wave occurrence.

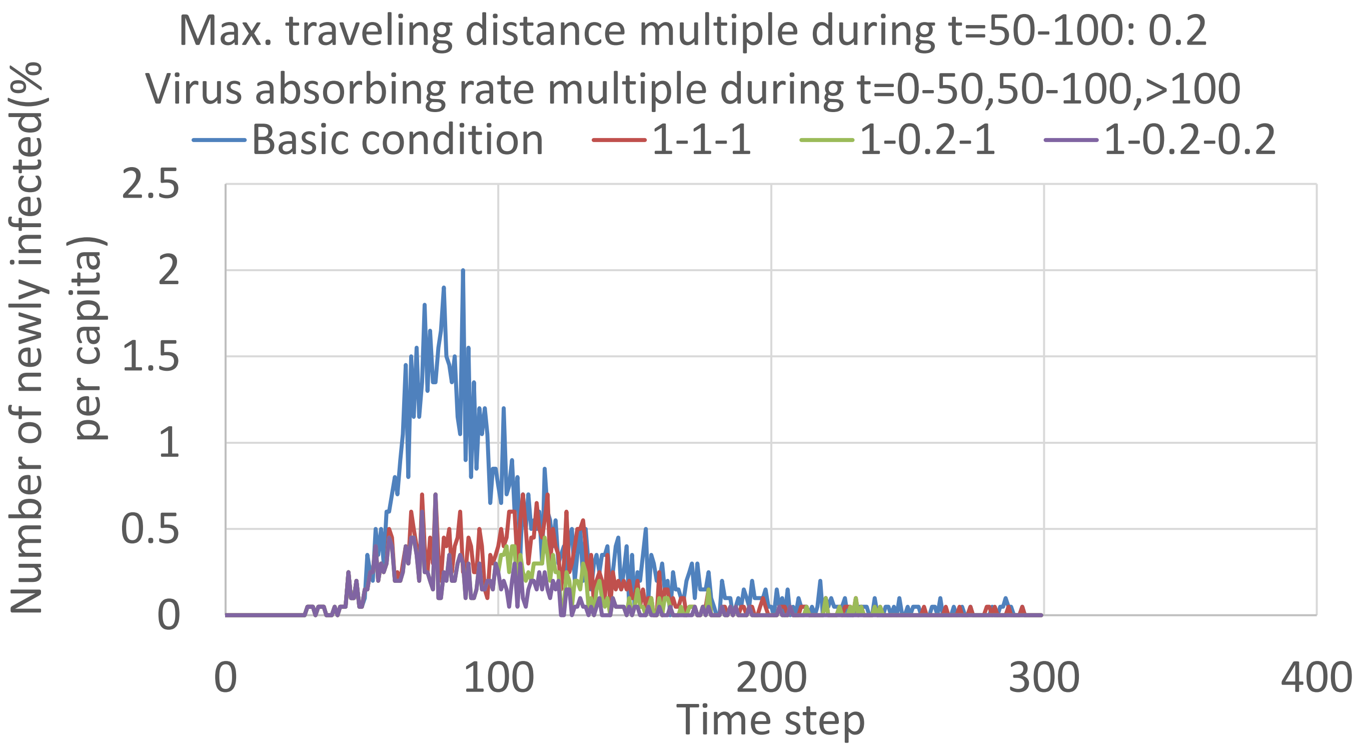
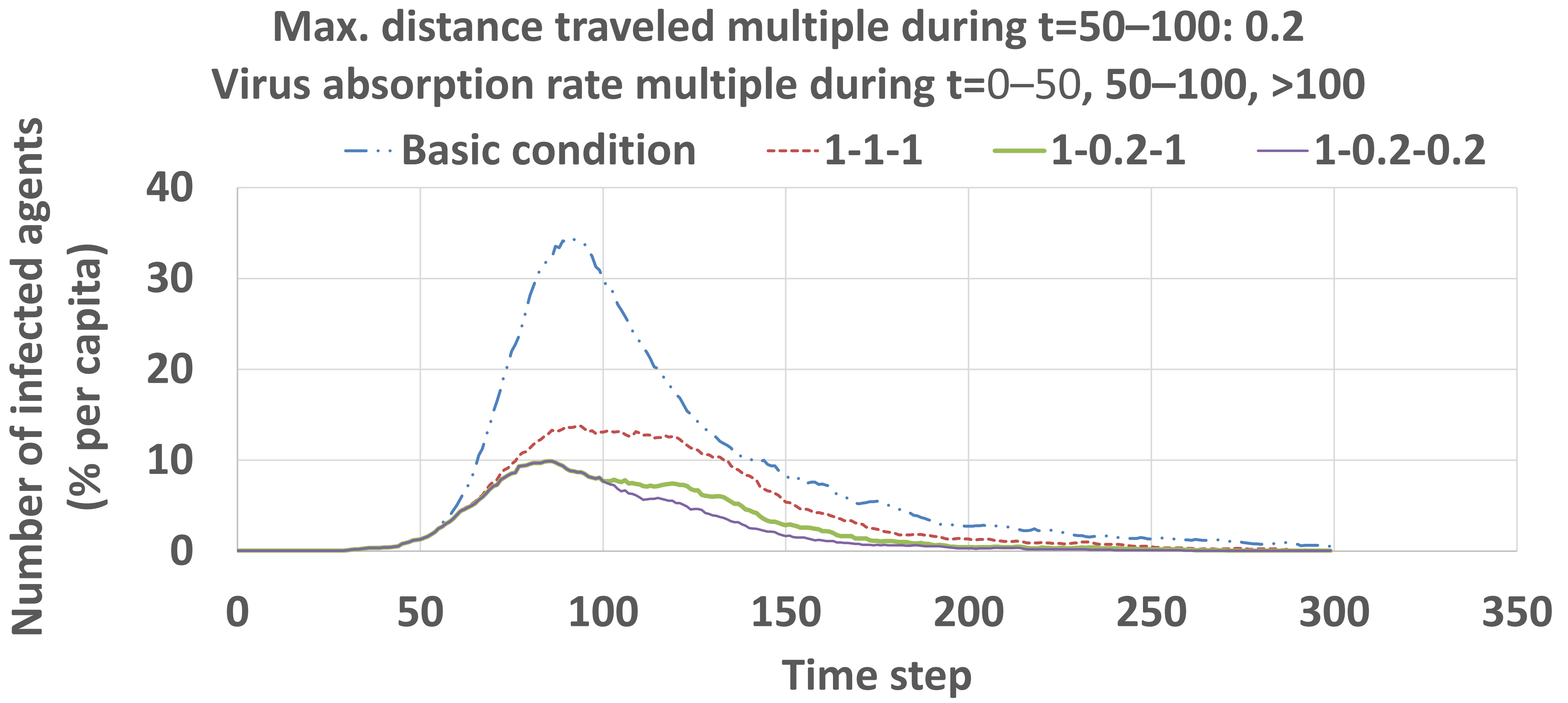


Fig. 24. Effect of the virus absorbing rate on the number of newly infected agents when movement regulation is applied.

3.3 Temporal regulation of movement with temporal regulation of wearing masks

- It drastically decreases the peak value of the number of infected agents.
- Resultant second wage is not remarkable,
  if the new infected person does not enter into the system from outside



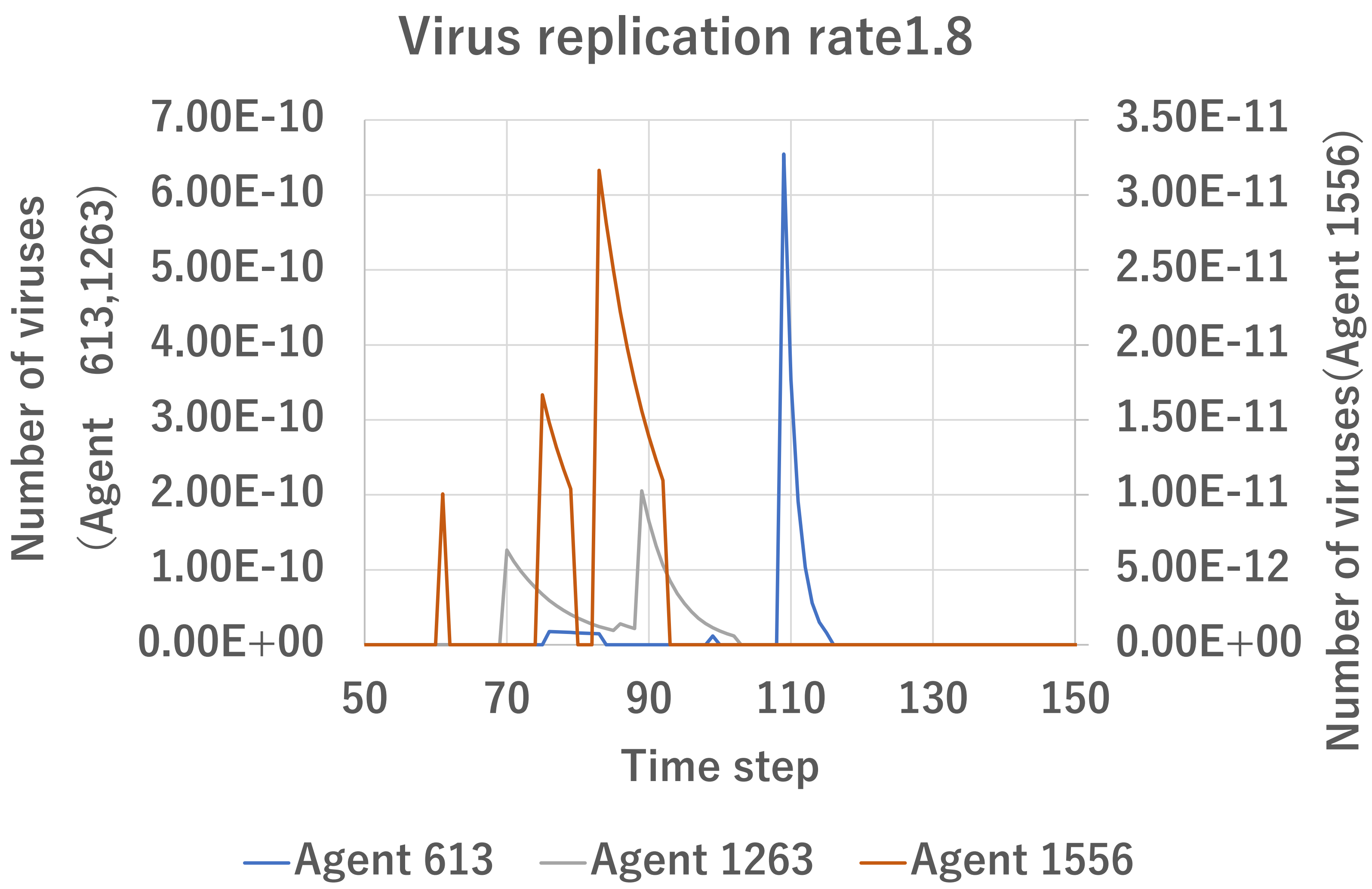


Fig. Examples of cases of multiple infections

6. The decrease in the number of viruses discharged every time step by the attack of immune cells and antibodies are assumed as proportional to the number of viruses.
This assumption corresponds to the role of fever, associated with immunity.
The proportional constant are defined as virus attack rate, specified by agent-specific random number.
The viruses multiplies at a virus replication rate which is assumed constant.

8 The number of viruses is redefined every time step as shown below.

$$N^i_{VP}(t+1) = \left(1 - R^i_{release} - R^i_{attack}\right) \cdot N^i_{VP}(t) \cdot Rate_{replication} + \Delta N^i_{infected}(t) \qquad (4)$$

$$\Delta N^i_{infected}(t) = \sum_{j \in neigbours} N^j_{VP}(t) \cdot R^j_{released} R^i_{absorbed} \qquad (5)$$

where, $R^j_{released}$: *Virus releasing ratio of agent j*

$R^i_{absorbed}$: *Virus absorbing ratio of agent i*

R^i_{attack} : *Virus attack rate of agent i*

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

$\Delta N^i_{infected}(t)$: *Increasing increment of the number of virses at the time t*

What is Agent-Based-Modeling(ABM)?

ABM is a bottom-up modeling method in which an artificial society is constructed on a computer and causal mechanism of the phenomenon under concern can be elucidated by a series of computer experiments.

The principle of this methodology is as follows:

1. Every aggregate phenomenon in the society is caused by the heterogeneous agents' behaviors and interactions.
2. Using ABM, we can construct an artificial society on a computer which works in the same principle of the actual society.
3. The model must incorporates a set of behavioral rules that is indispensable to reproduce actual phenomenon, which is a cause of the phenomenon and can be elucidated by a series of computer experiments.
4. Then, we can elucidate the causal mechanisms of the phenomenon by considering the reason why those factors are indispensable.

This procedure is a new validation method of ABM that I have been proposing ,

1. Introduction

1) Although coronavirus pandemic has been calmed down, various new sources of the pandemic are showing up worldwide, and effective countermeasures are required.

2) Many infection models have been so far developed for understanding the infection problems, but they do not model the recovery process .

- ■ System dynamic model (SIR model, SIER model etc.)
  An equation-based model which assumes the set of constant parameters Thus, heterogeneity of agents ,regarding both infection and recovery processes is not implemented in the model.
- ■ Agent-based model (ABM model)
  Most of the previous infectious-diseases-related ABM models deal with the infection process in detail using geographical data, but the recovery process is not modeled from bottom-up, i.e. heterogeneity of agents' immunity is not implemented in the model.

1. Introduction

1) Mechanism-oriented agent-based modeling.

■ All social phenomena ,including infectious diseases pandemic , emerge as a result of heterogeneous human behaviors of various type and their interactions.

■ As agent-based modeling (ABM) is a bottom-up modeling method, using ABM we can construct an artificial society in which various phenomena emerge in the same principle in a real world, where the set of behavioral rules is the cause of the phenomenon in this artificial society.

■ By systematically changing the behavioral rules, and observing if the qualitative feature of the emerged phenomenon is the same as that of real world, we can determine an indispensable set of behavioral rules to reproduce the phenomenon .

■ The reason why the set of behavioral rules is indispensable, helps us to get better understanding of the causal mechanism of the phenomenon.

This procedure is a new validation method of ABM that I have been proposing , providing us a scientific methodology to understand the causal mechanism of social phenomena. The present study is one of such works.

The pandemic phenomenon in the real world that should be reproduced by the model.

1. The number of newly infected agents first increases and decreases .
   Then the number of newly recovered agents increases and exceeds the number of newly infected agents at some point.

2. When the number of recovered agents exceeds the number of infected agents
   The total number of infected agents shows its peak value.

3. A regulation of the movement of people and wearing masks are effective for quick convergence of the pandemic.

4. Human being historically encountered various types of the pandemics, such as cholera, tropical infectious diseases , etc. the viral particles of which was showed wide range of replication rates .
   However, human being has overcome those pandemics and survived without being perished.

Actual data observed during the early stage of corona pandemic in Japan.

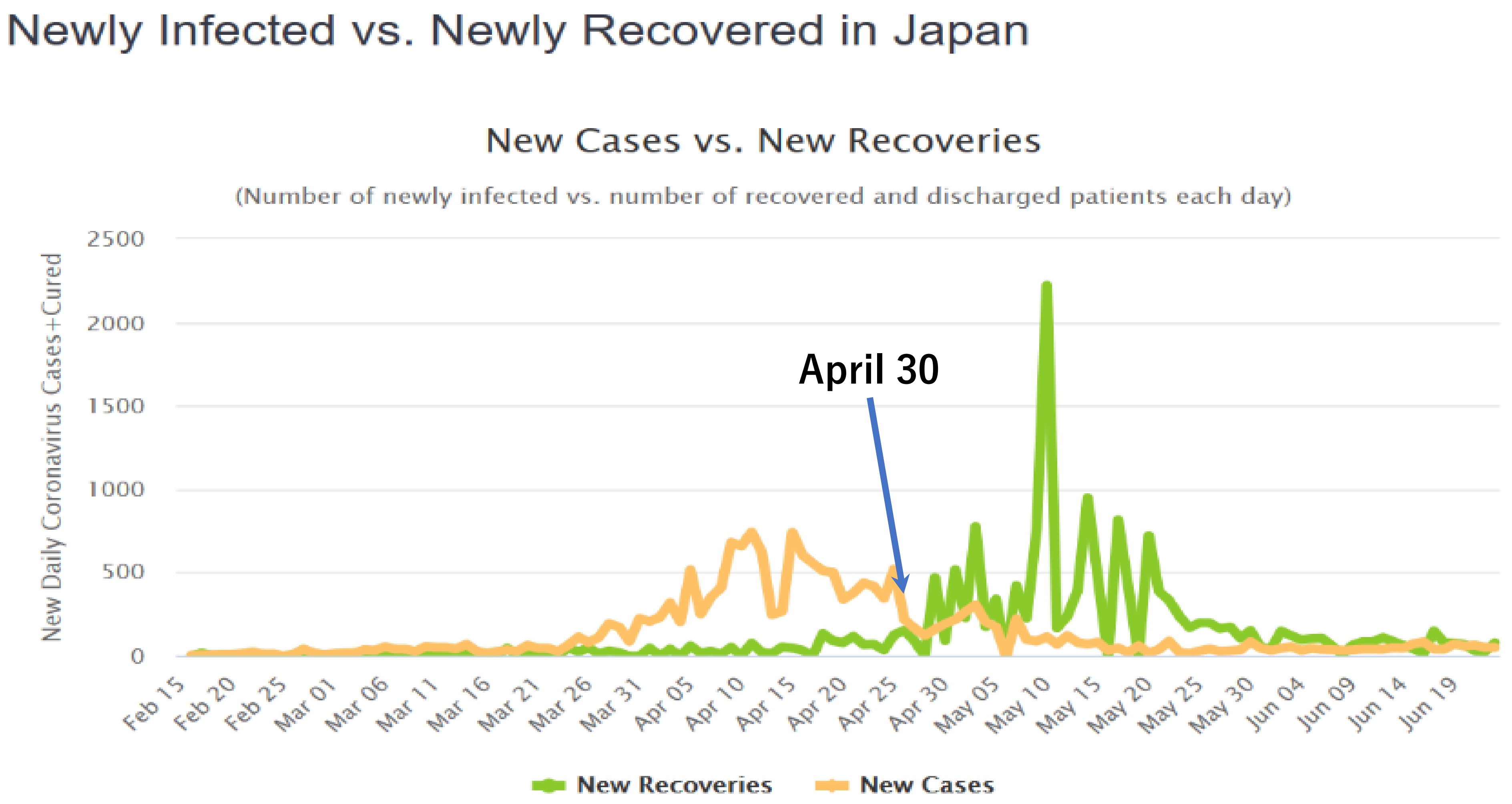


Figure 17. Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020.[17)]

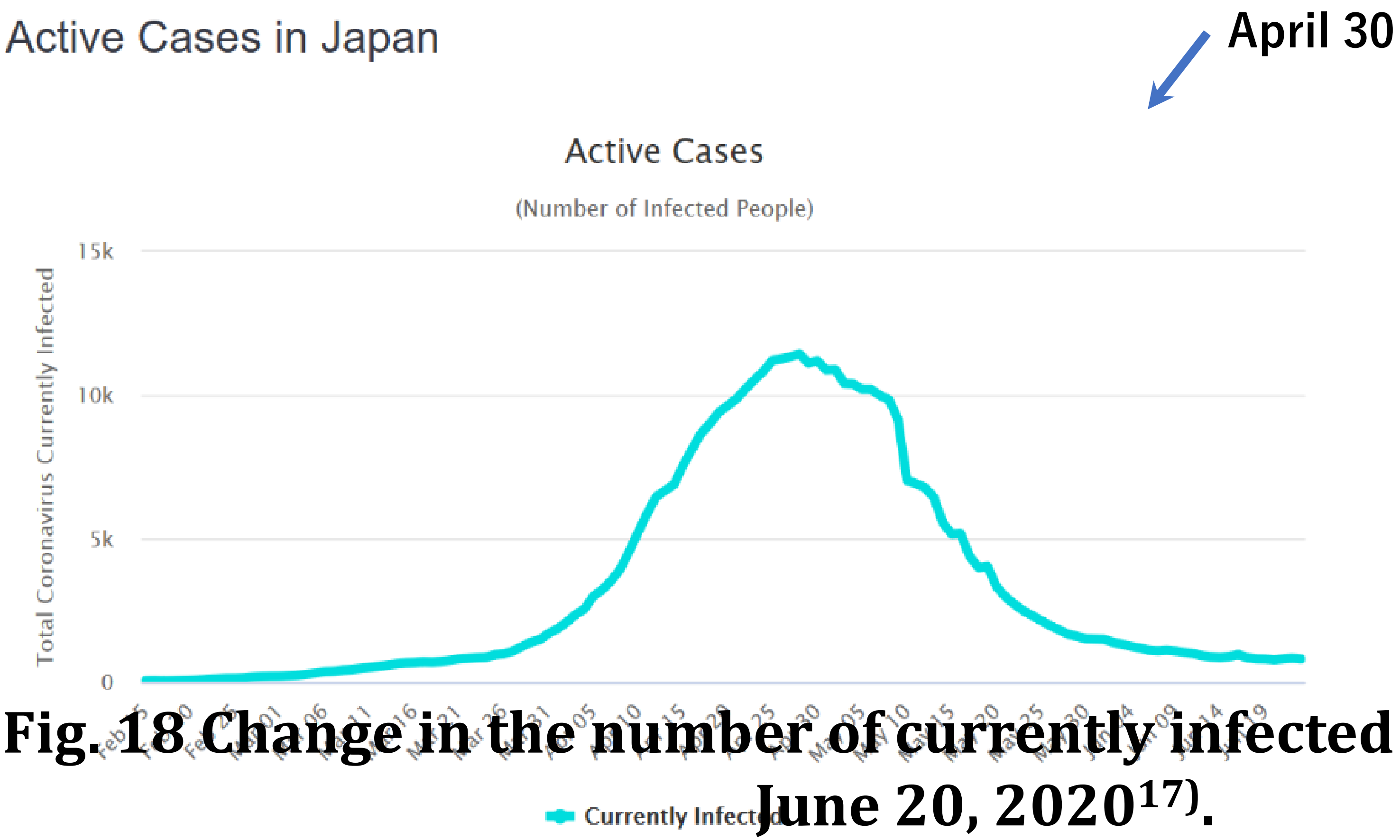
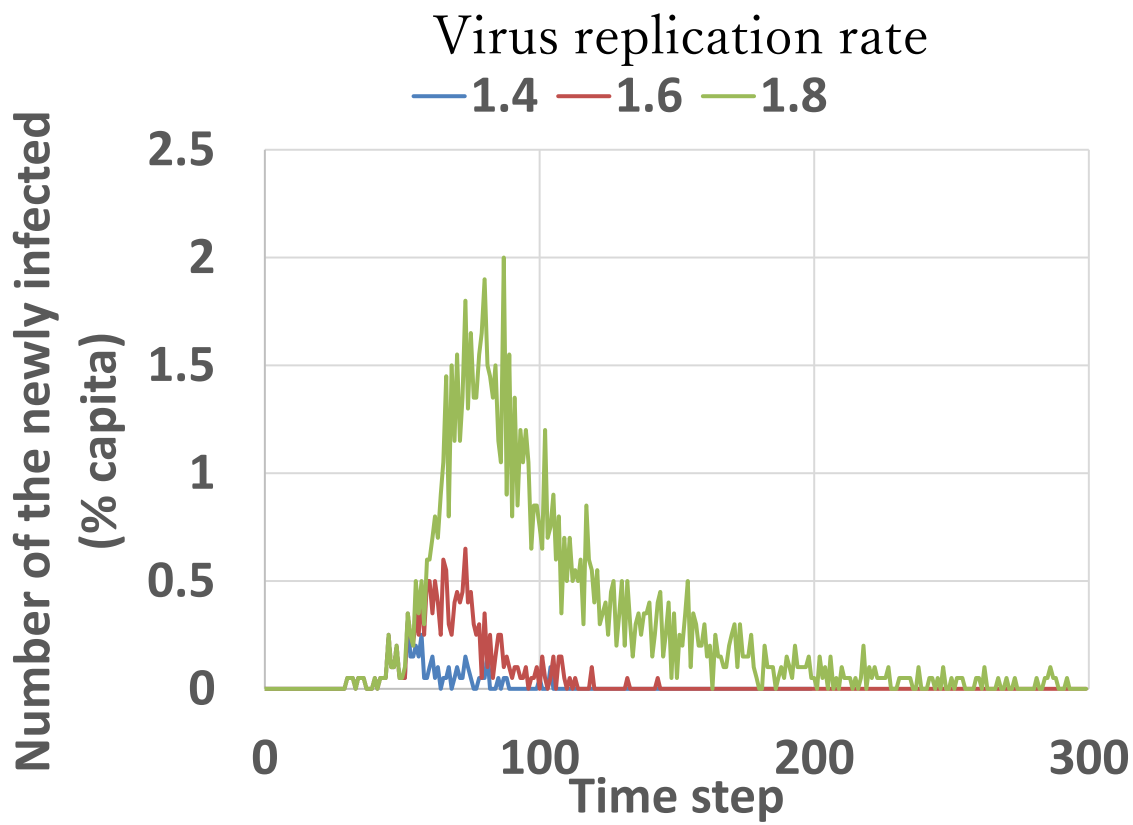


Fig. 18 Change in the number of currently infected people in Japan as of June 20, 2020[17].

Newly infected agents



Newly recovered agents

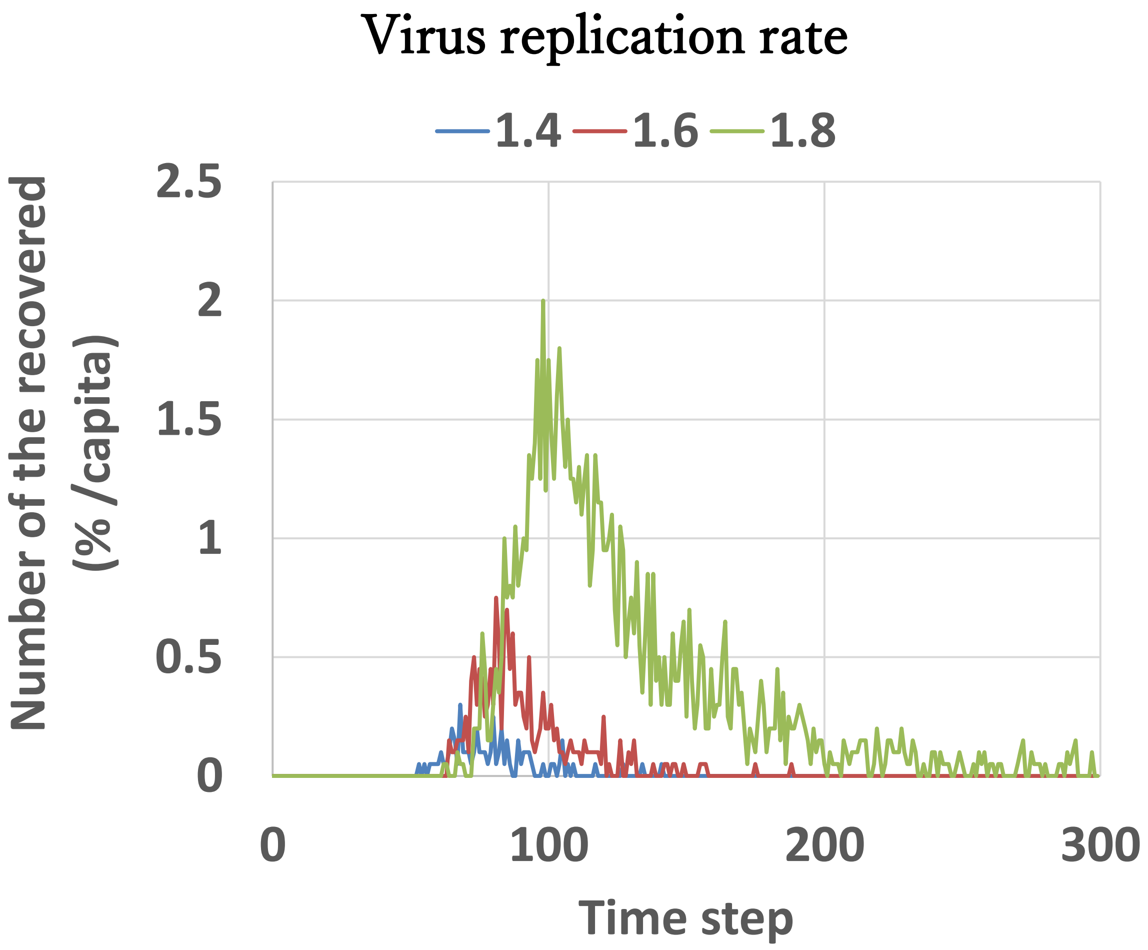


Fig. Effect of virus replication rate on the number of newly infected agents. And the number of newly recovered agents.

3.4 Effect of countermeasures on the pandemic behavior.

3.3.1Regulation of the movement

It is effective throughout the whole stage of the pandemic.

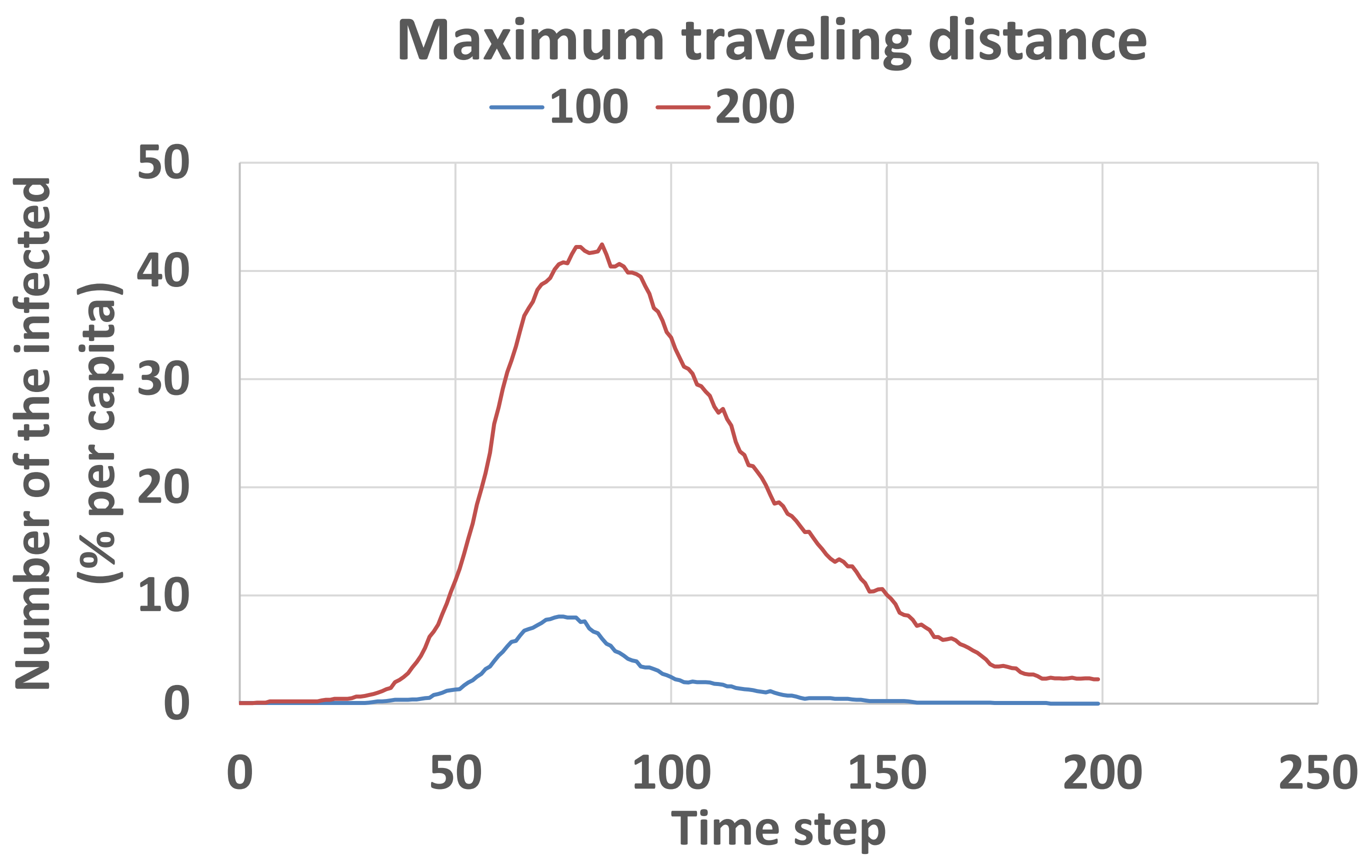


Fig. Effect of the maximum traveling distance on the total number of infected agents (virus replication rate: 1.6).

Effect of virus absorbing rate, which corresponds to the effect of wearing a mask.

Decreasing the virus absorbing rate by wearing masks decreases the number of infected persons, , meaning that wearing masks is effective for preventing the infection.

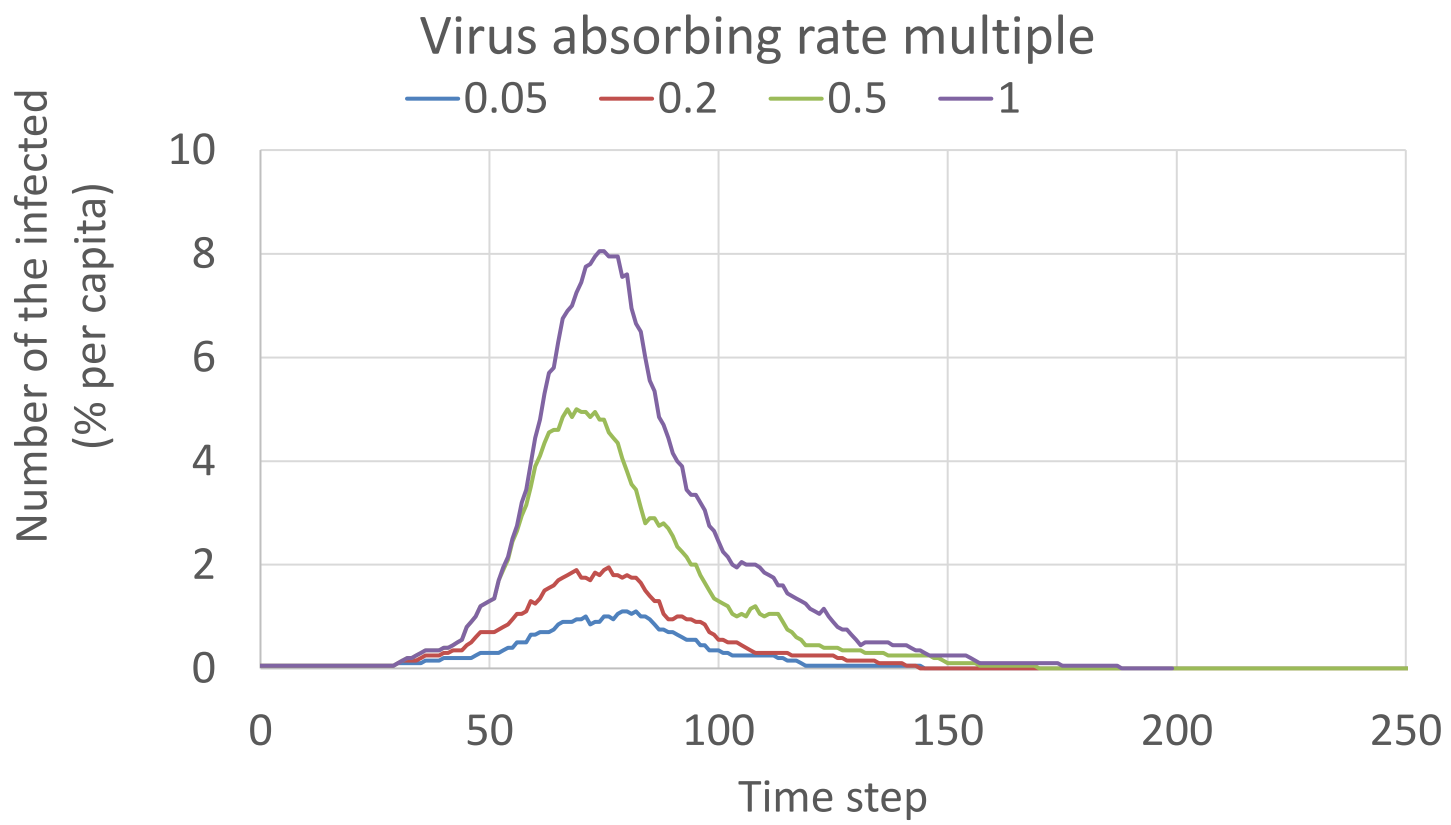
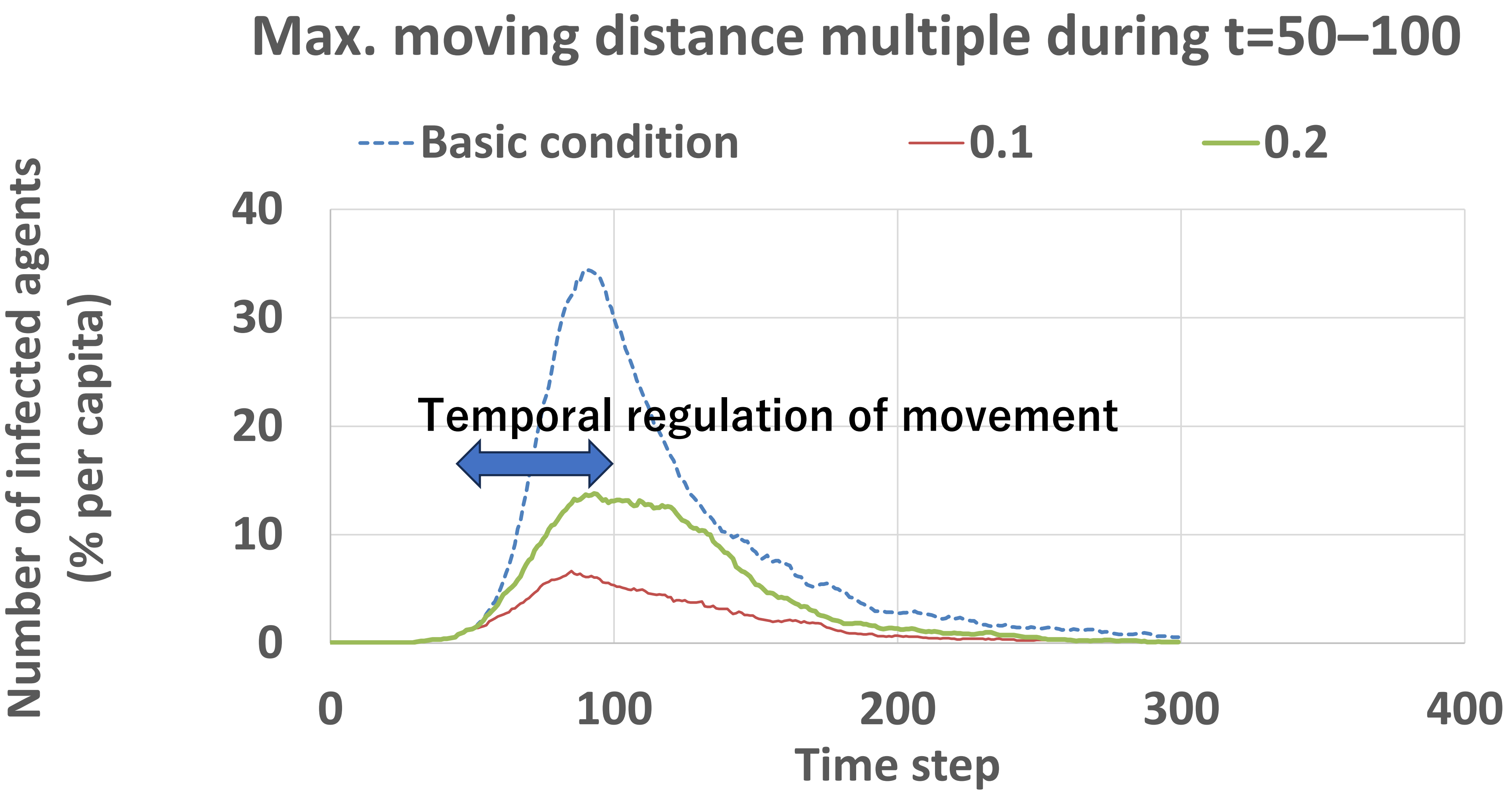


Fig. 16 Effect of the virus absorbing rate on the number of infected agents.

Temporal regulation of movement

- It drastically decreases the peak value of the number of infected agents.
- Resultant second wave, i.e., re-increase in the number, does not occur, if the new infected person does not enter into the system from outside.



One of the important features that characterize the pandemic convergence is that the number of viruses at the time of infection decreases with time.

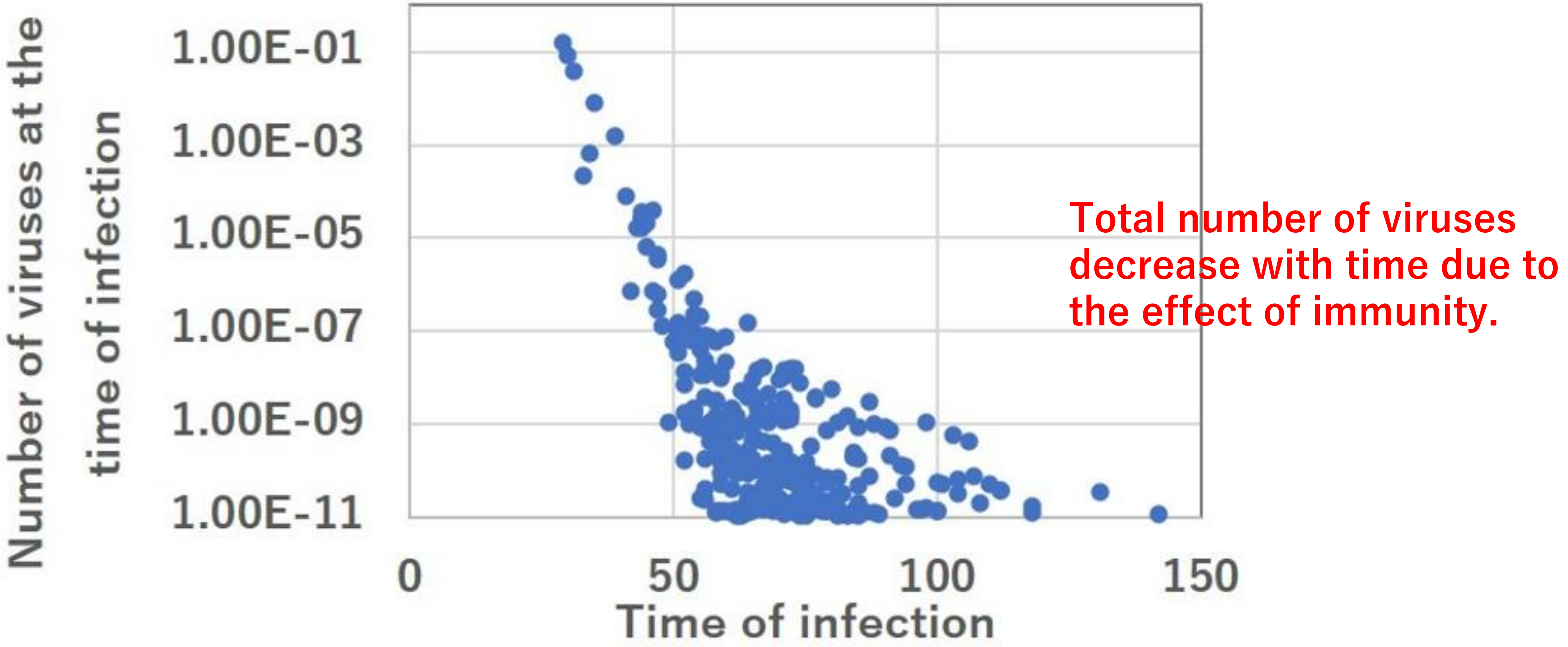
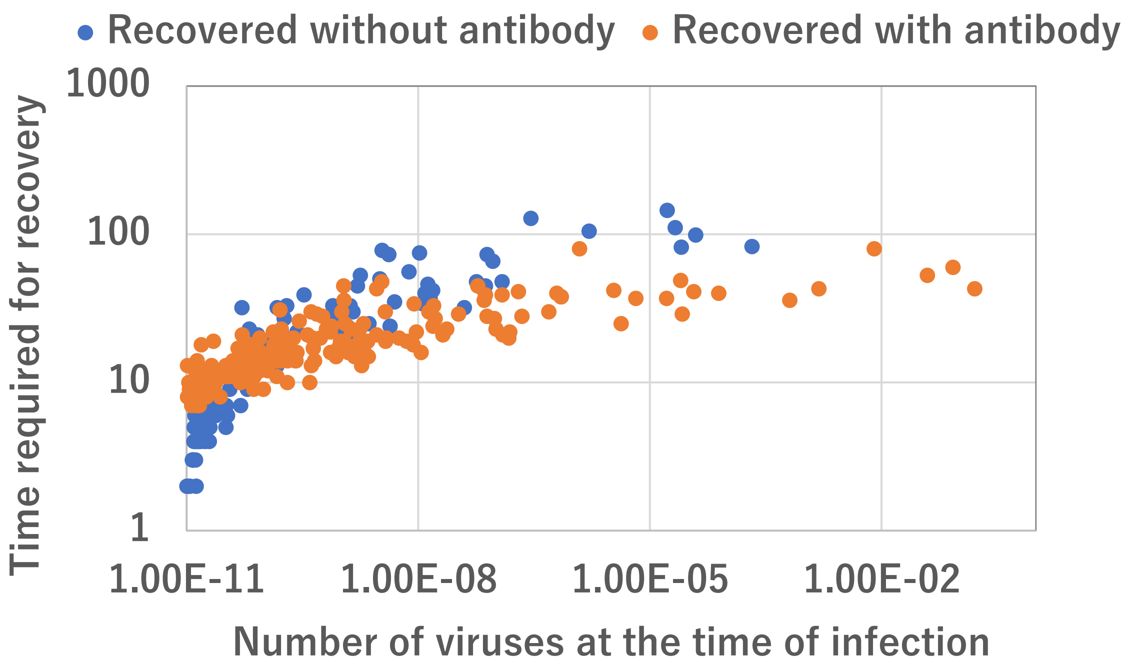


Fig. Change in the number of viruses at the time of infection during infection spread and convergence.


Recovered without antibody
Recovered with antibody
Time required for recovery
1000
100
10
1
1.00E-11
1.00E-08
1.00E-05
1.00E-02
Number of viruses at the time of infection

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

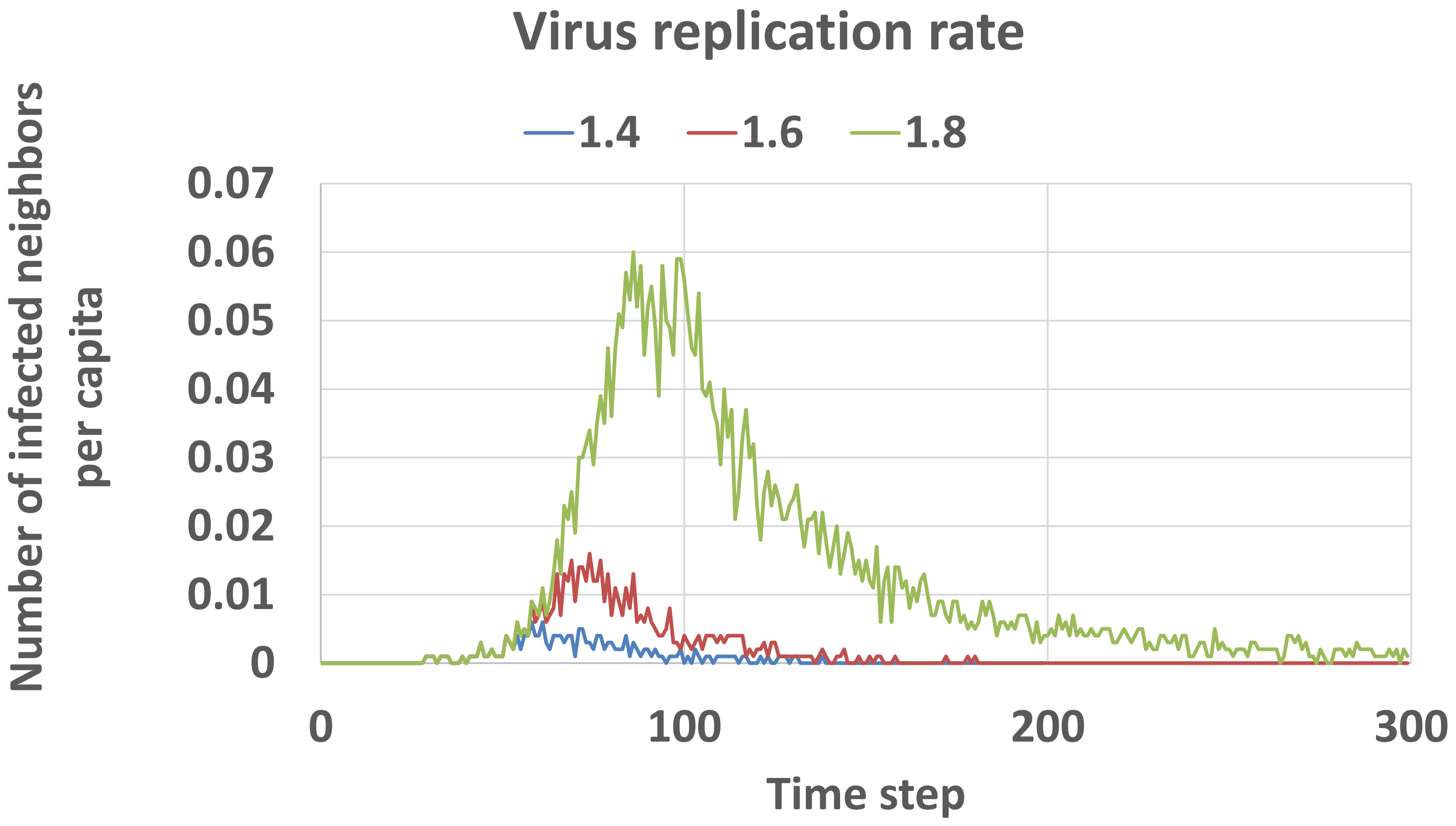


Fig. Effect of virus replication rate on the average number of infected neighbors.

The infection spread and convergence are essentially governed by the probability of a healthy person encountering the infected person. The essential cause of recovery is that the number of viruses in the system decreases with time due to the effect of immunity, which progressively shorten the time for recovery.

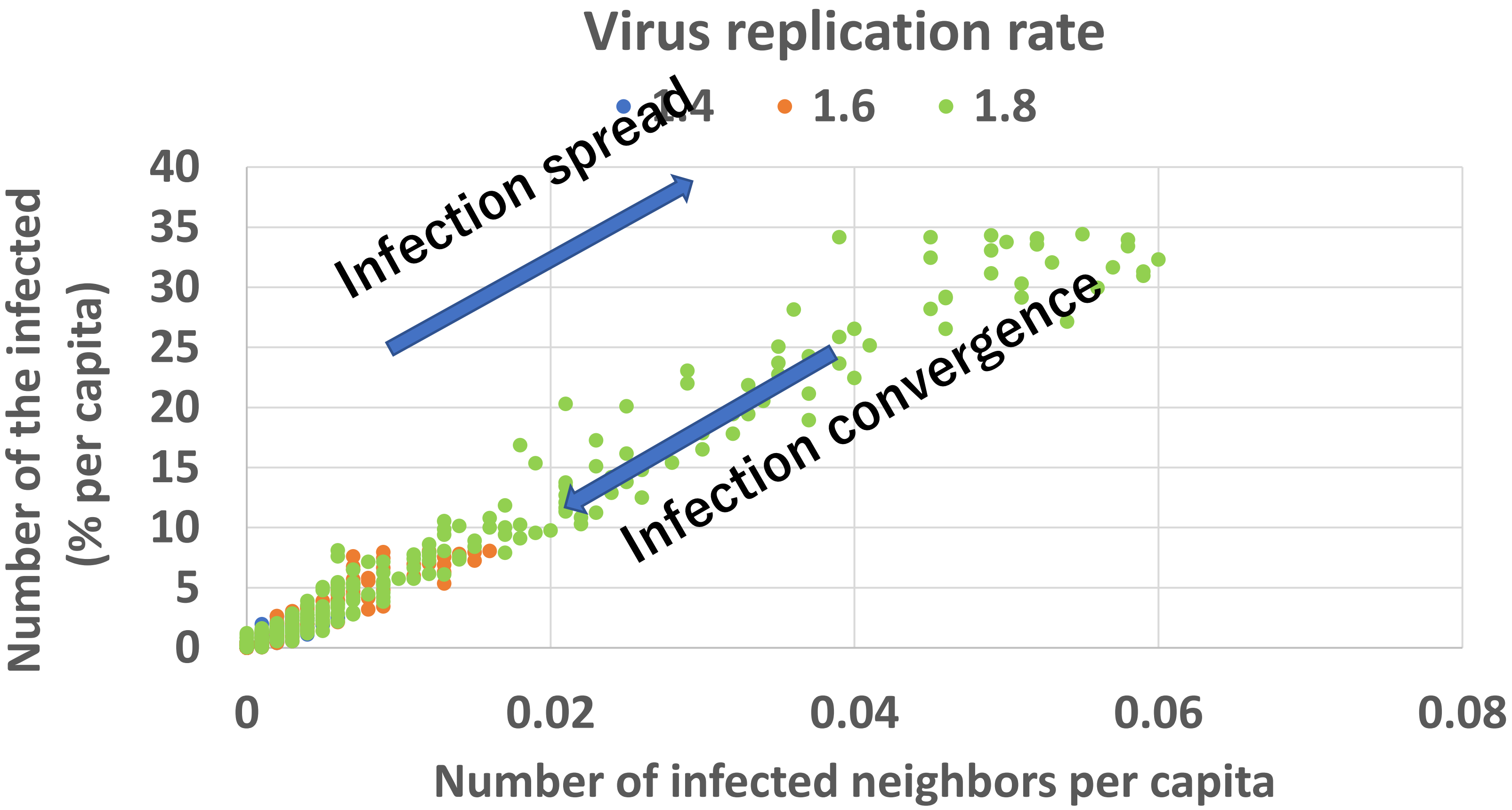
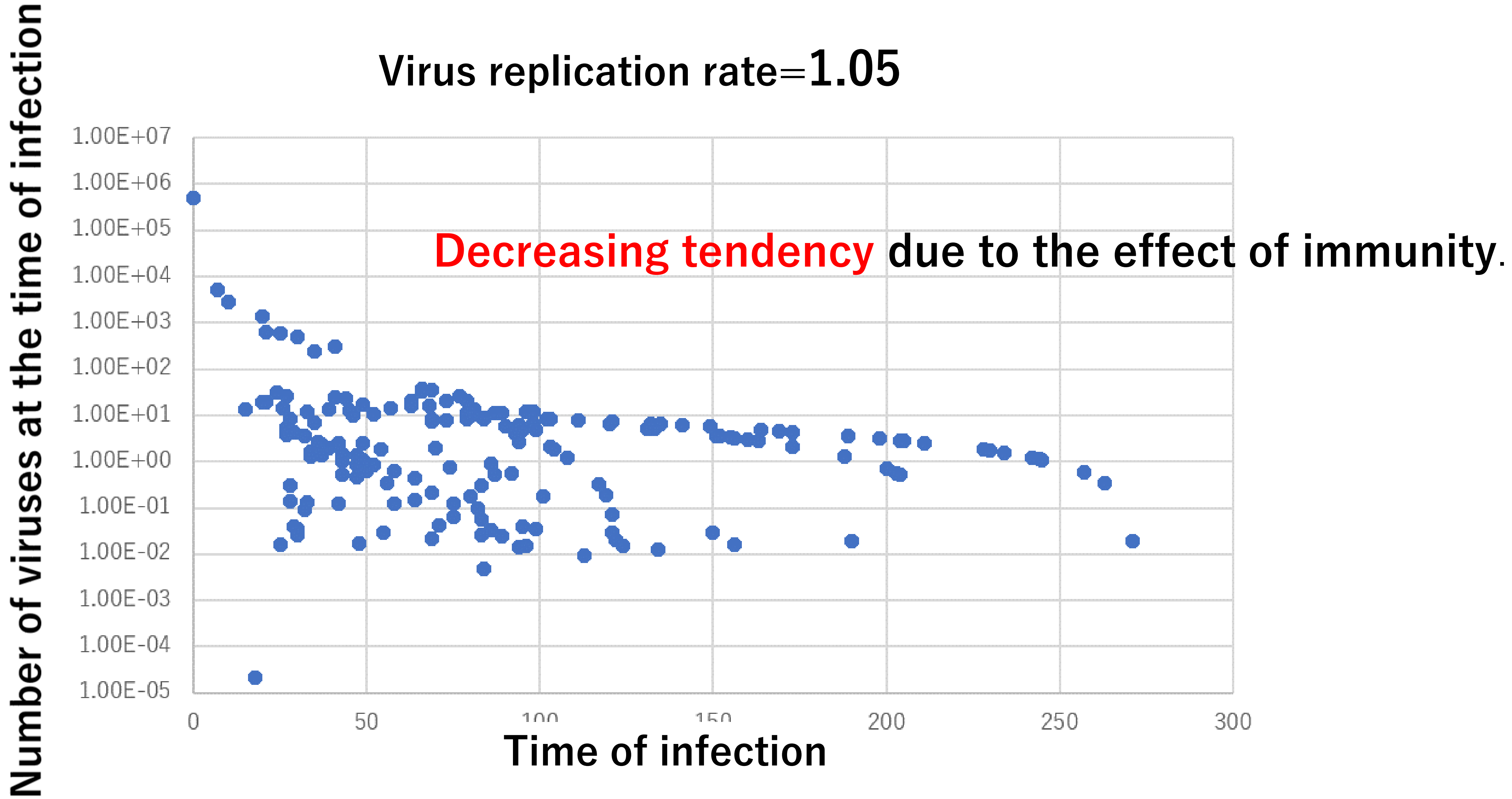
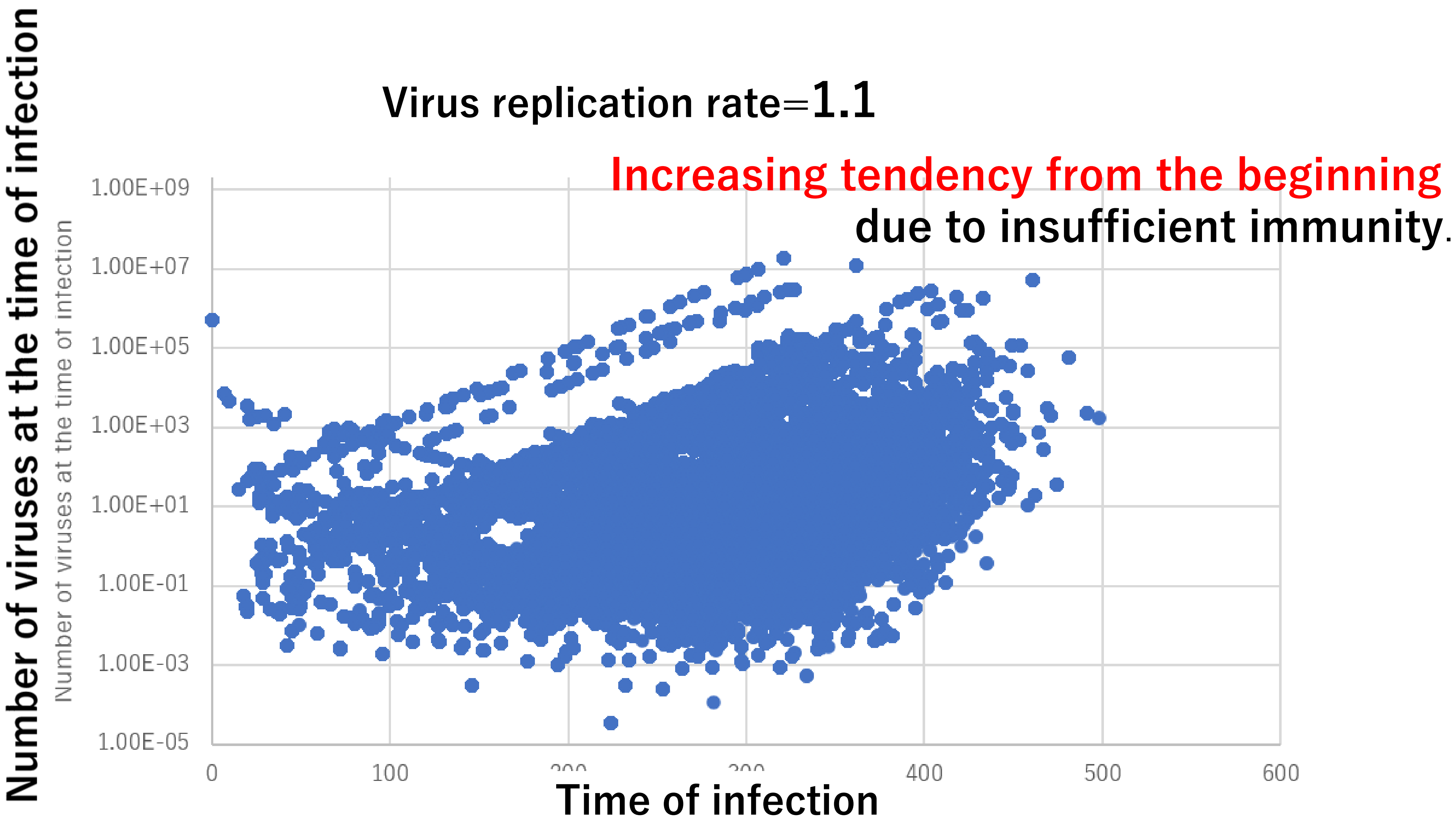


Fig. Relationship between the number of infected agents and the average number of infected neighbors.

The number of viruses shows decreasing tendency with time when VRR is 1.05, but increasing tendency with time when VRR is 1.1.



Virus replication rate=1.1



4. Summary of the calculated results.
Fundamental mechanism of infection spread and convergence

1) Fundamental mechanism of infection spread and convergence is the progressive increase and decrease in the probability of a healthy person or a recovered person meeting with infected people.

2) Fundamental mechanism of the recovery is that total number of viruses in the system decreases with time due to the effect of immunity overcoming the virus replication effect.

3) The pandemic never converges if there exists a person whose immunity response is too small compared to the virus replication effect unless completely isolated, because of the infinitely increase in the total number of viruses in the system .

4) The most essential factor for the pandemic convergence is the role of fever associated with immunity. Without the effect of fever, the actual fact that the pandemic converges for the wide variety of virus replication rate cannot be reproduced.

5) The role of antibodies is to increase the discharging rate of viruses, thereby enlarging the upper limit of the virus replication rate for the pandemic convergence.

5. A proposed strategy for controlling the pandemic while saving the economy

1) To identify the infected people and isolate the severly infected individuals or refuse their entry at the national border or at the comertial establishment.

Body temperature measurement followed by PCR test if necessary is the most reasonable, because

a fever is a sign of being infected ,showing the severity of infection ,highly infected individuals are characterized by high fever who are the minority and body temperature measurement requires the least cost , while PCR test provides ON/OFF information and requires much time and cost.

2) Each individual's self-monitoring body temperature and self-regulating his movemen on the bases of this information.

Each person should recognize his own normal temperature, and self-identify his state of infection by monitoring body temperature and self-regulate his movement if necessary. If many of the individuals employ this measure, the number of newly infected persons will drastically reduce and the pandemic will converge much faster.

3) Wearing masks and ventilation at the densely populated closed area

4) Temporary regulation of the movement of people followed by its mitigation for the short period is also effective for the pandemic convergence with small extent of the deterioration of the economy if the temporal period is short and the item 1) is perfectly conducted.