3rd International Conference on Infectious Diseases

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

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1. Introduction

1) Although the coronavirus pandemic, which originated in December 2019 in China, 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.

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.

3) ABM model of the present research

The ABM model of present study is entirely bottom-up type for both infection and recovery processes , constructed based on the medical knowledge.

【Main assumptions】

1. 2000 agents are initially randomly locate in the 2 dimensional space, one of which is assumed as an infected agent having huge number of viruses.
2. Two agents are called neighbors if they locate within a critical distance limit.
3. Viruses are released from an infected agent , a portion of which is absorbed by neighbor agents.
4. When infected, immune cells first attack the viruses and if their effect cannot keep up with the virus replication, antibodies emerges depending on the agent-specific delayed time after infection and the agent-specific ratio of the number of viruses at that time.

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

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

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

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

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

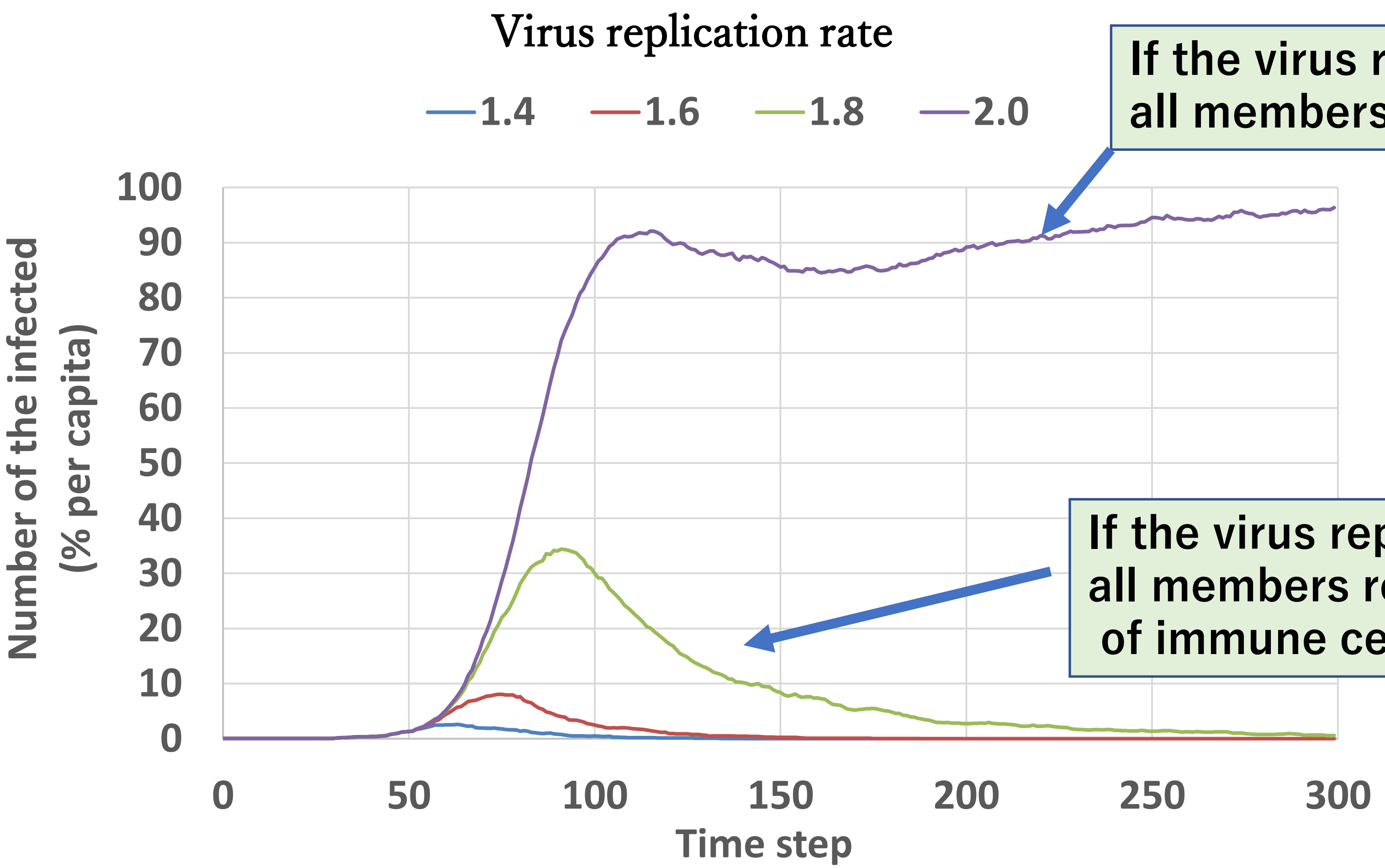
$Rate_{replication}$: Virus replication rate defined as a constant value

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

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

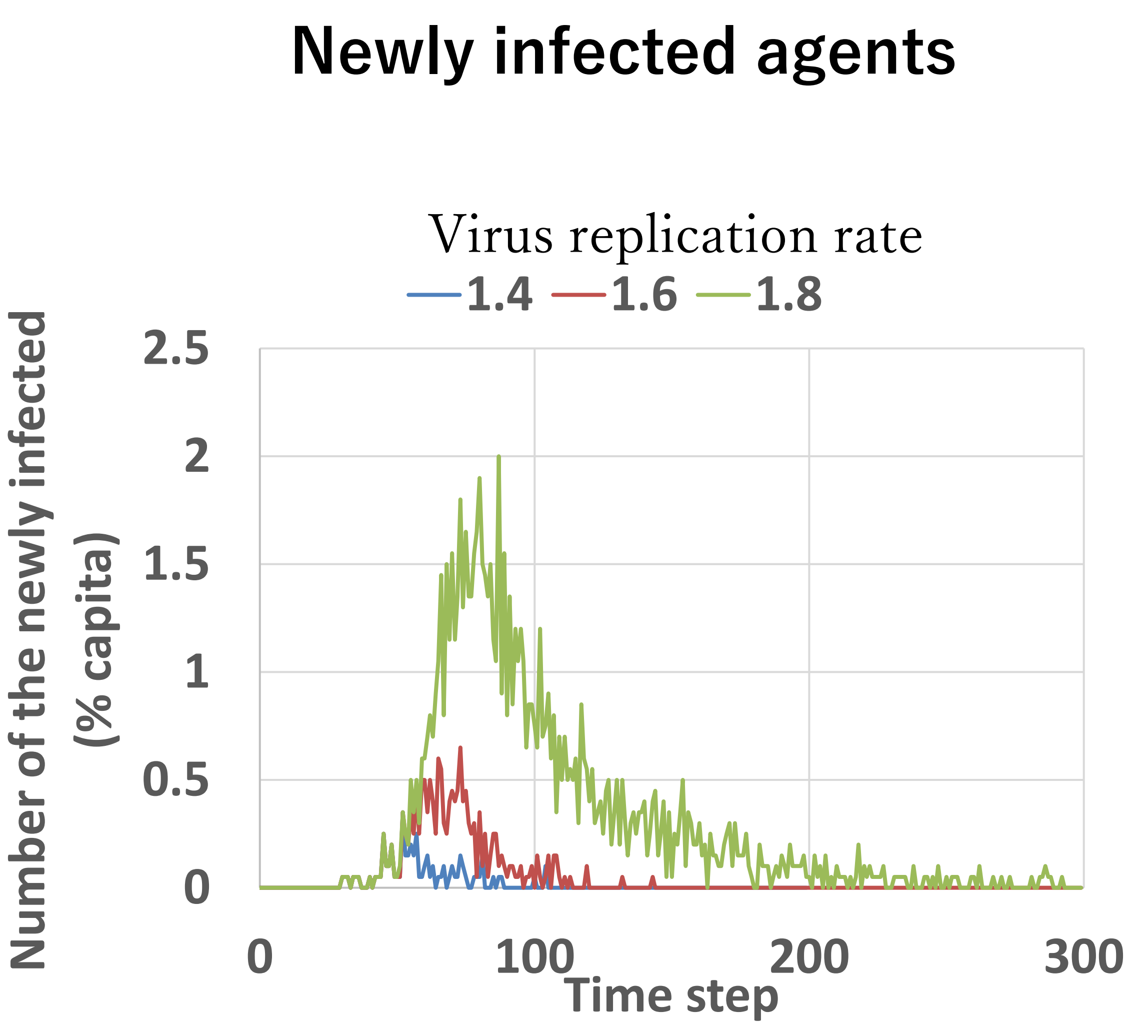
3.1 Fundamental behavior during infection and recovery. and comparison with the actual data.



If the virus replication rate is too large all members do not recover.

If the virus replication rate is not too large all members recover due to the effect of immune cells and antibodies.

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



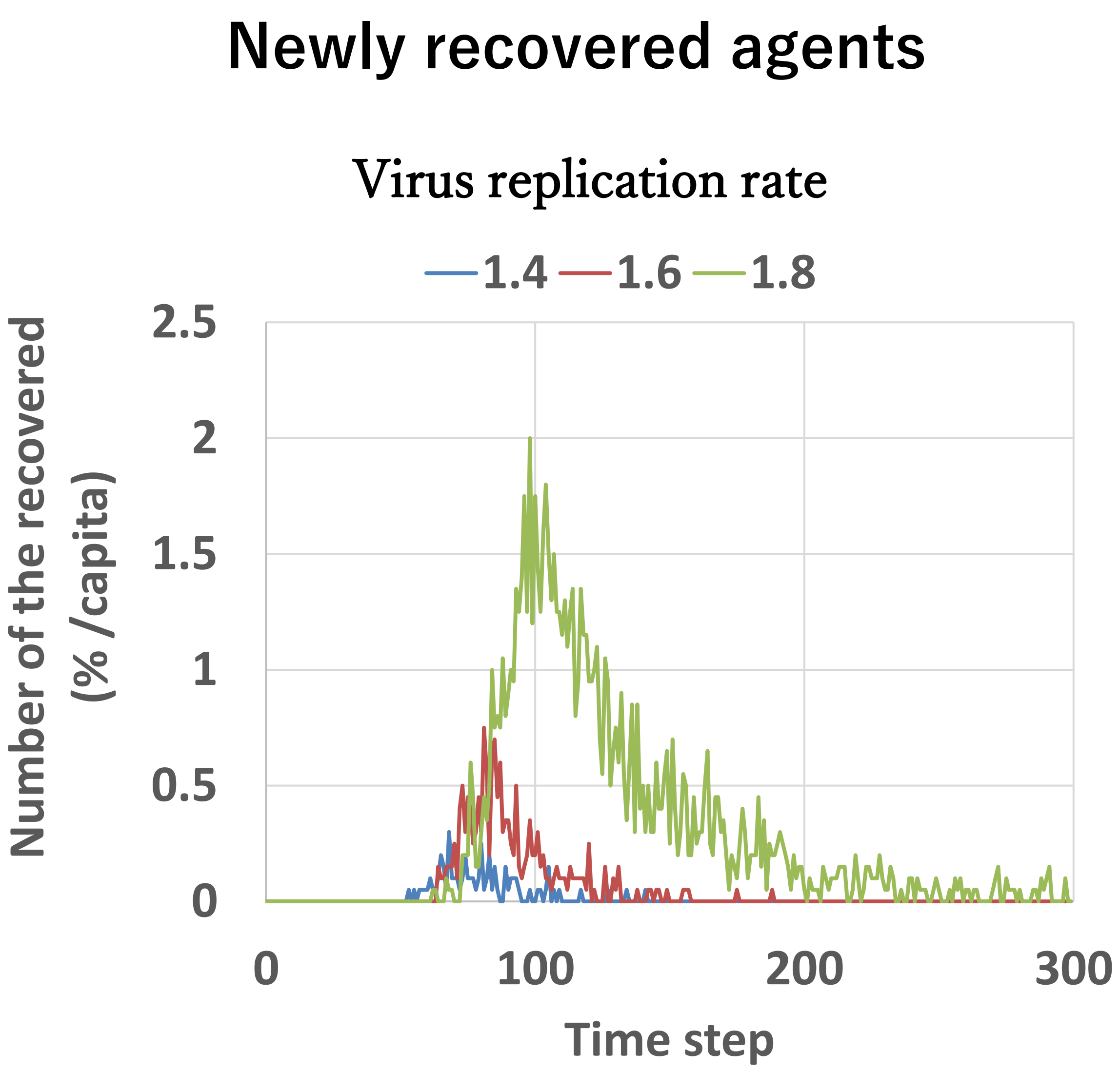


Fig. Effect of virus replication rate on the number of newly infected agents. And the number of newly recovered agents.

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

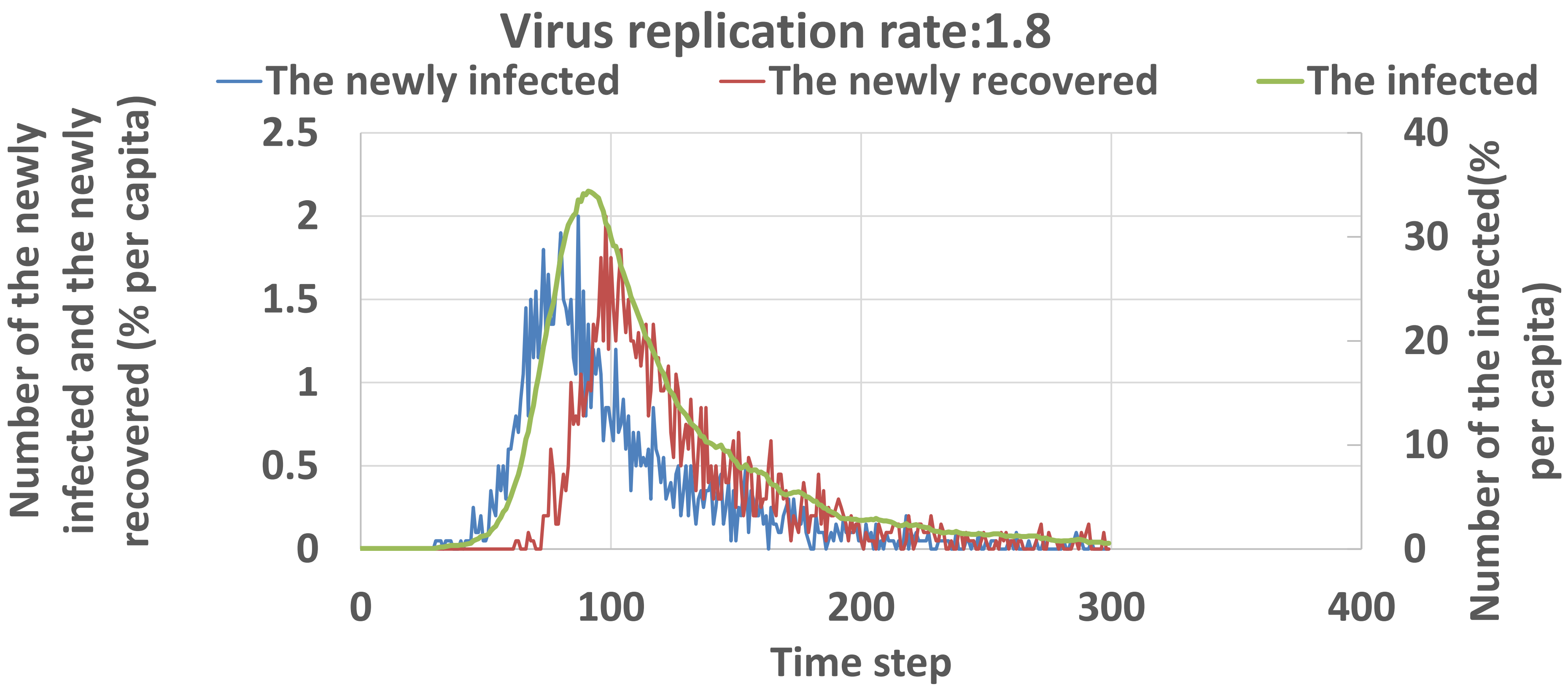


Fig. Changes in the numbers of newly infected, newly recovered, and total infected agents.

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

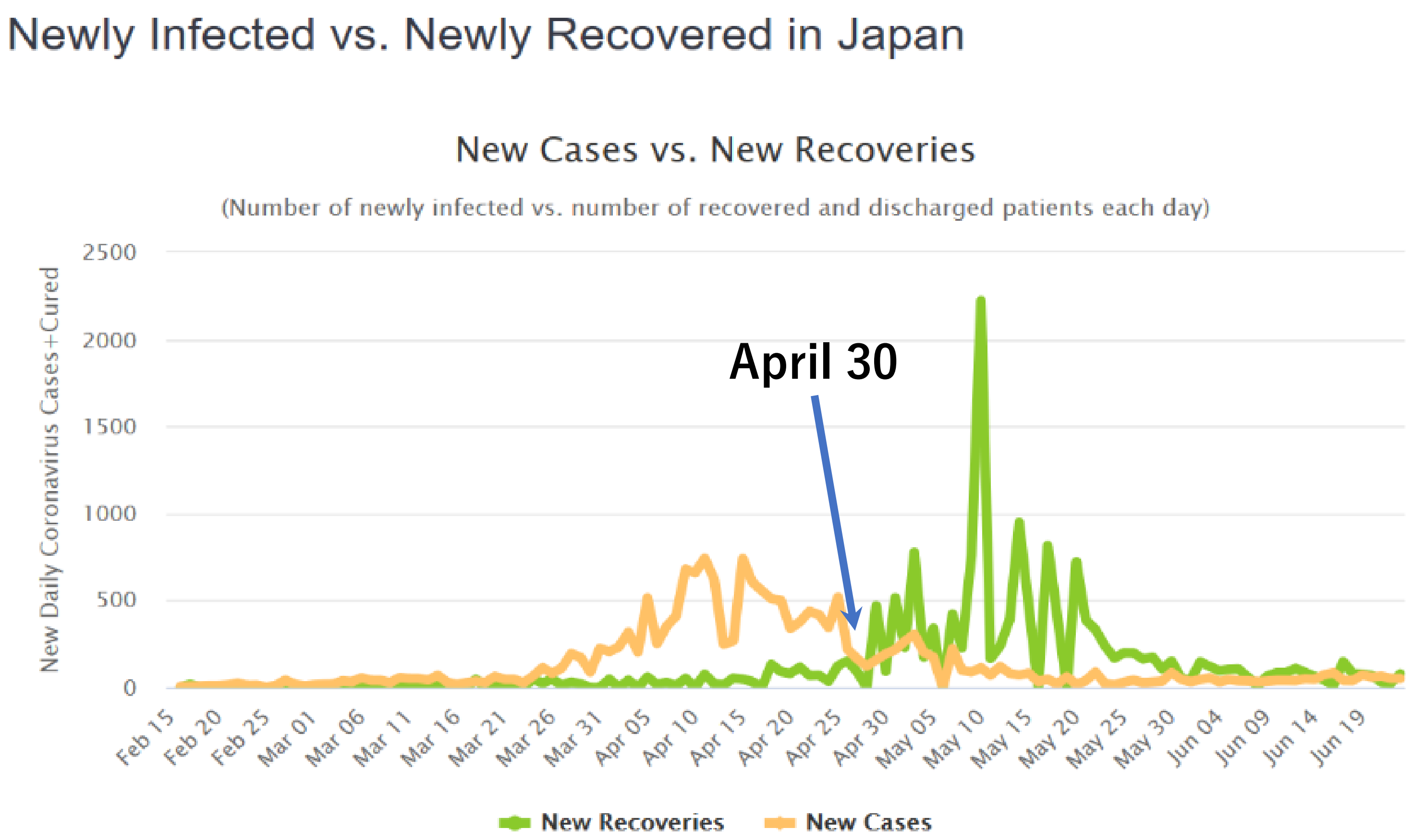


Figure 17. Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020.[17)]

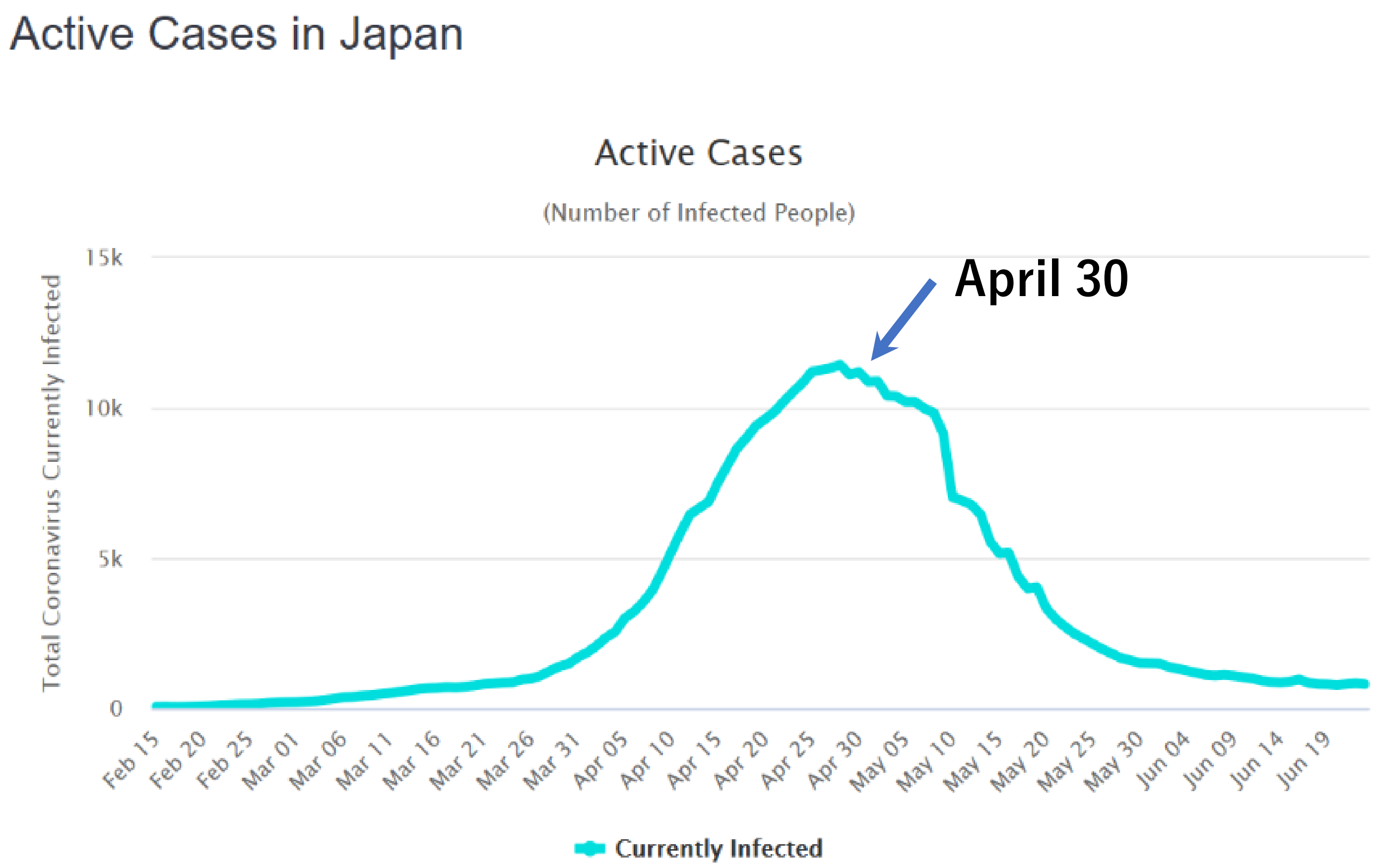


Fig. 18 Change in the number of currently infected people in Japan as of June 20, 2020[17].

3.2 Mechanism of the pandemic convergence.

Fundamental behavior of the number of viruses of each agent during the beginning of infection period.

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

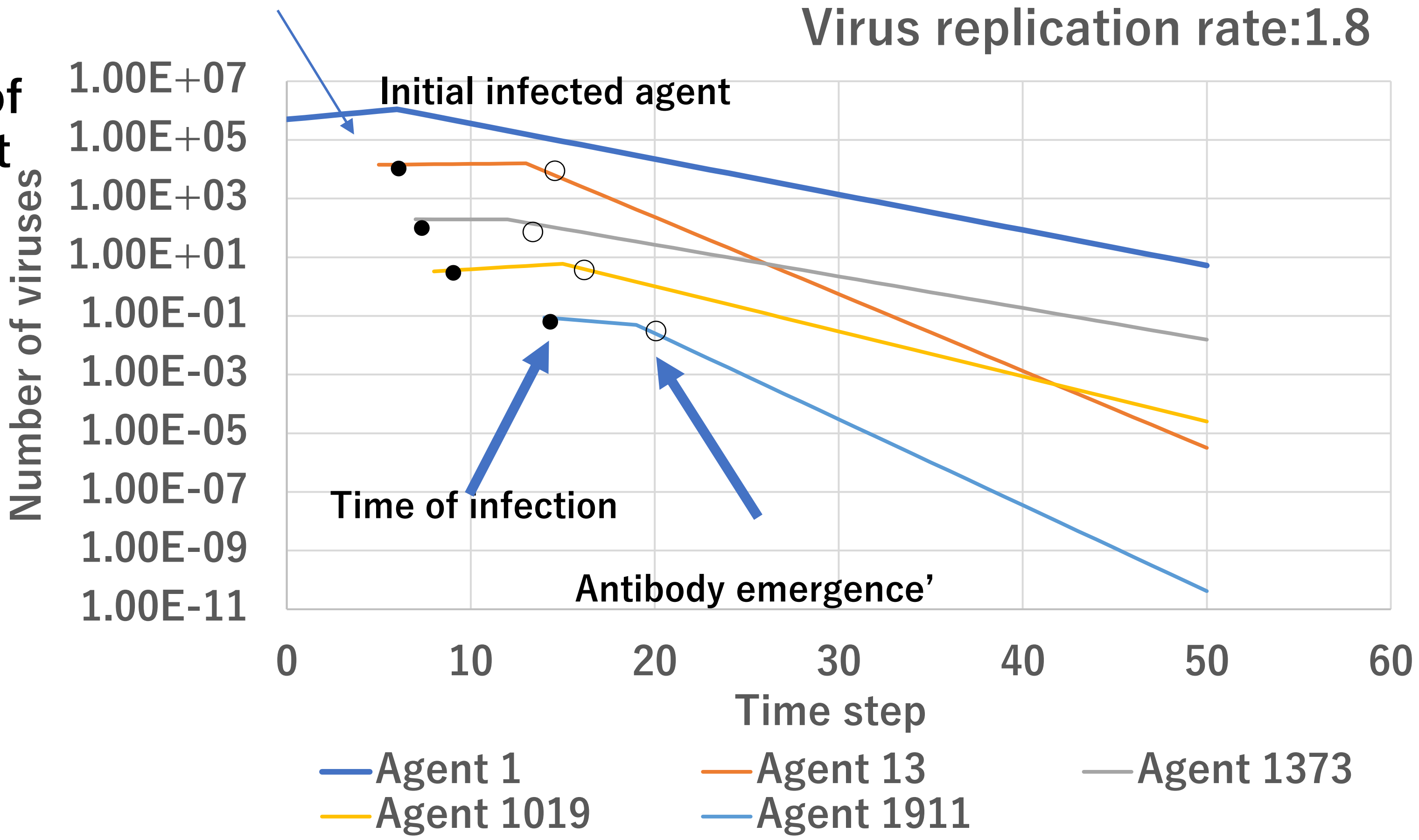
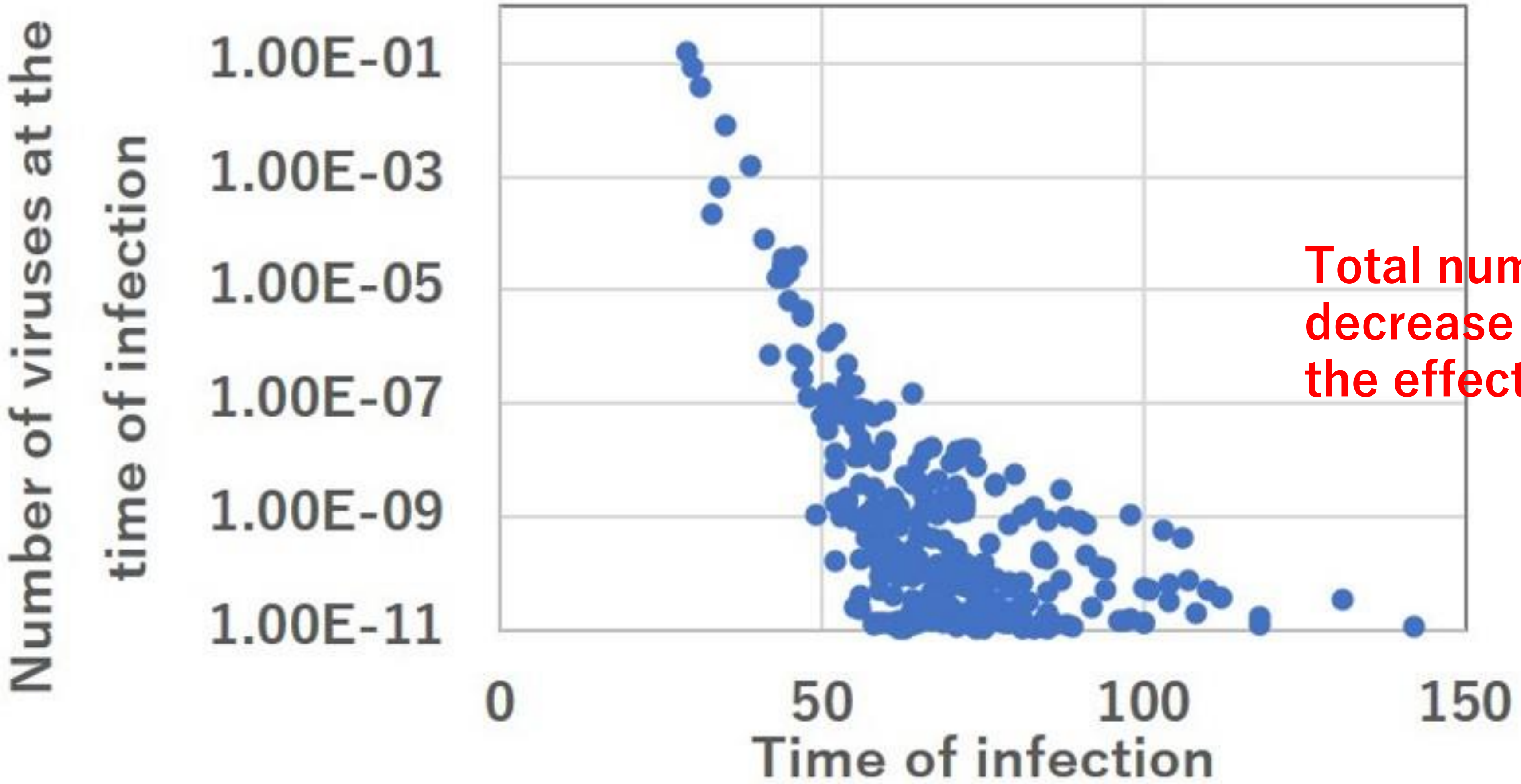


Fig. Change in the number of viruses of each agent during the beginning of infection spread.

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



Total number of viruses decrease with time due to the effect of immunity.

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

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

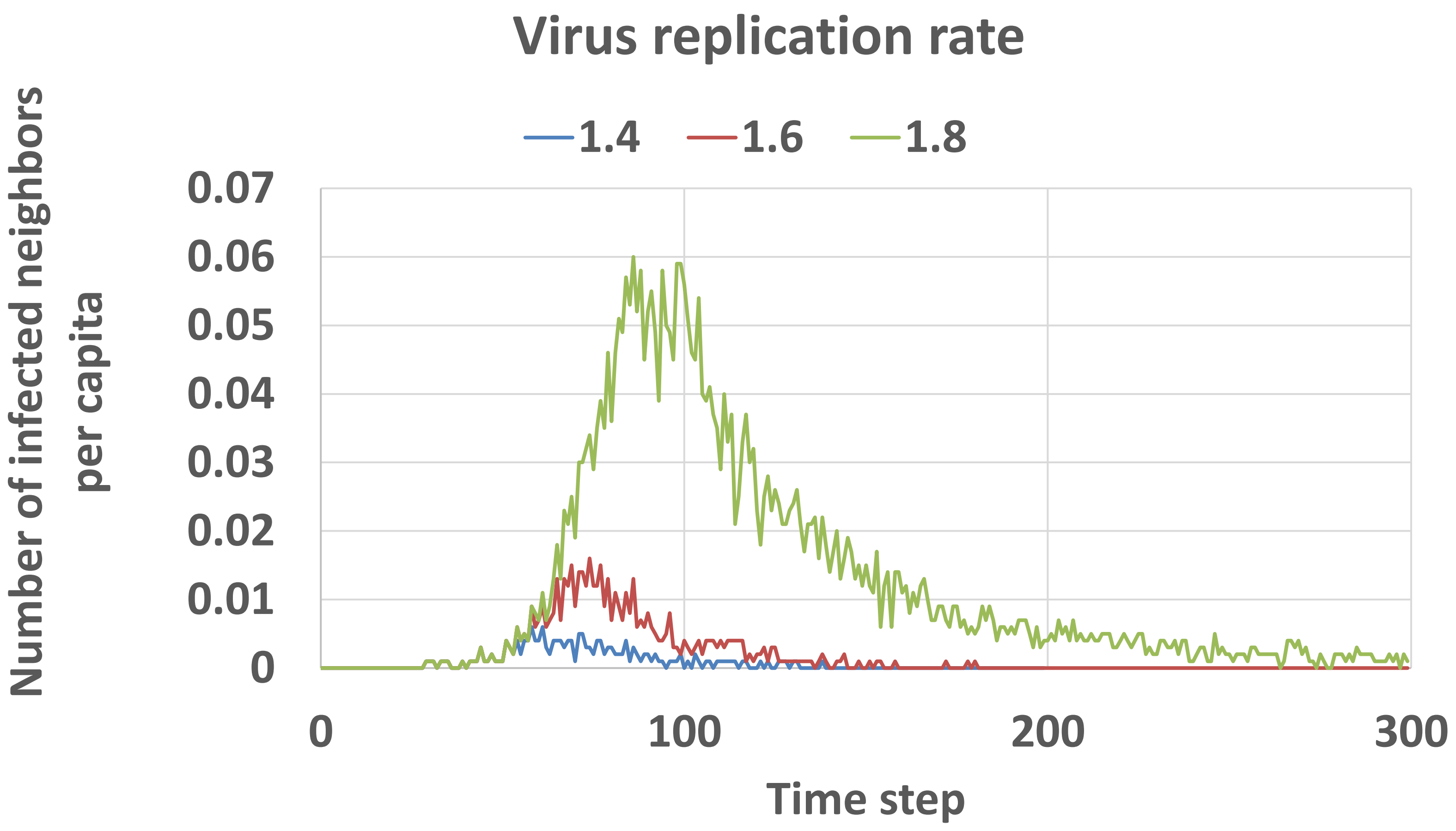


Fig. Effect of virus replication rate on the average number of infected neighbors.

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 decreases the time for recovery.

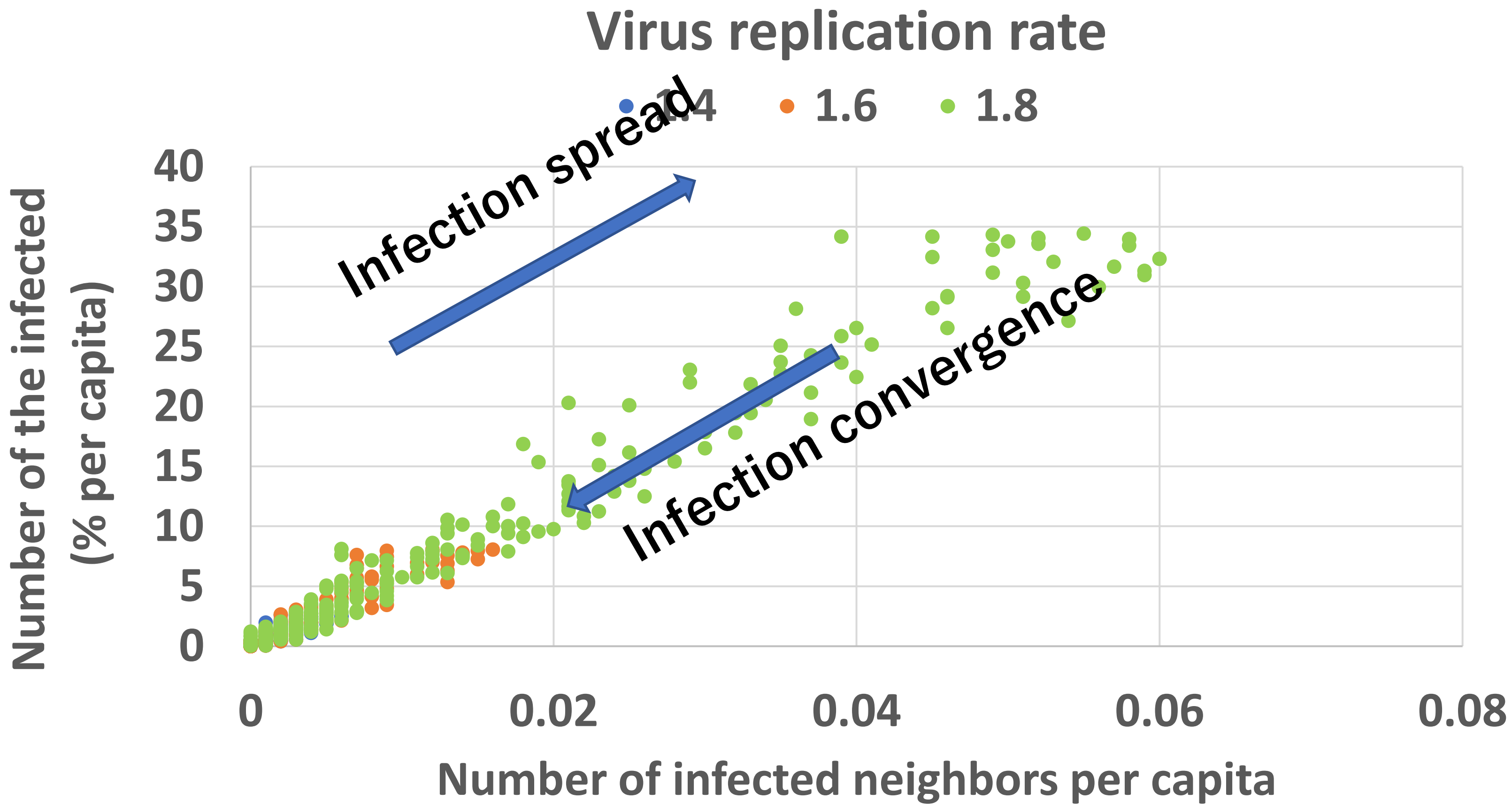
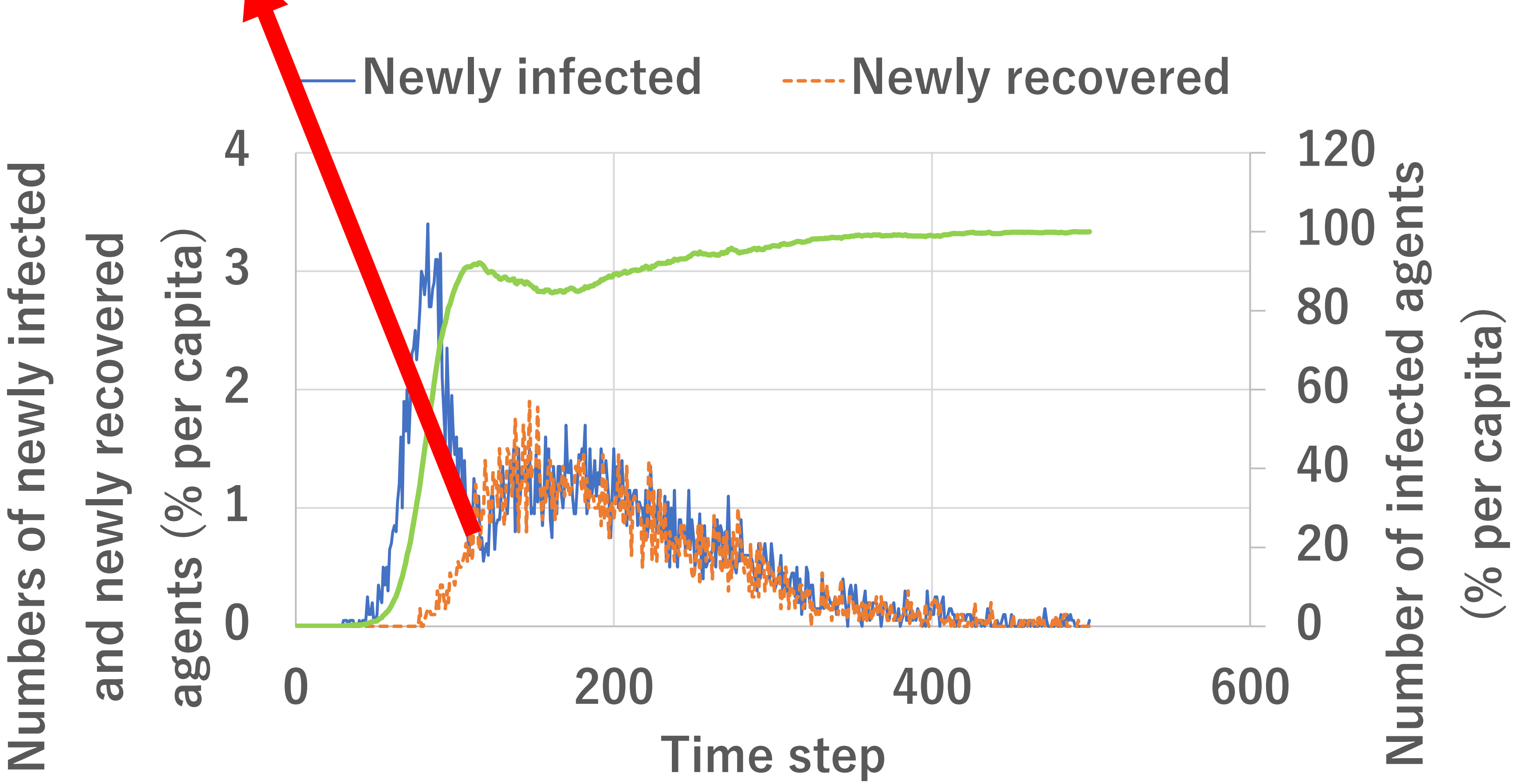


Fig. Relationship between the number of infected agents and the average number of infected neighbors.

3.3 Mechanism that the pandemic does not converge. What happens?

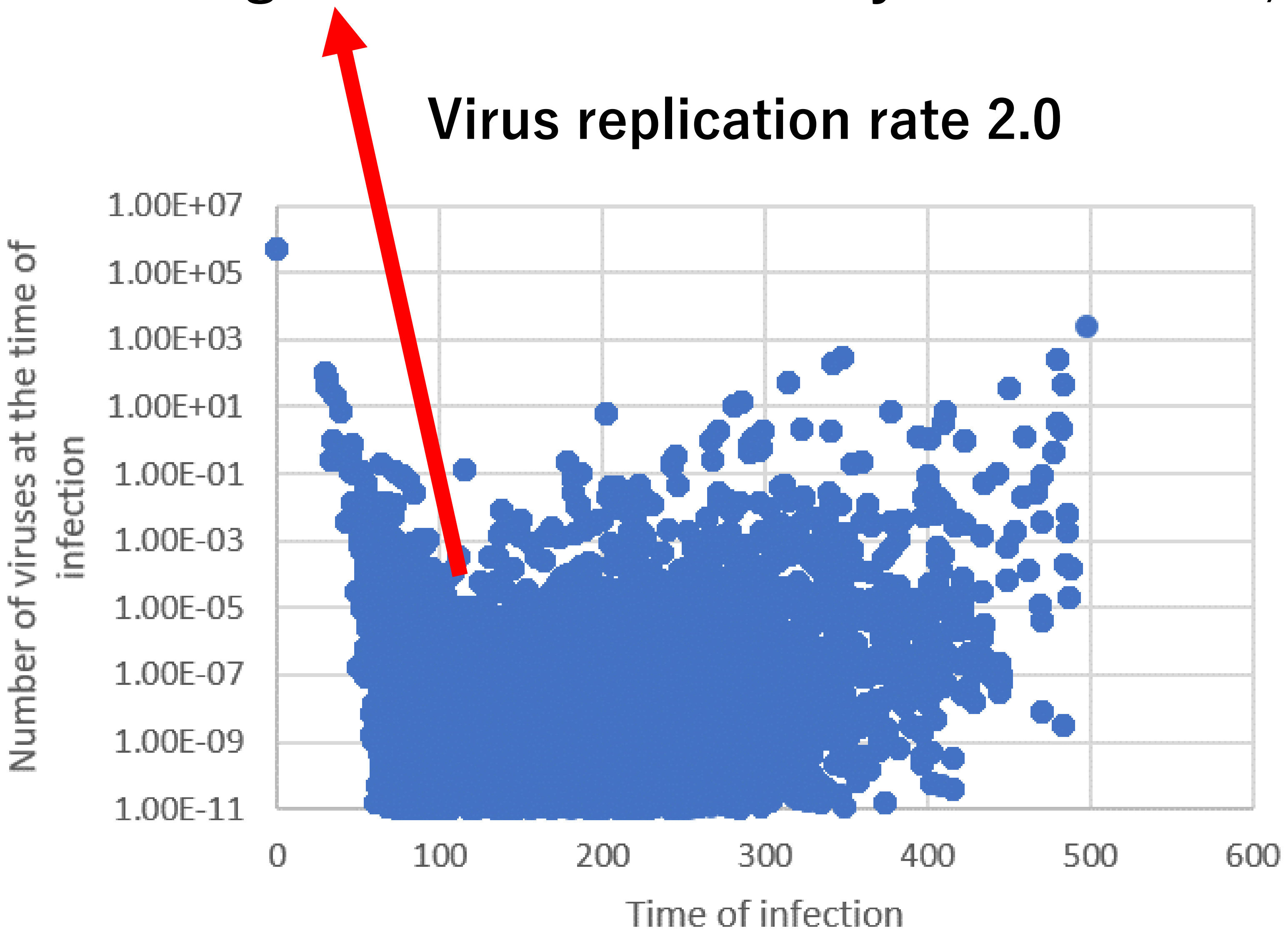
The behavior of Infection spread and recovery when the pandemic dose not converge.

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



Virus replication rate 2.0

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

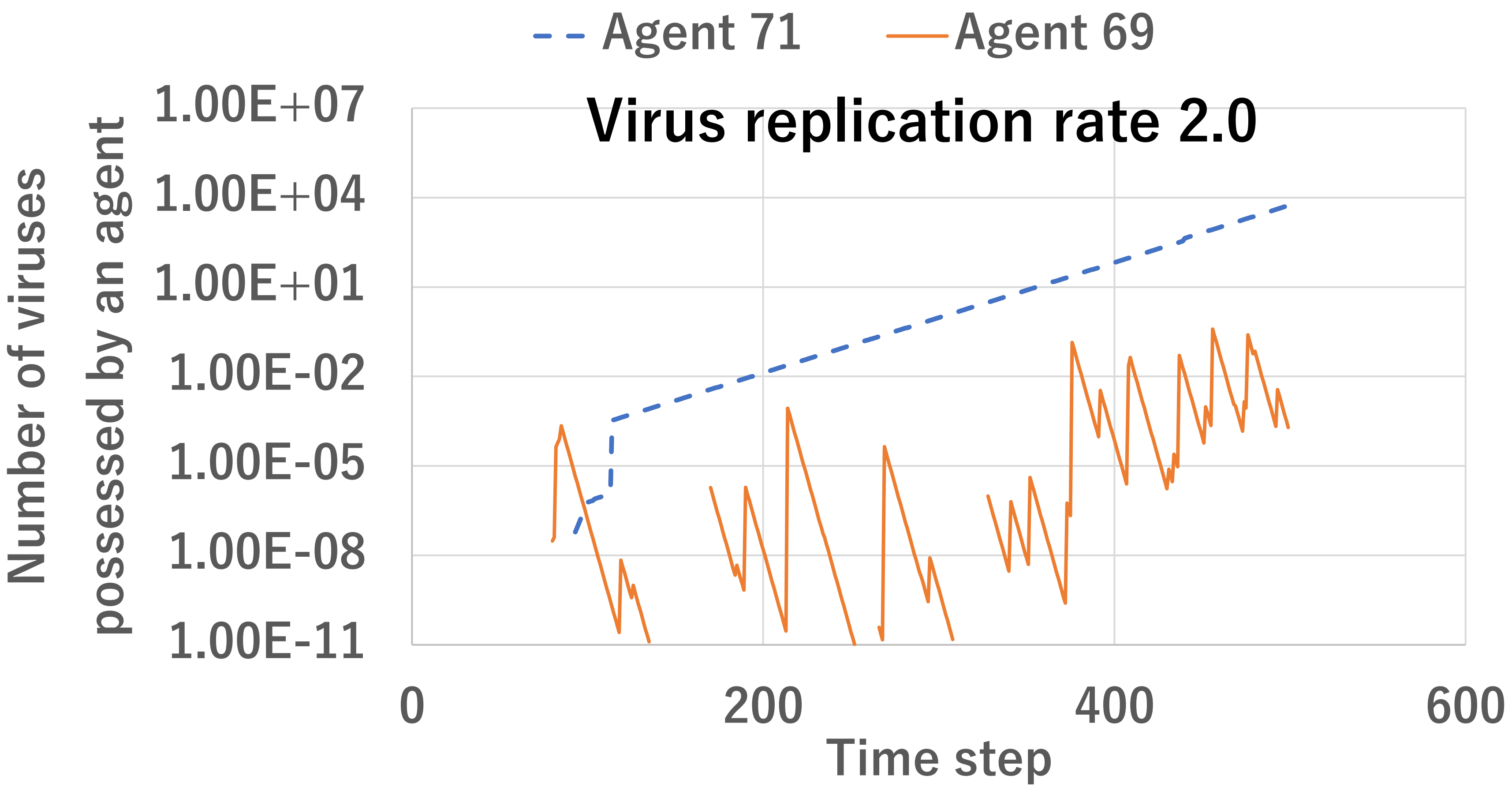


Agent71(Agent with weak immunity) :　Infected at t=92, and at t=113.

The number of viruses indefinitely increases due to the viruse replication.

Agent 69(Normal agent)　:　Infected multiple times.

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



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.

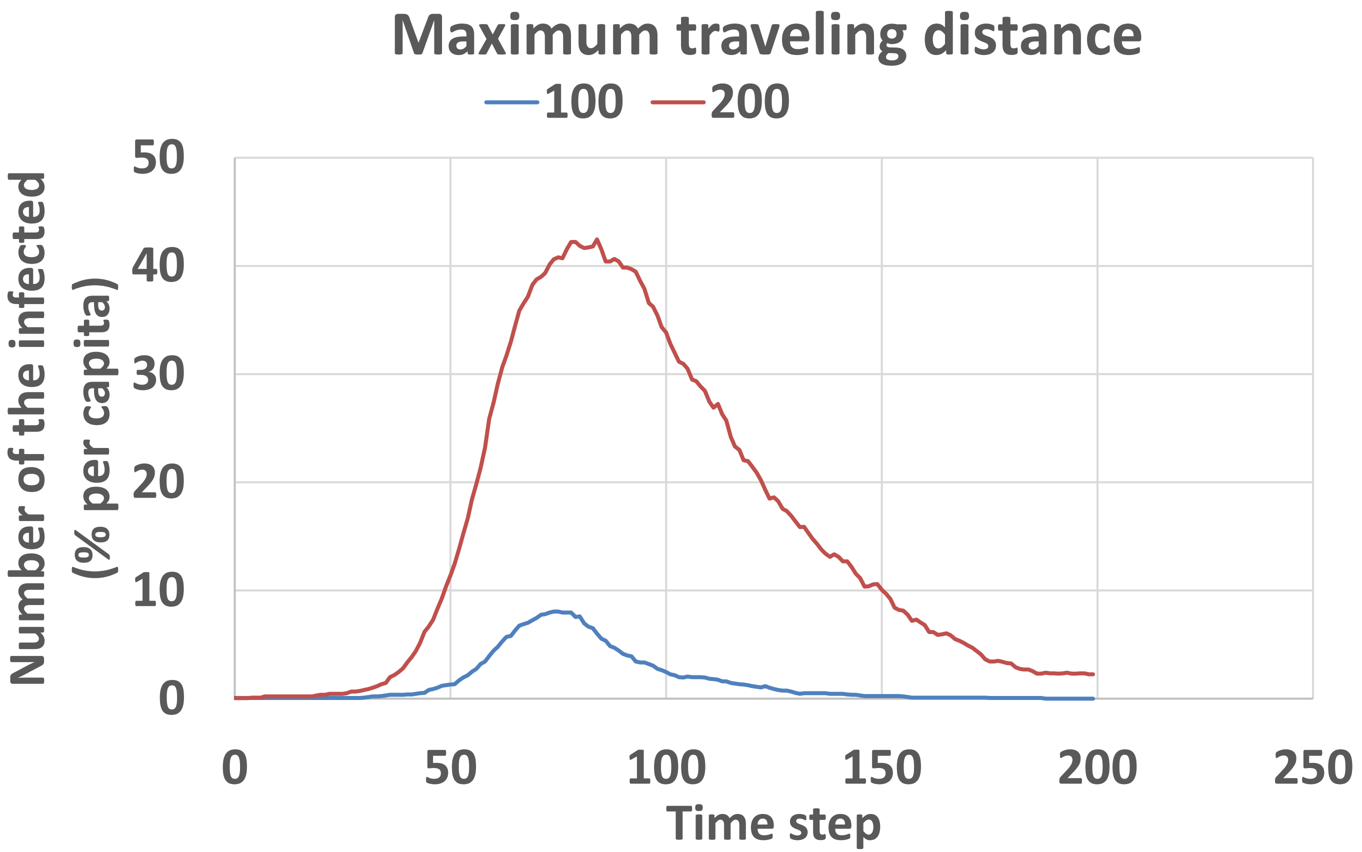
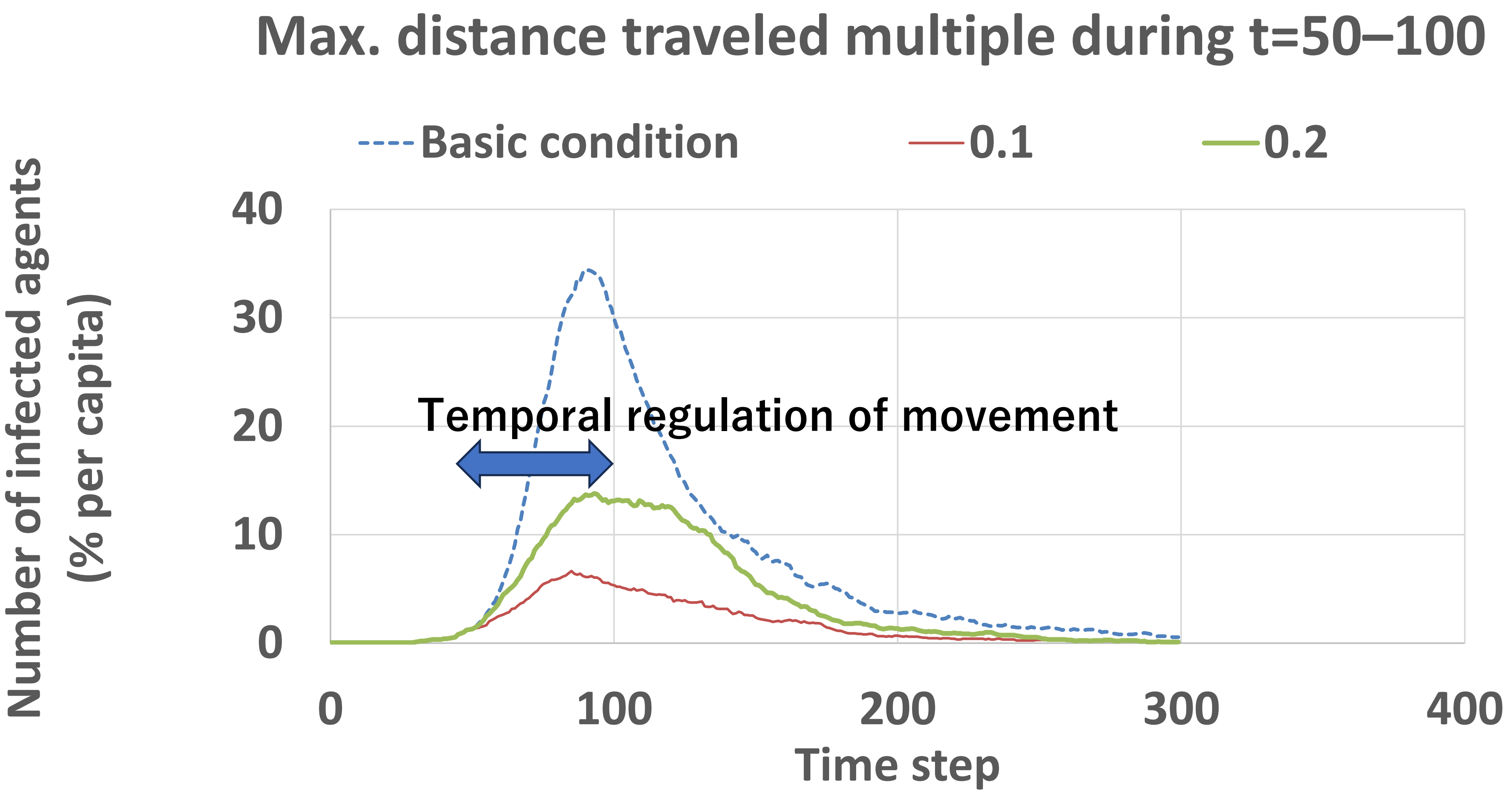


Fig. Effect of the maximum traveling distance on the total number of infected agents (virus replication rate: 1.6).

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.



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.

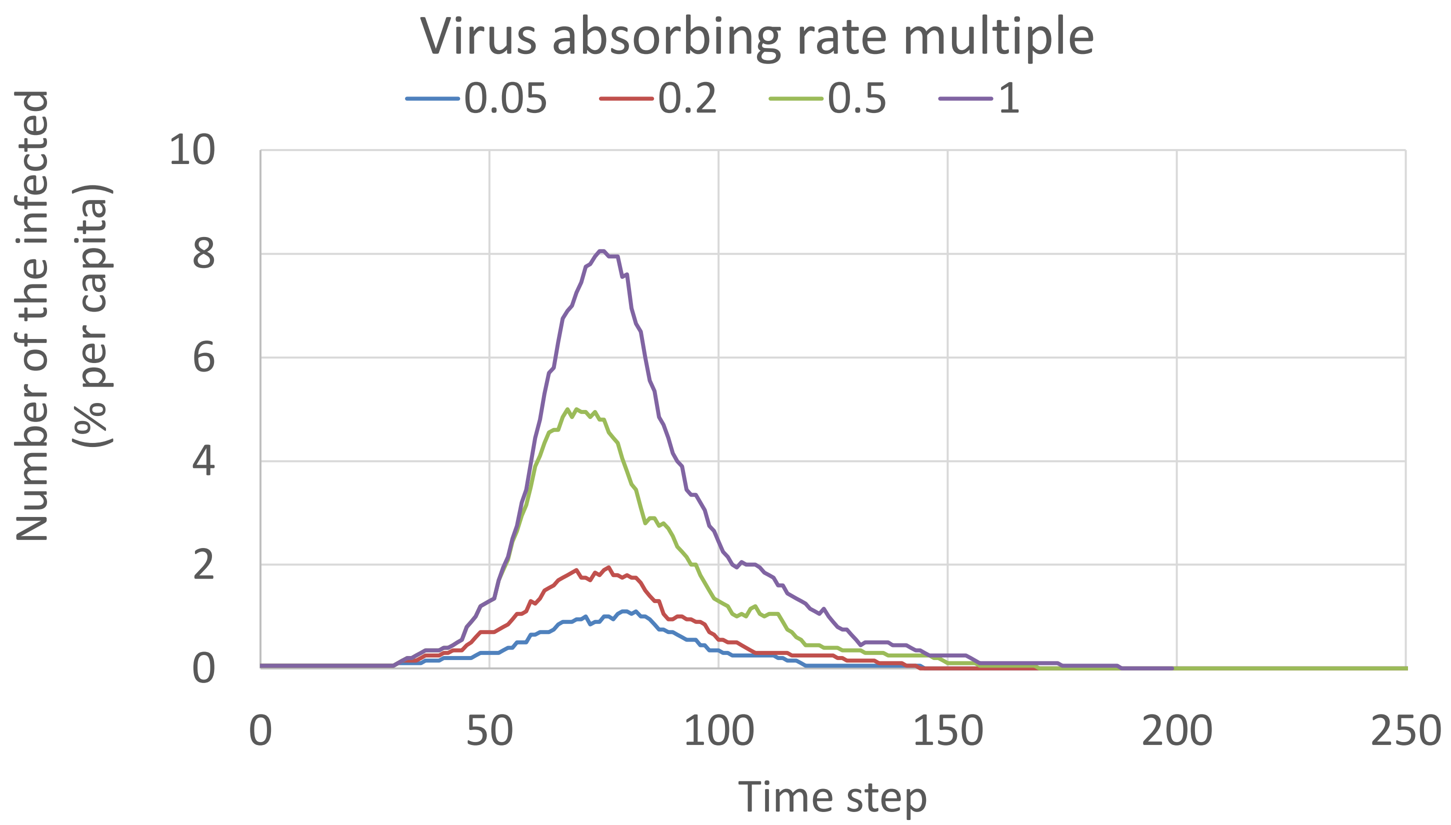


Fig. 16 Effect of the virus absorbing rate on the number of infected agents.

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.

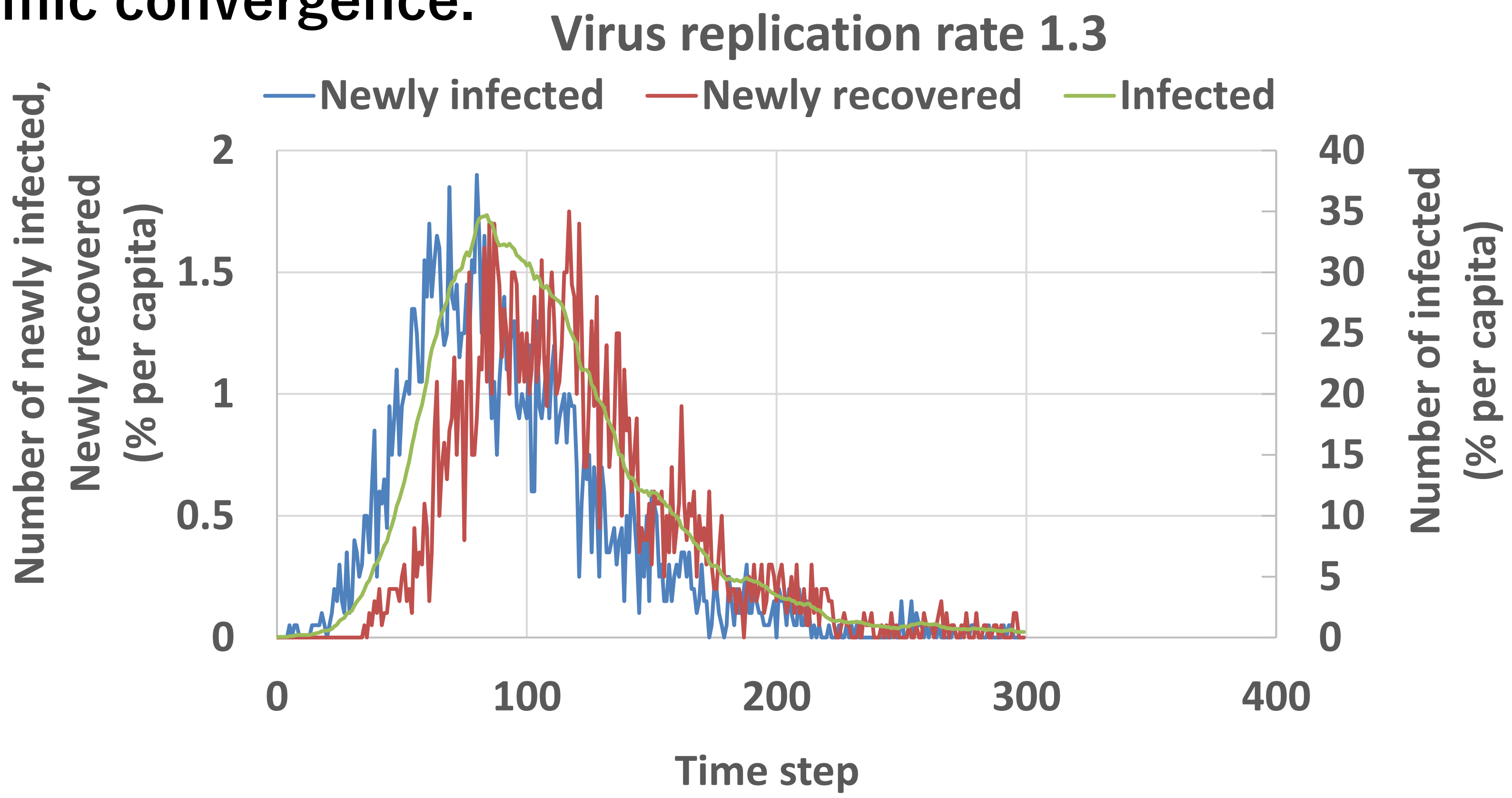
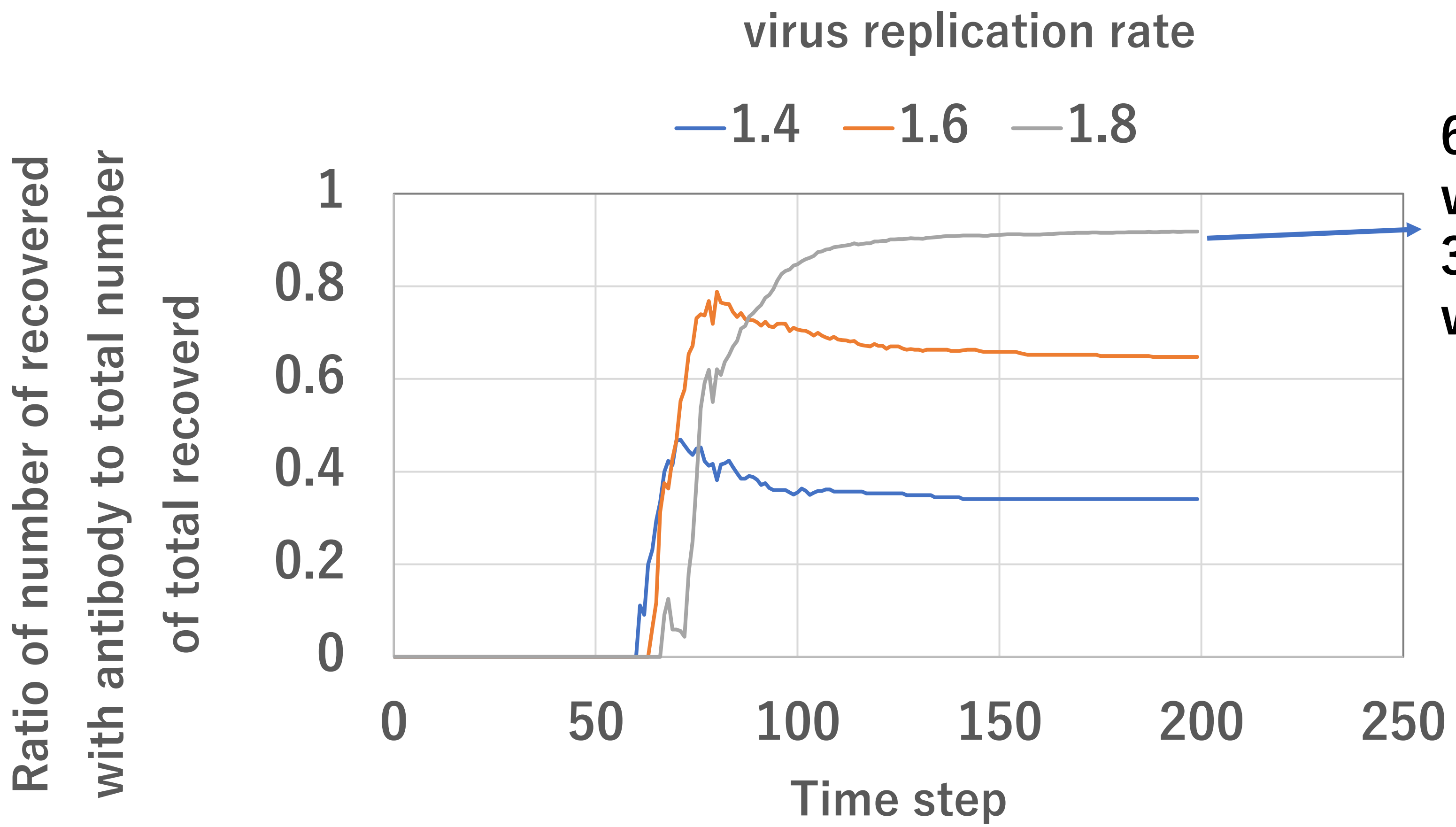


Fig. 27 An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case without antibodies.

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.

3.6 Effect of the role of fever on the pandemic behavior

What happens if the assumption for virus discharging rate is changed from “being proportional to the number of viruses” to “being constant”?
(This corresponds to the role of fever from “present” to “not present”.)

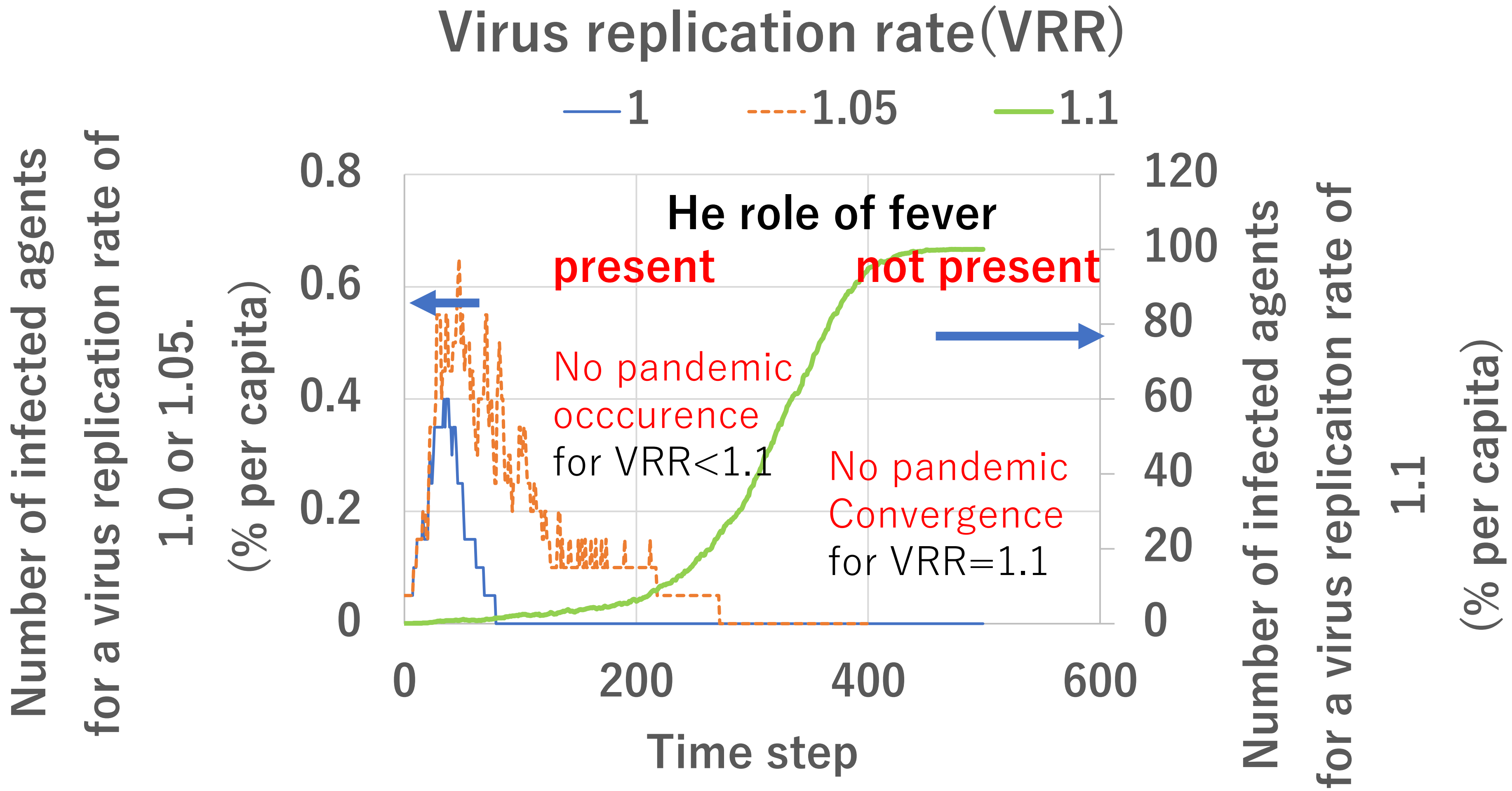
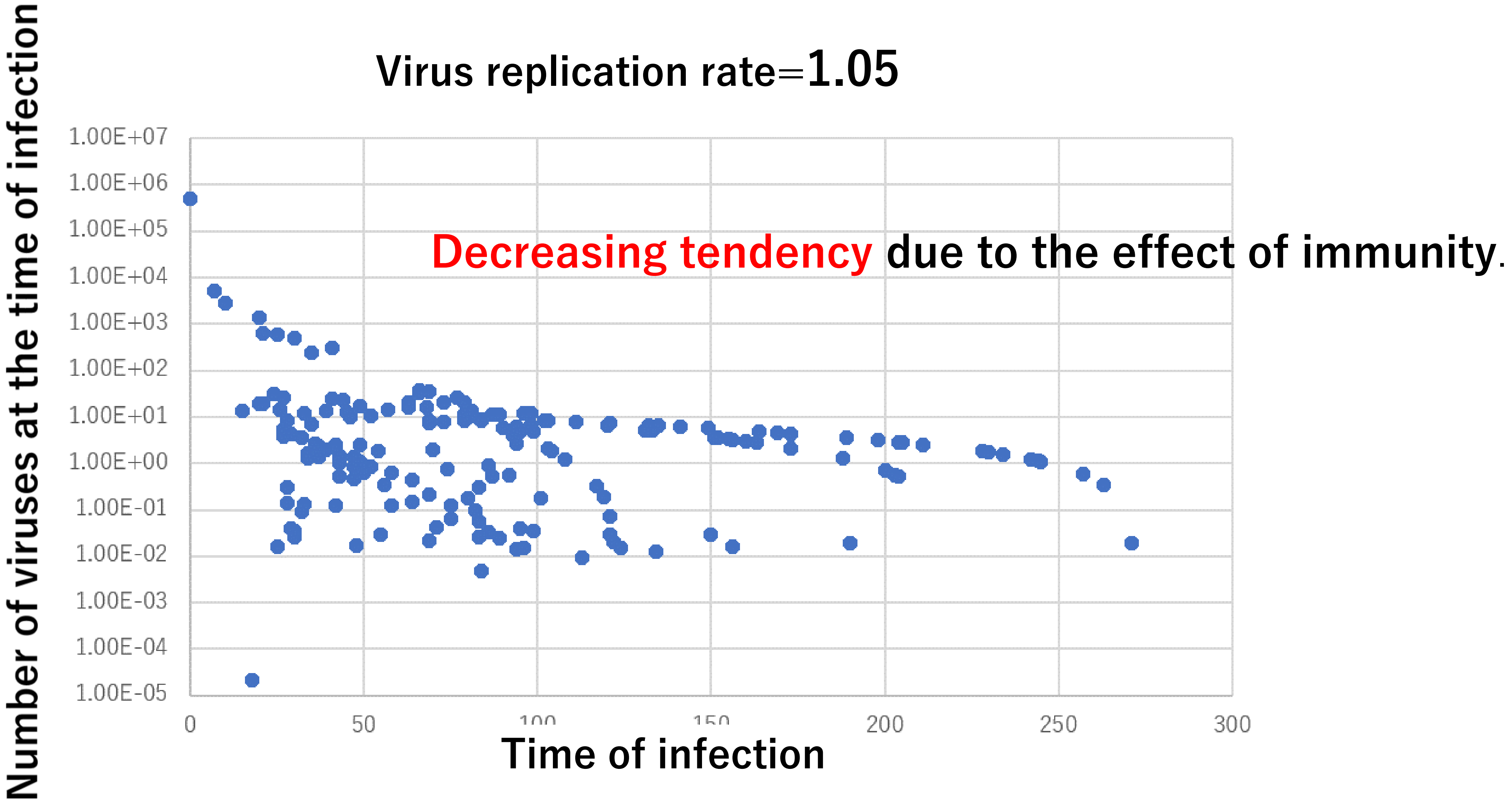
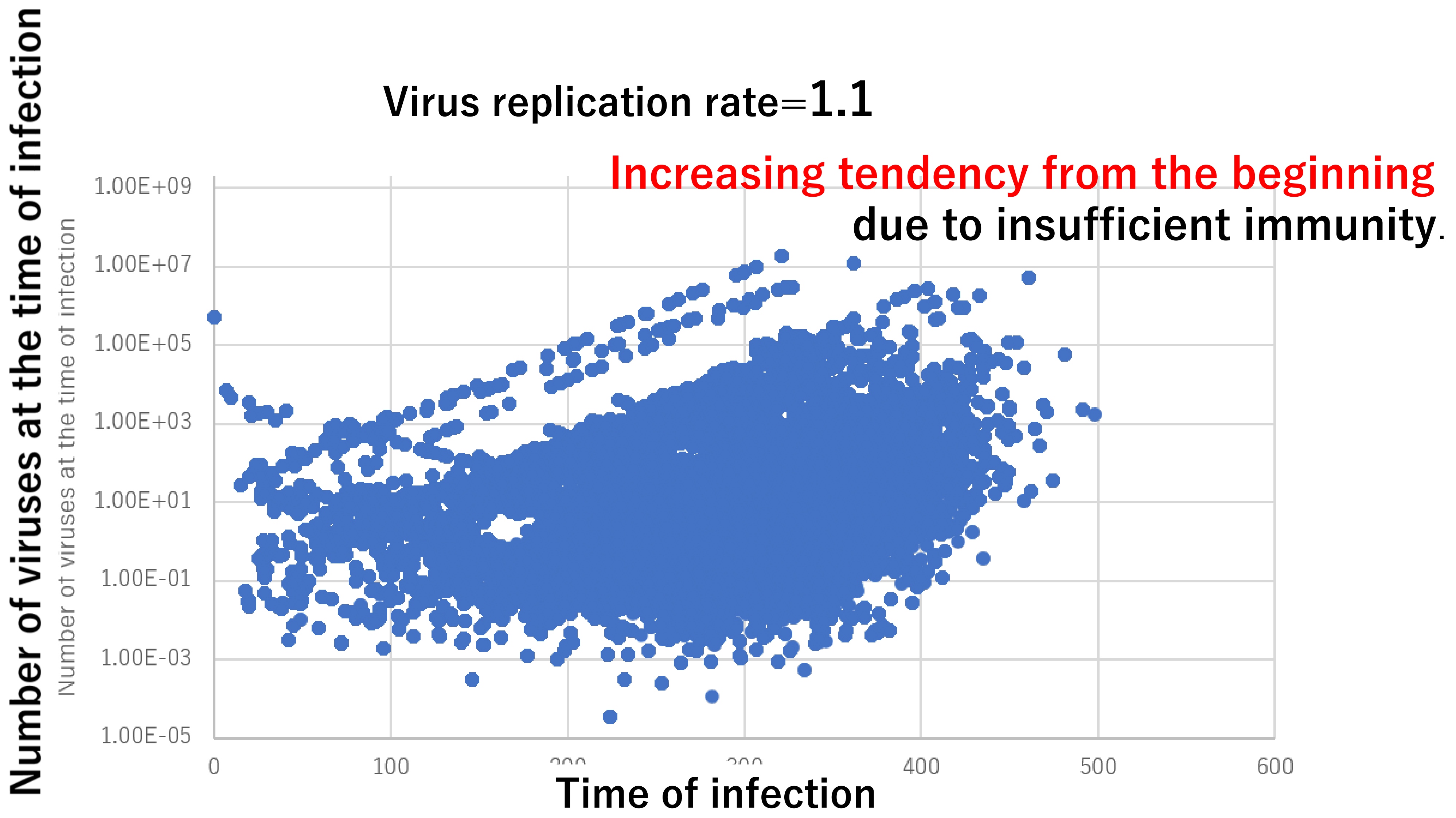


Fig. The behavior of the pandemic when the role of fever is not present.

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.

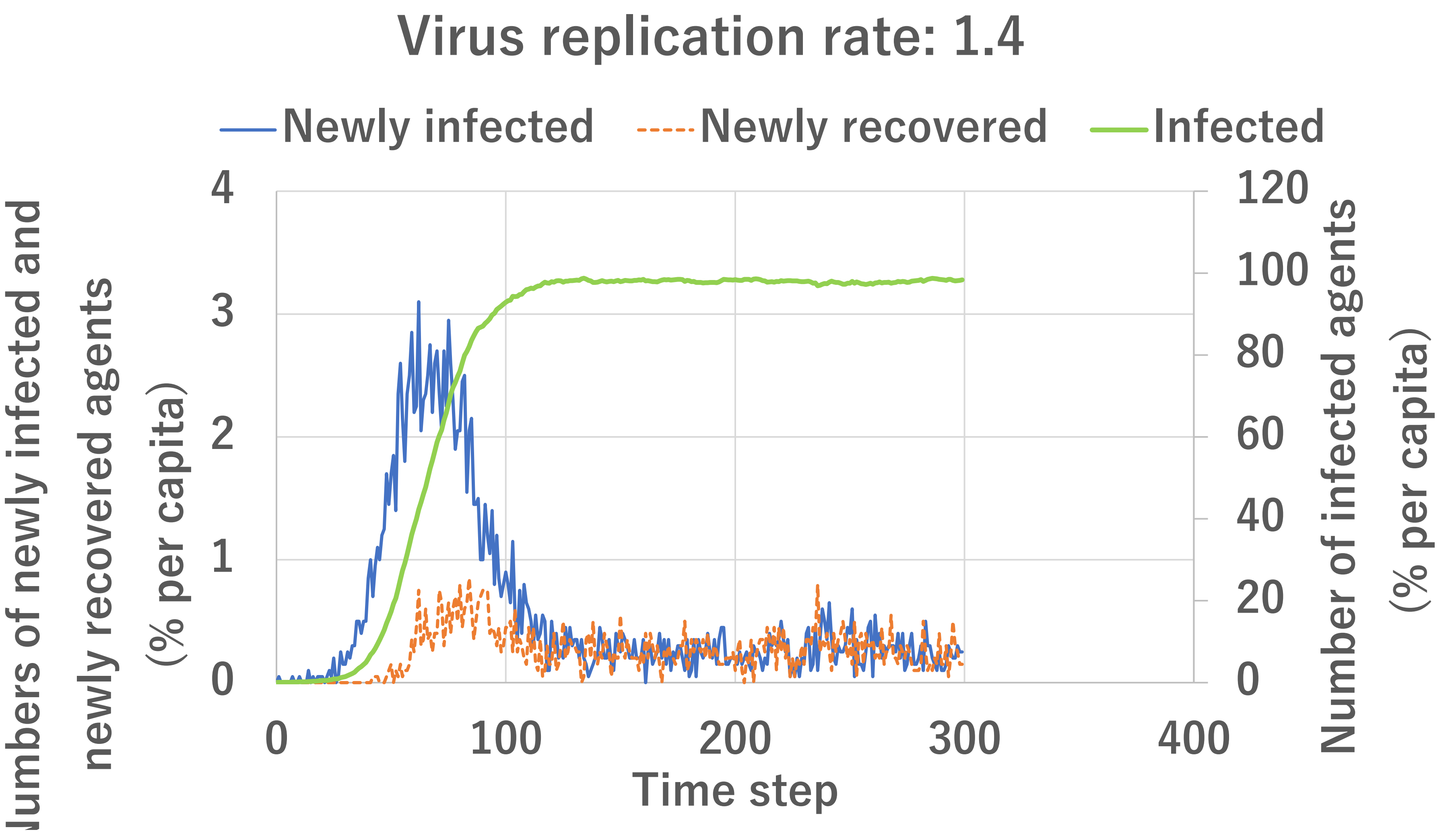
6. Conclusions

1) **An agent-based infection model that incorporates the role 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 results of the increasing and decreasing trend of the number of Infected , newly infected and newly recovered individuals are in good agreement with the actual data..**

3) **The most essential factor that is indispensable to reproduce the features of the pandemic phenomenon is the role of fever, not the role of antibodies. Based on this finding, individual's self-monitoring body temperature followed by self-restriction of movement if necessary is considered the most effective for individual's faster recovery as well as the rapid pandemic convergence in the society.**

4) **I have been proposing a new methodology to elucidated the causal mechanism of the emergence of social and economic phenomena using ABM and this research is an example of such trials. I hope this methodology will help understanding the causal mechanism of various social phenomena .**


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

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

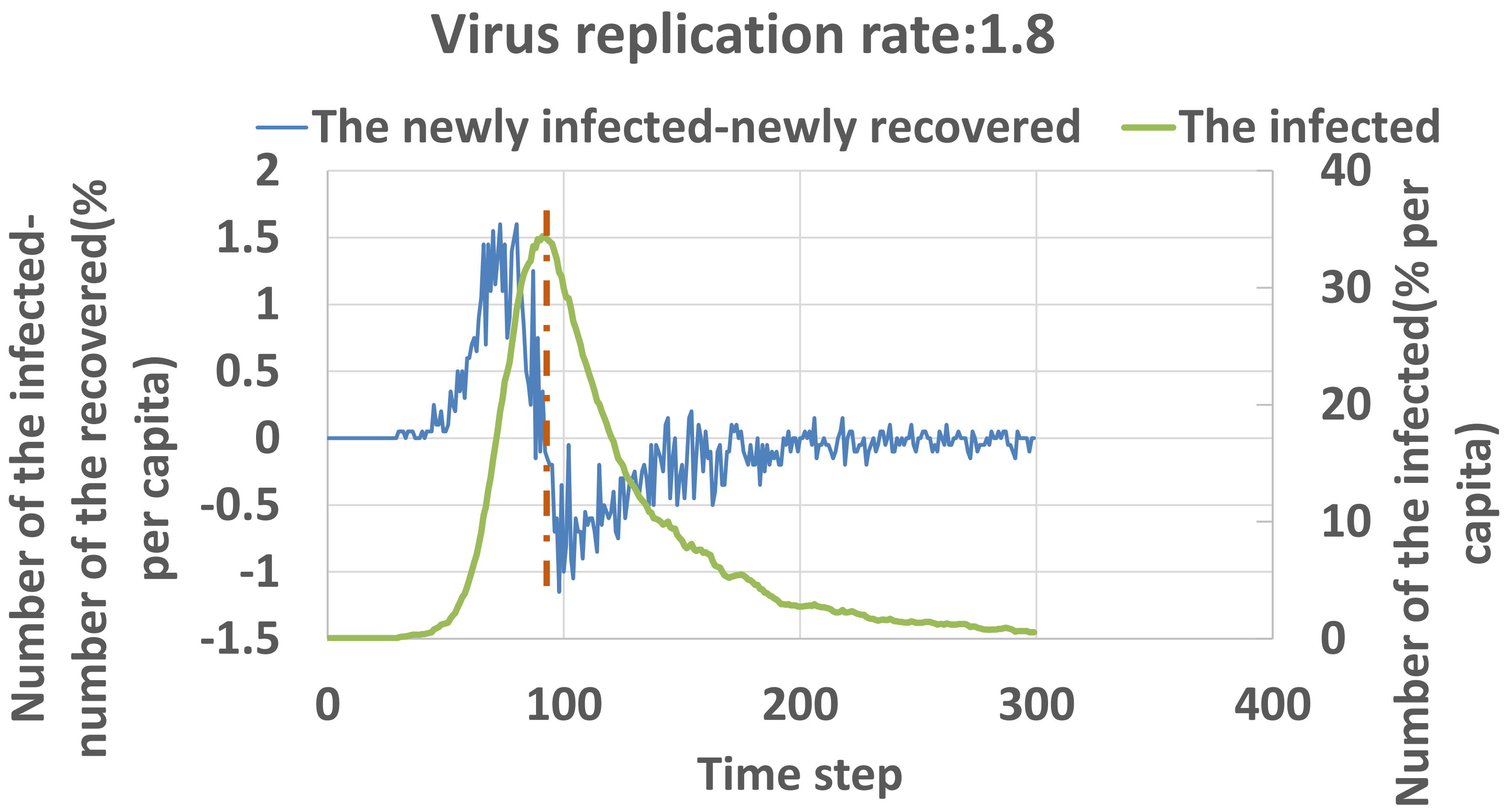


Fig. Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents.

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.

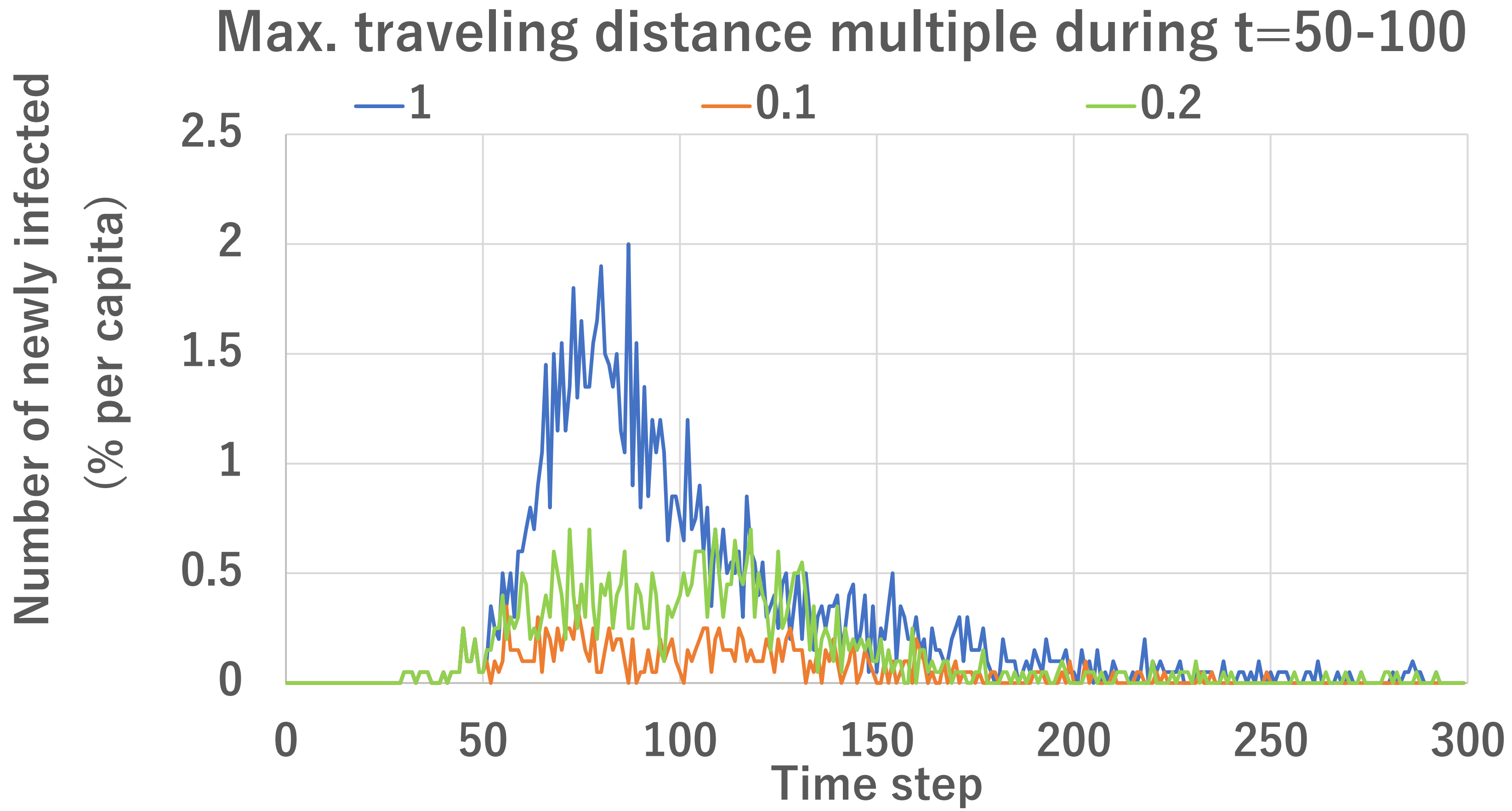


Fig. Effect of temporary regulation of traveling distance and its release on the number of infected neighbors (virus growth rate: 1.8).

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.

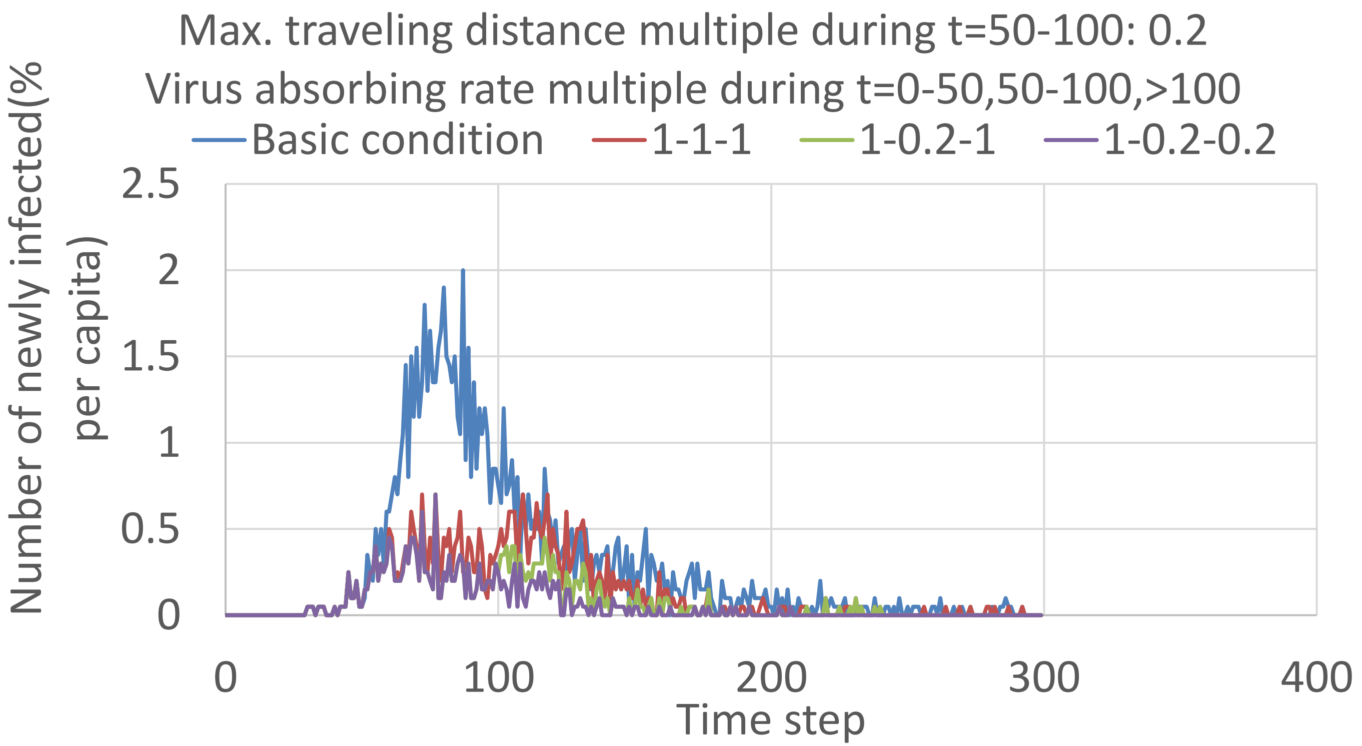
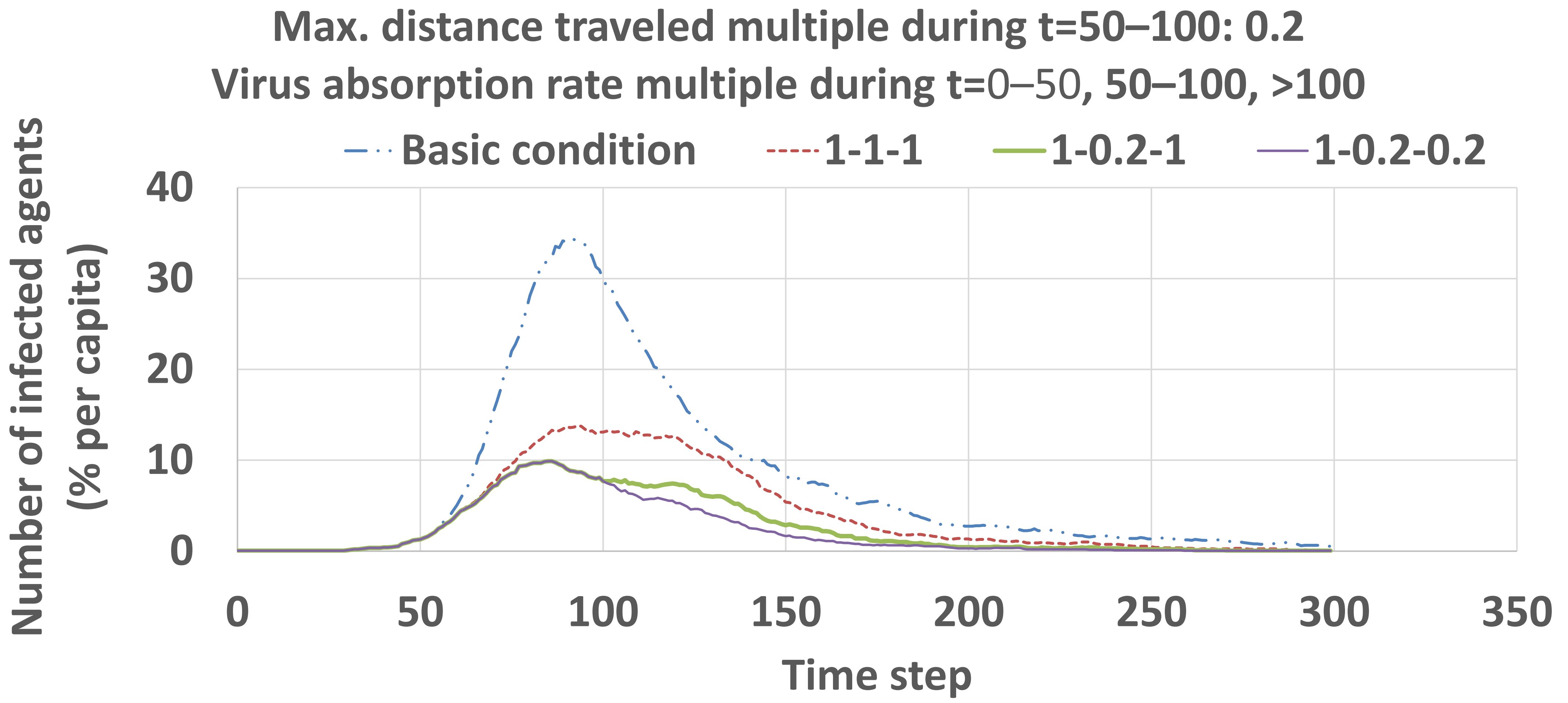


Fig. 24. Effect of the virus absorbing rate on the number of newly infected agents when movement regulation is applied.

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



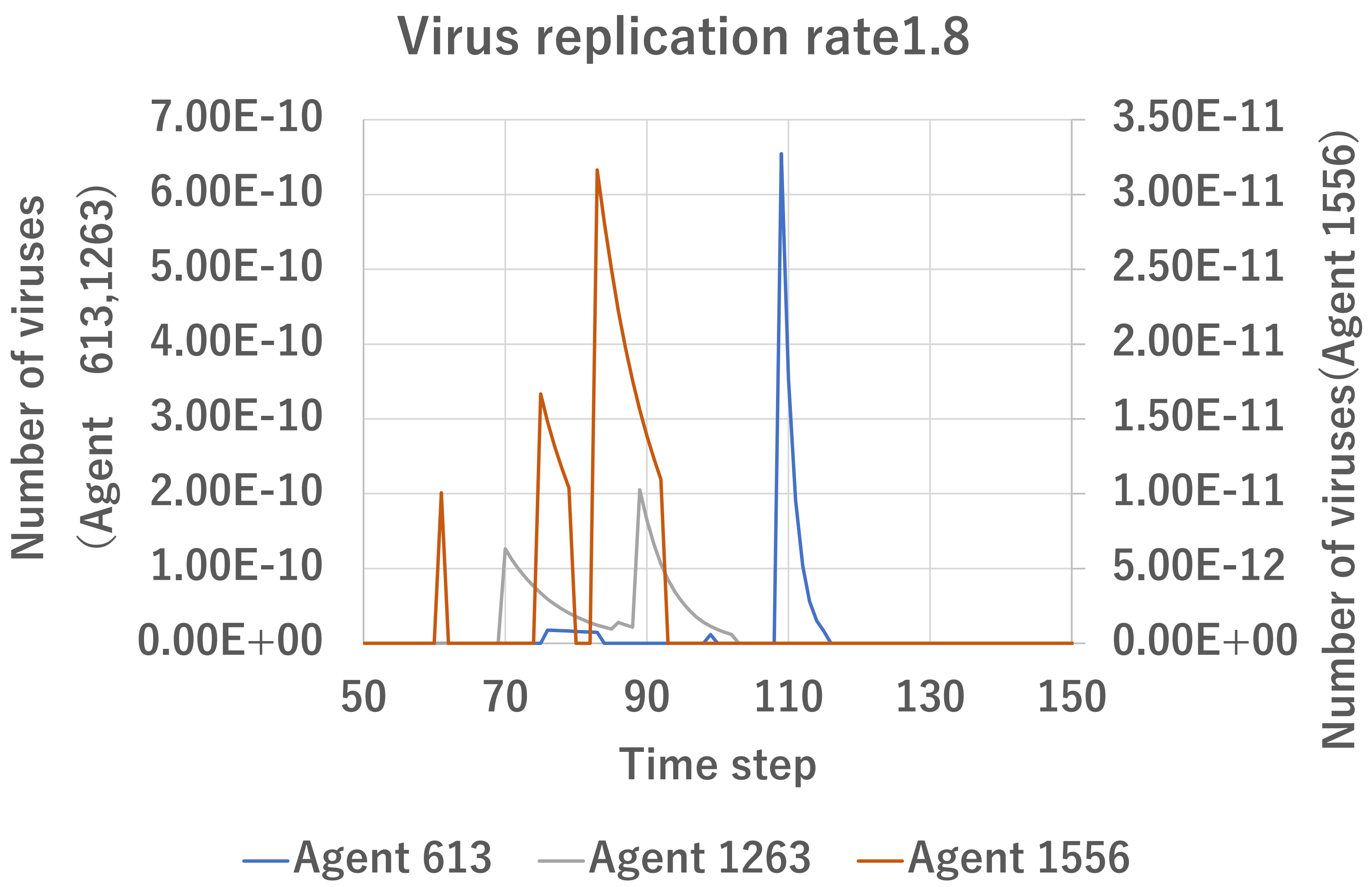


Fig. Examples of cases of multiple infections