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

October 3-4, 2024 at the Infectious Disease Conference in Amsterdam

Shigeaki Ogibayashi
Emeritus Professor, Chiba Institute of Technology, Japan

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 that we can elucidate the causal mechanism of various social phenomena using 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. There exists 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 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

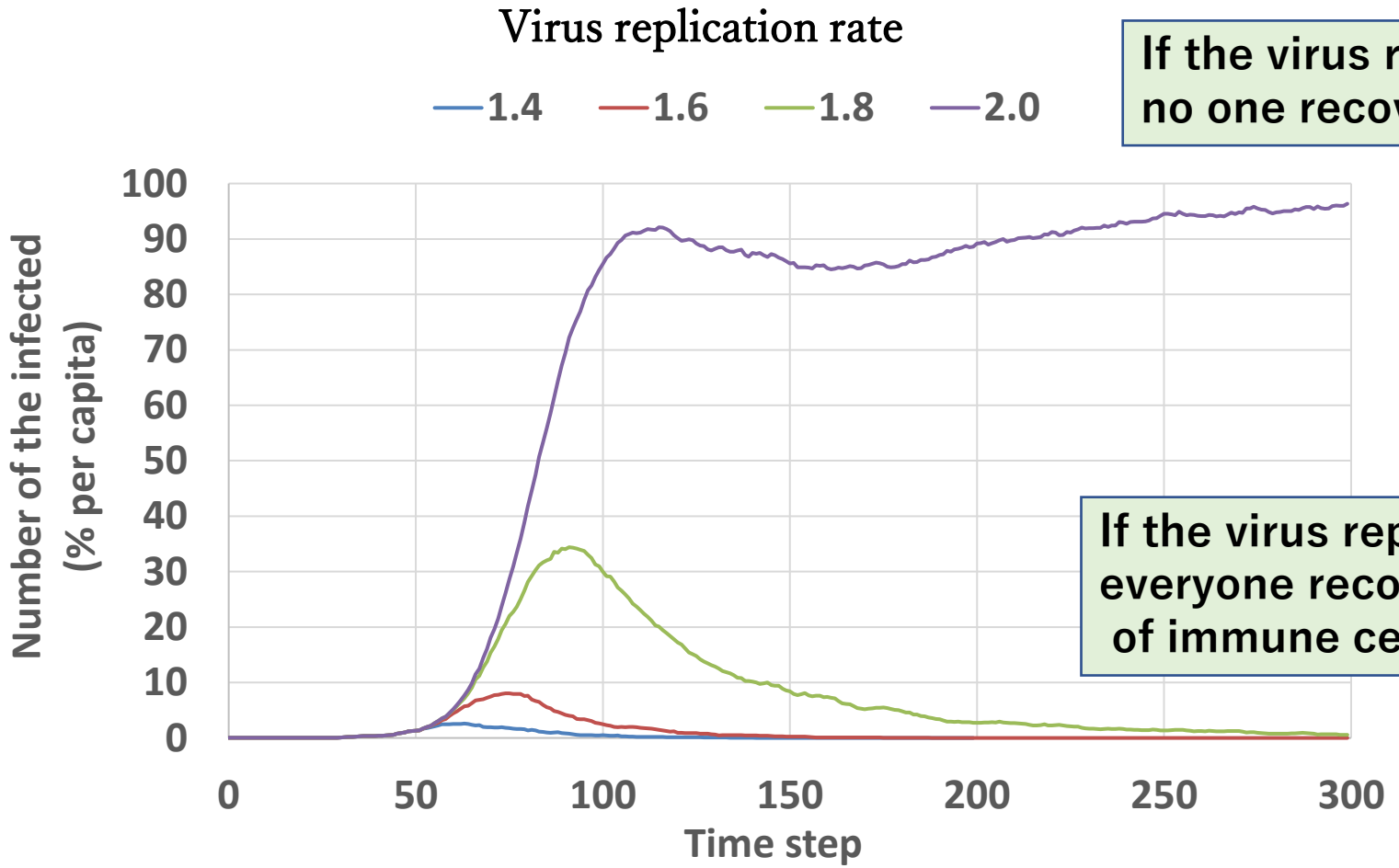
$\Delta N^i{}_{infected}(t)$: Increasing increment of the number of virses at the time t

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.

3.1.1 Effect of virus replication rate on the number of infected and recovered agents

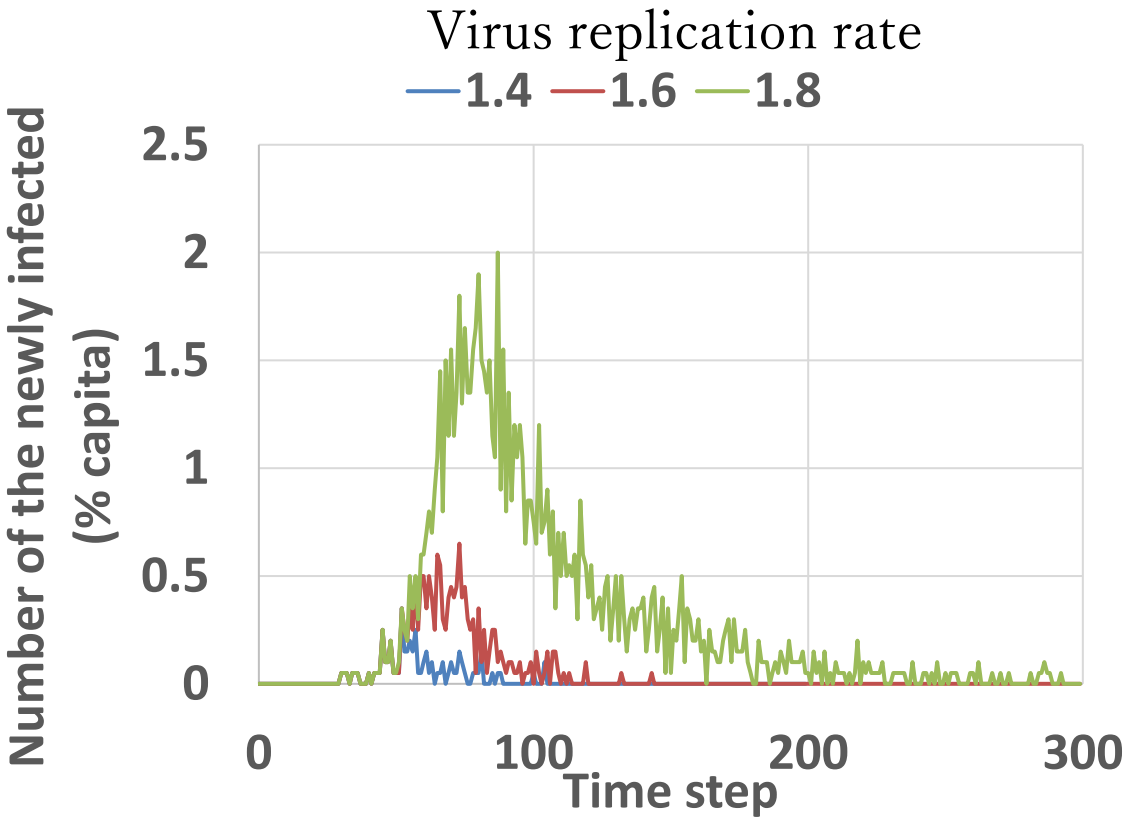


If the virus replication rate is too large no one recovers.

If the virus replication rate is not too large everyone recovers, due to the effect of immune cells and antibodies.

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

Newly infected agents



Newly recovered agents

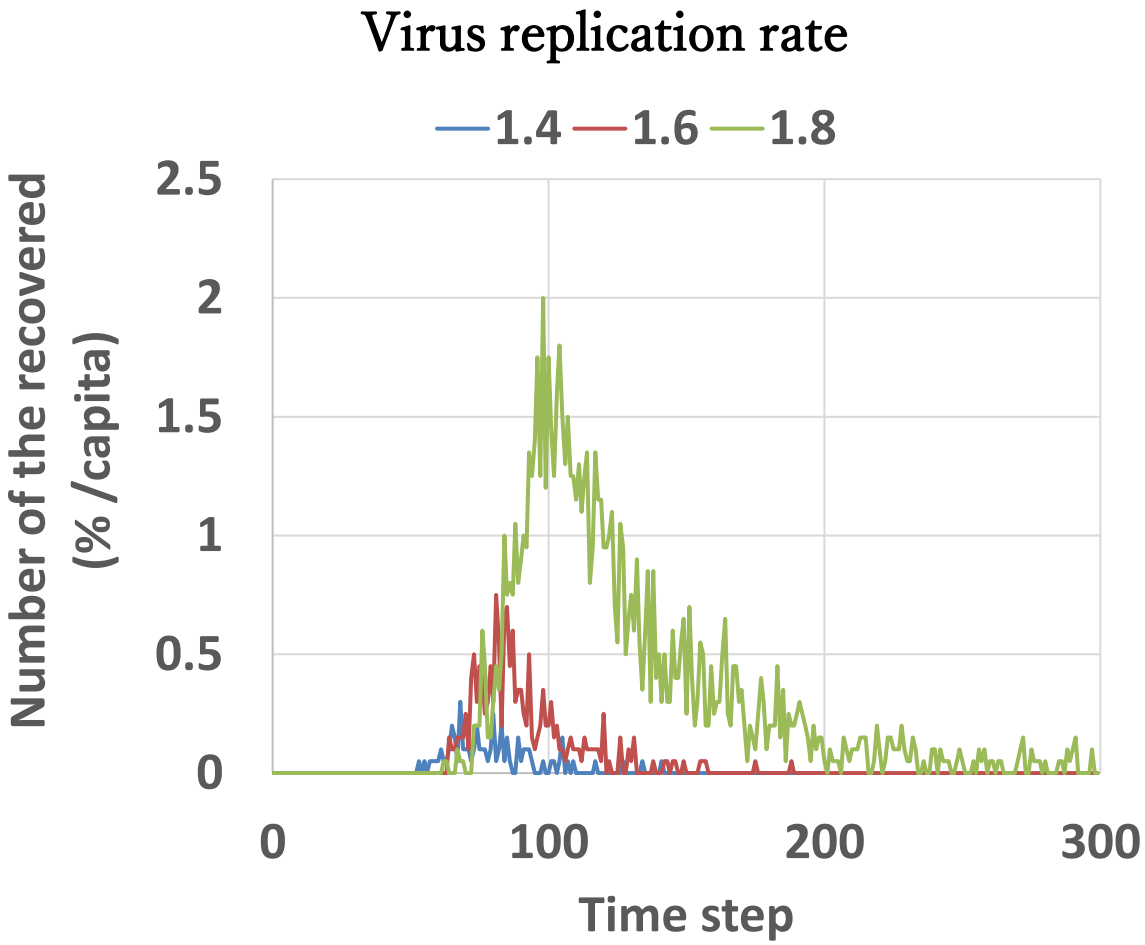


Fig. Effect of virus replication rate on the number of newly infected agents. And the number of newly recovered agents.

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

The peak time is in the order of a newly infected person, infected person, and recovered person.

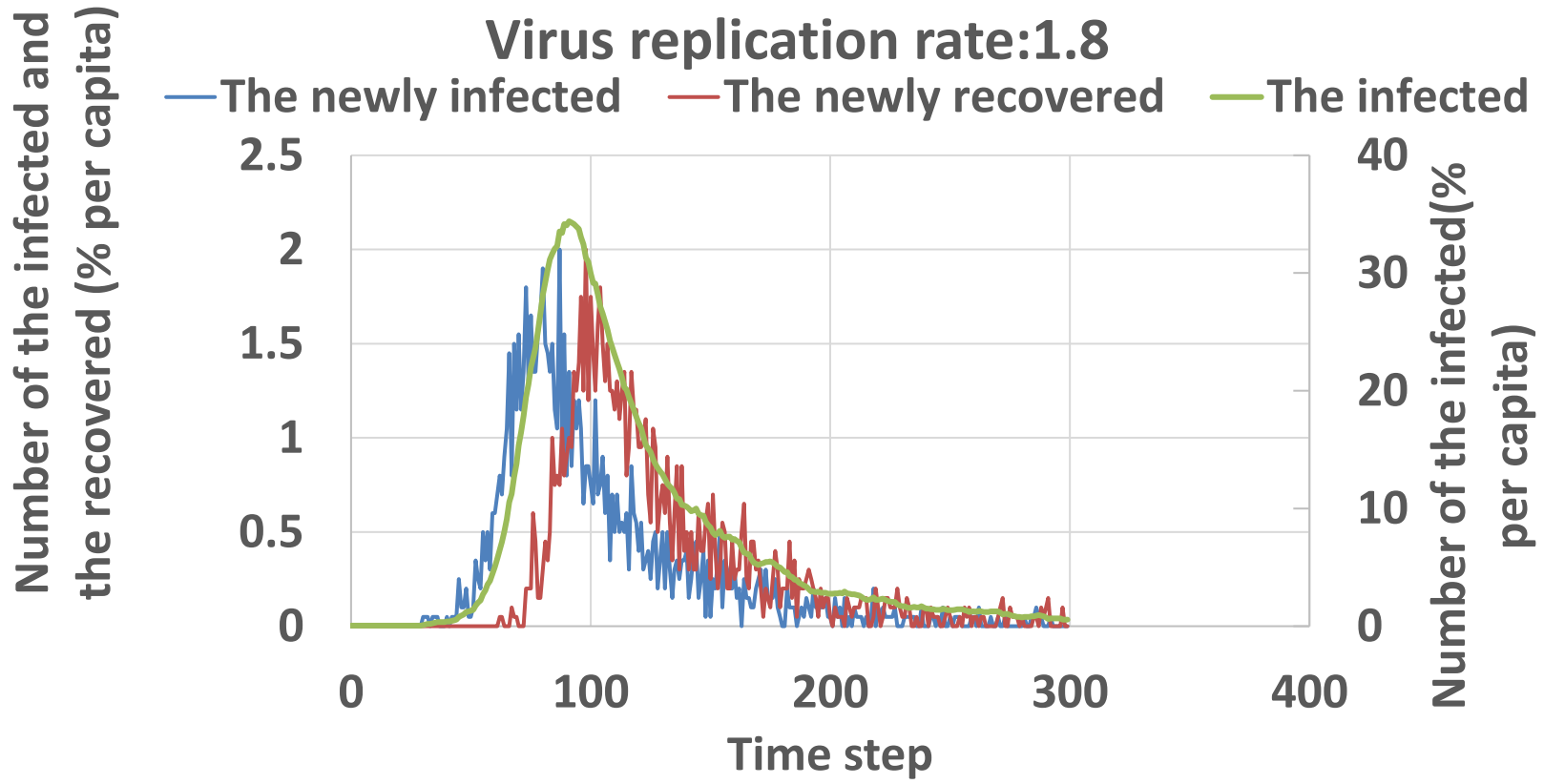


Fig. Changes in the numbers of newly infected, newly recovered, and total infected agents.

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

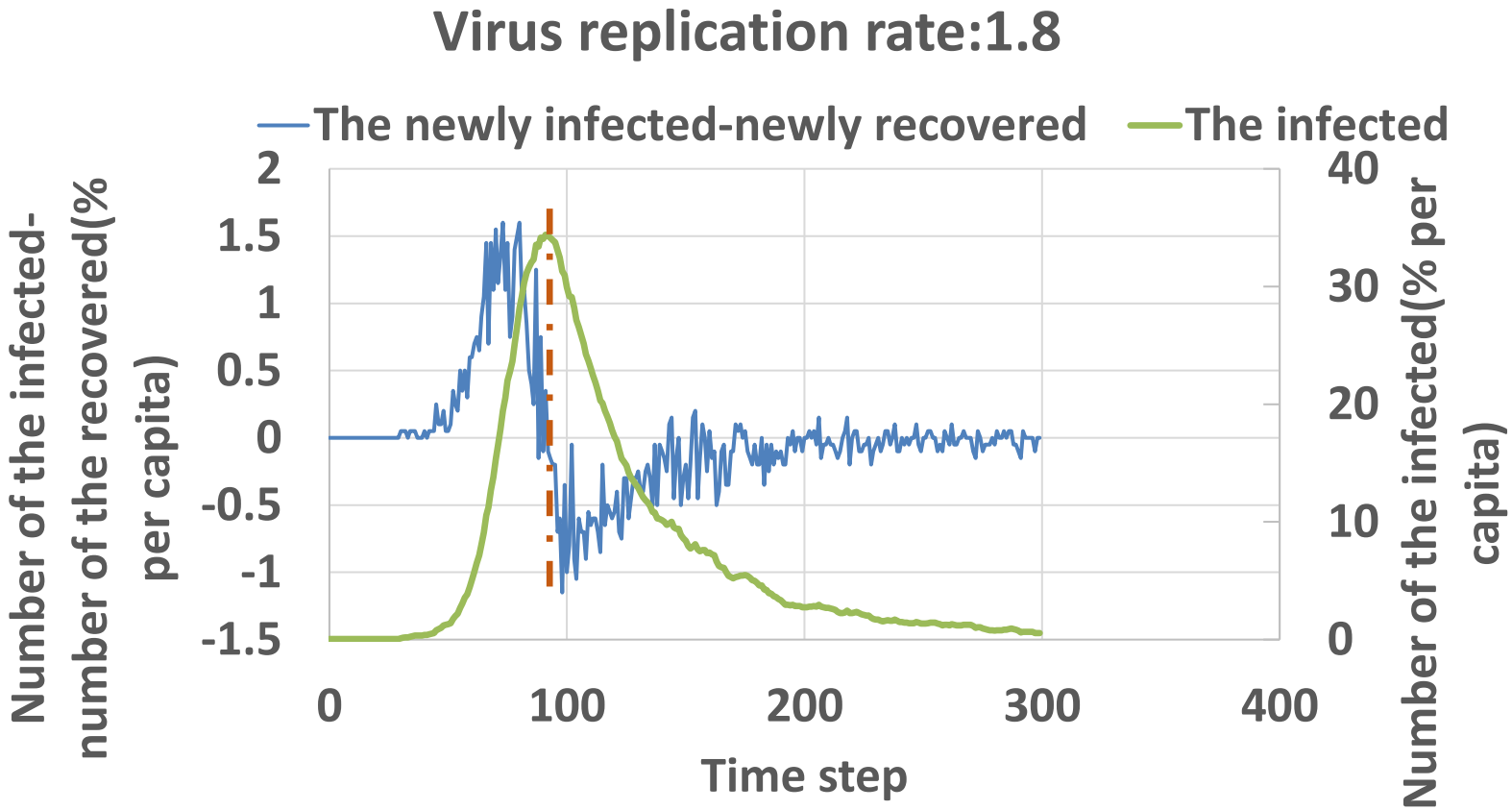


Fig. Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents.

3.2 Comparison of the calculated pattern of infection spread and convergence with real-world data.

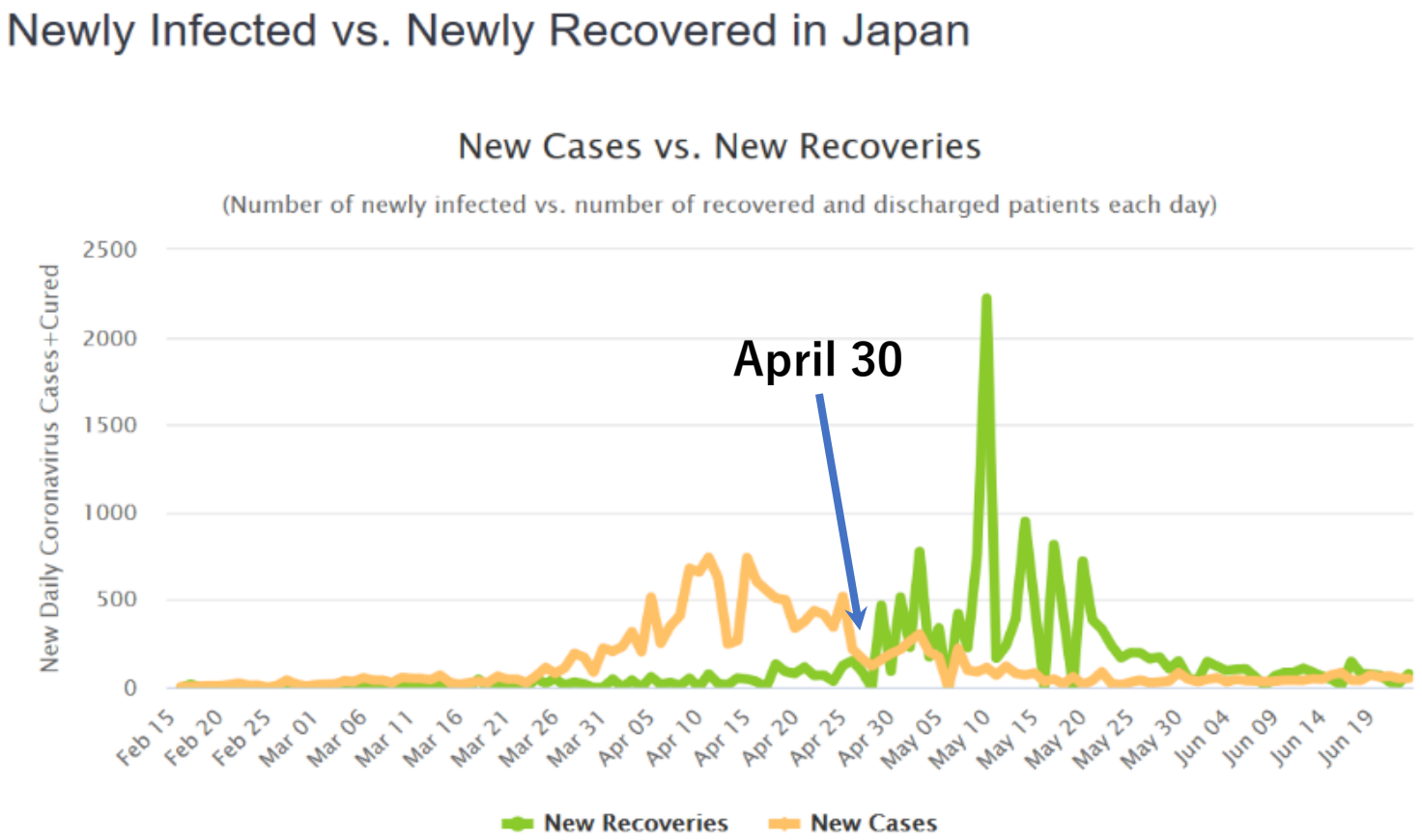


Figure 17. Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020.[17)]

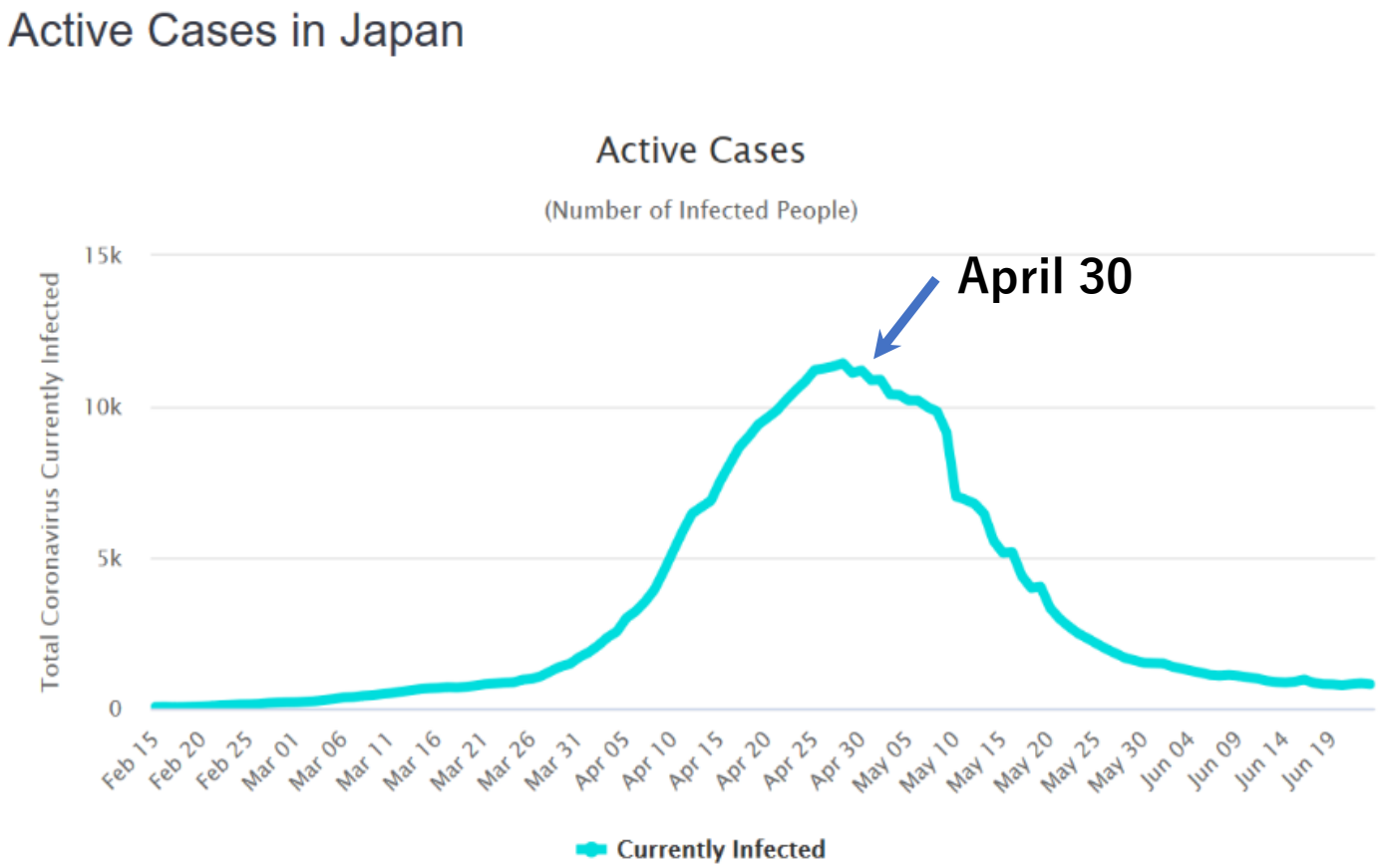


Fig. 18 Change in the number of currently infected people in Japan as of June 20, 2020[17)].

3.1 Fundamental behavior during infection and recovery. Examples of the changes in the number of viruses.

Slope is positive if virus replication rate >immune cells attack rate
Slope is negative if immune cells' attack rate> and virus replication rate.

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	

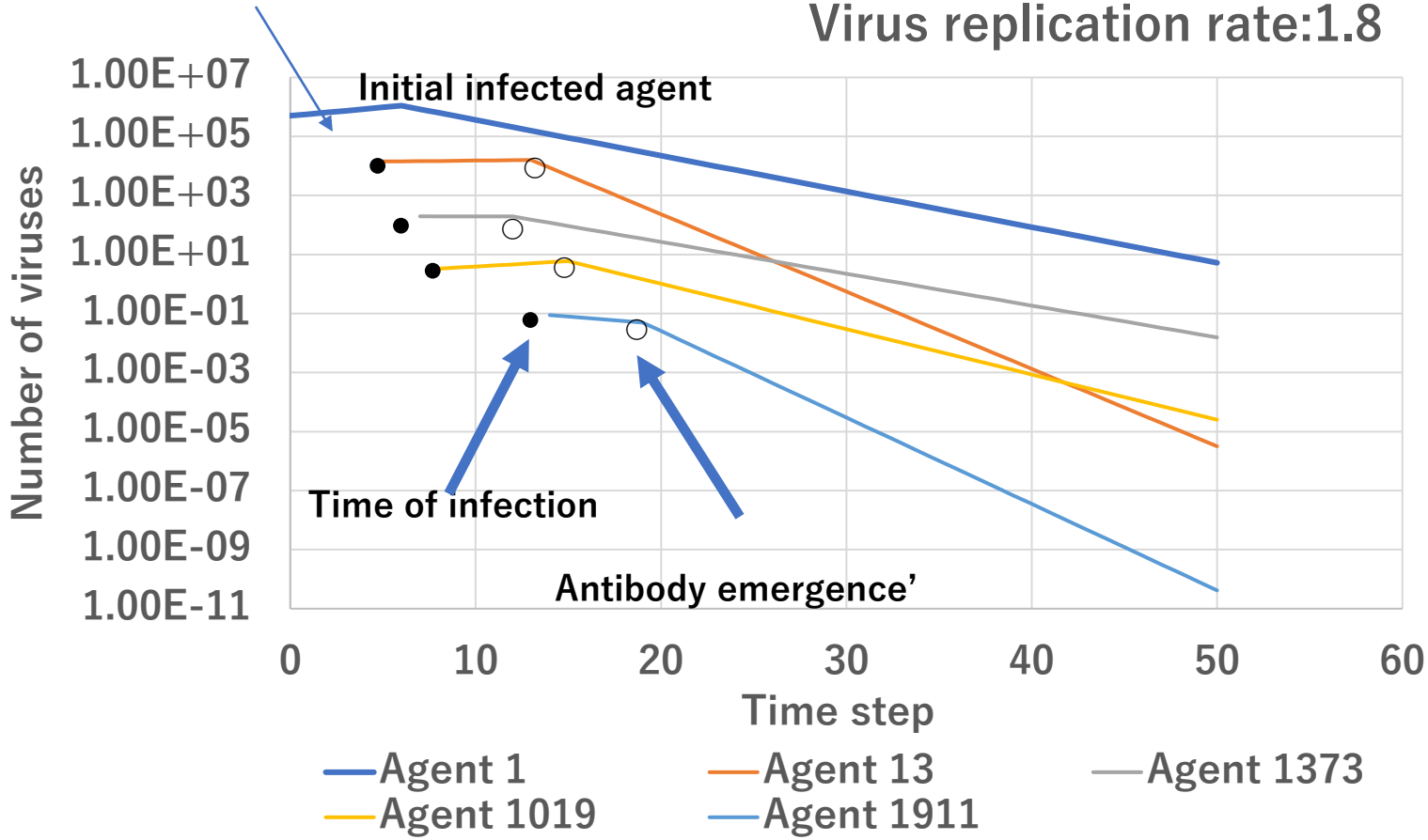


Fig. Change in the number of viruses of each agent during the beginning of infection spread.

The number of viruses at the time of infection decreases with time due to the effect of immunity.

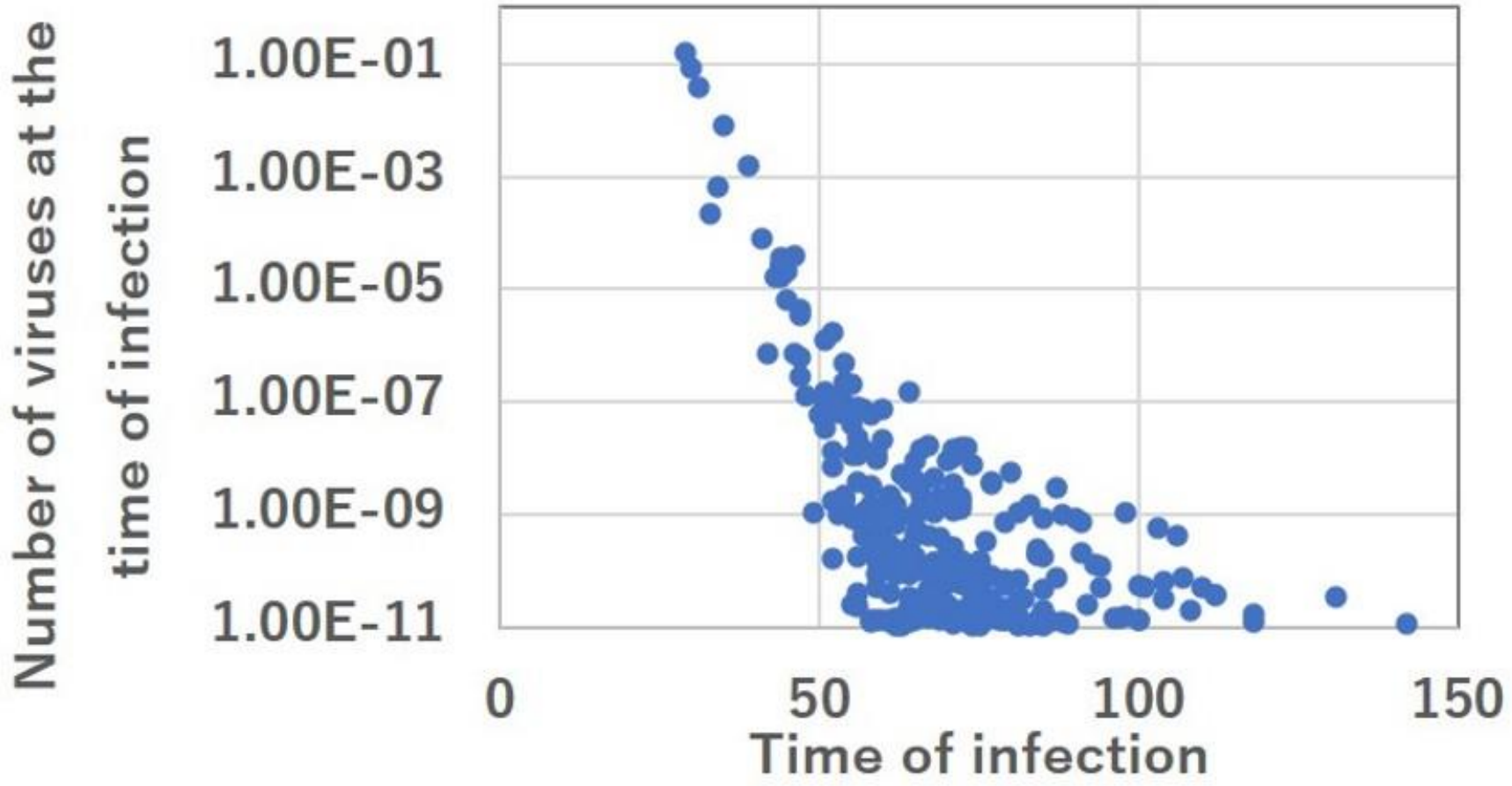


Fig. Change in the number of viruses at the time of infection during infection spread and convergence.

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

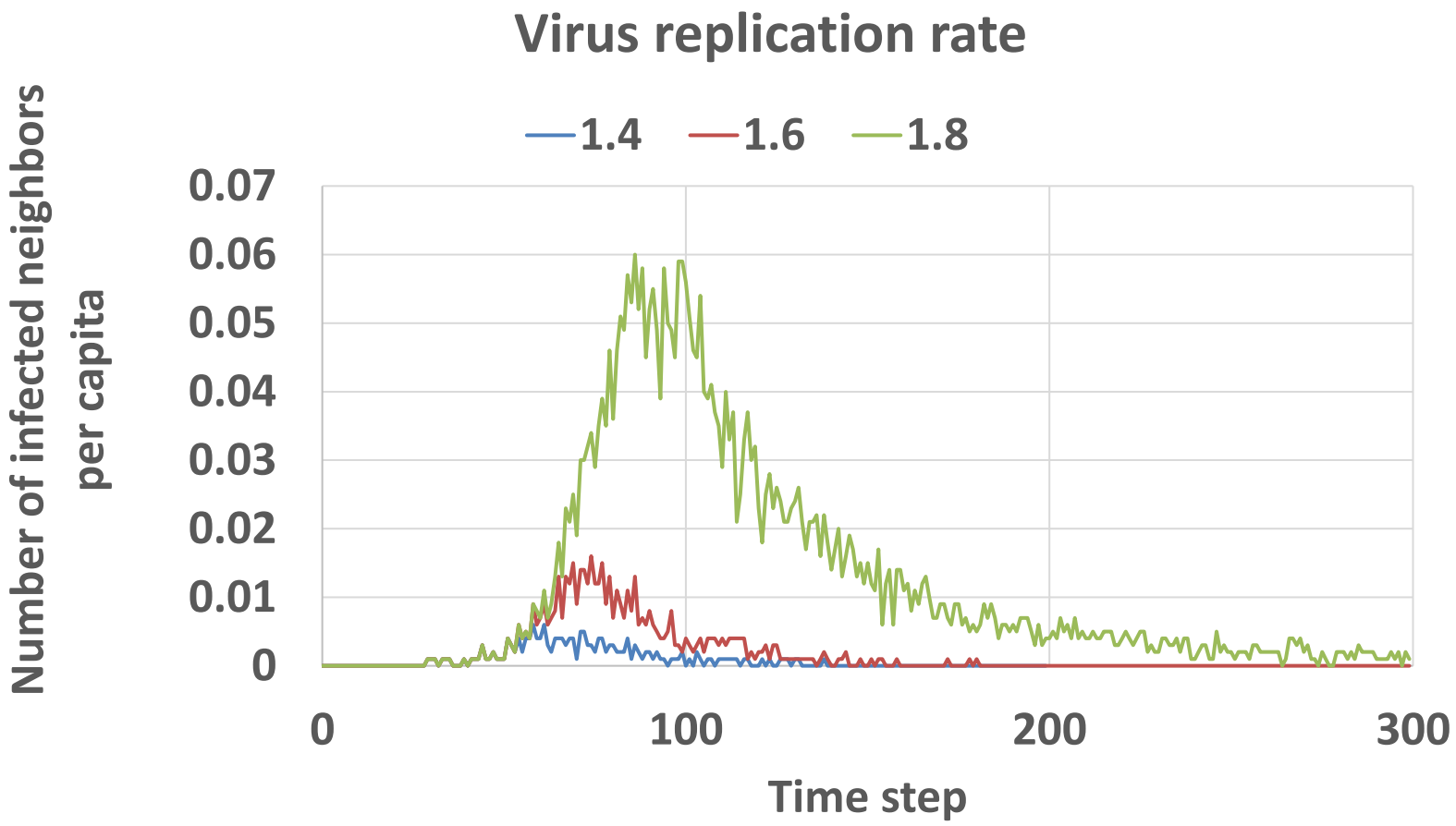


Fig. Effect of virus replication rate on the average number of infected neighbors.

The infection spread and convergence are essentially governed by the probability of a healthy person encountering the infected person. This fact causes the progressive increase and decrease in the number of infected persons.

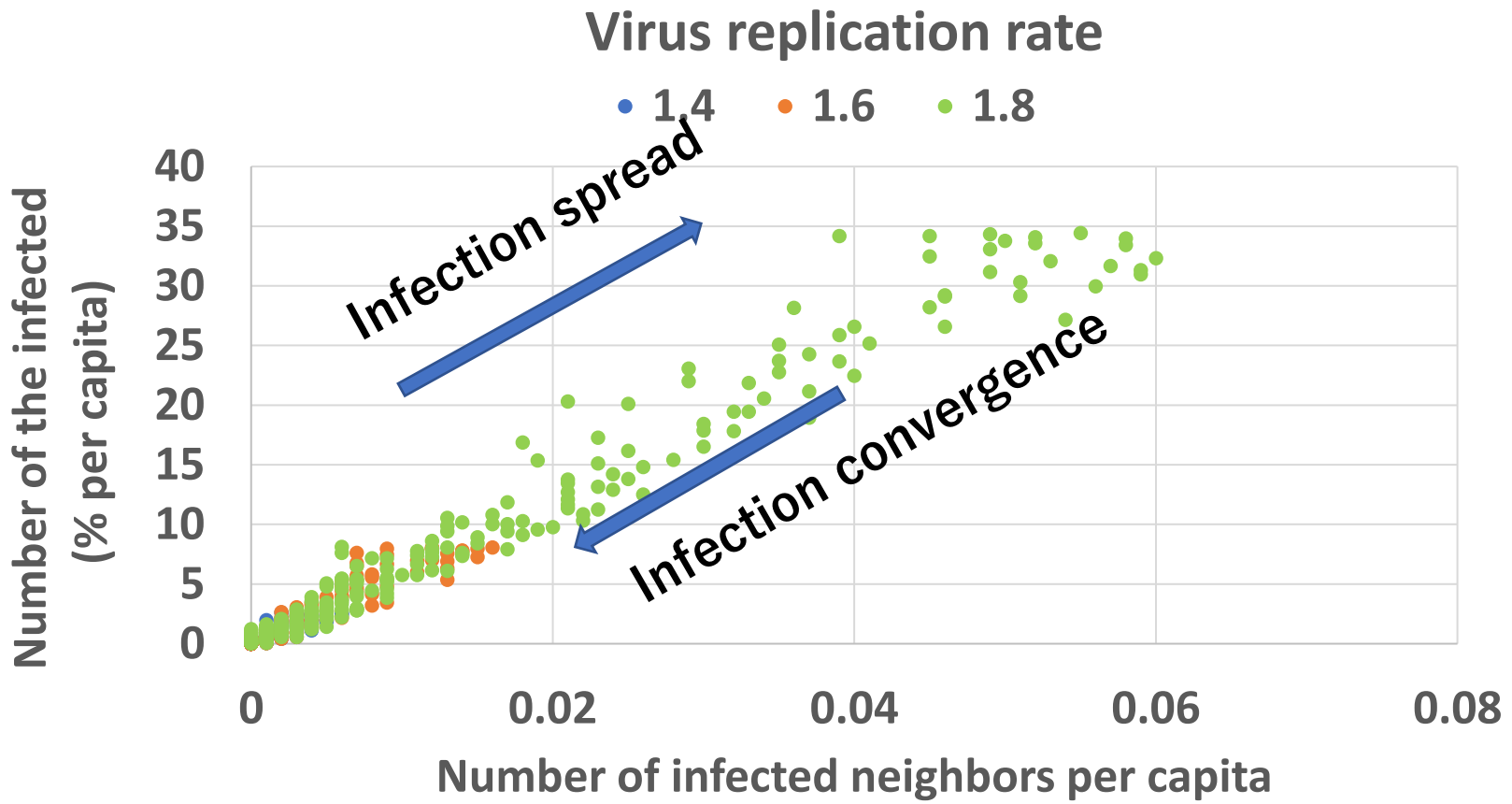
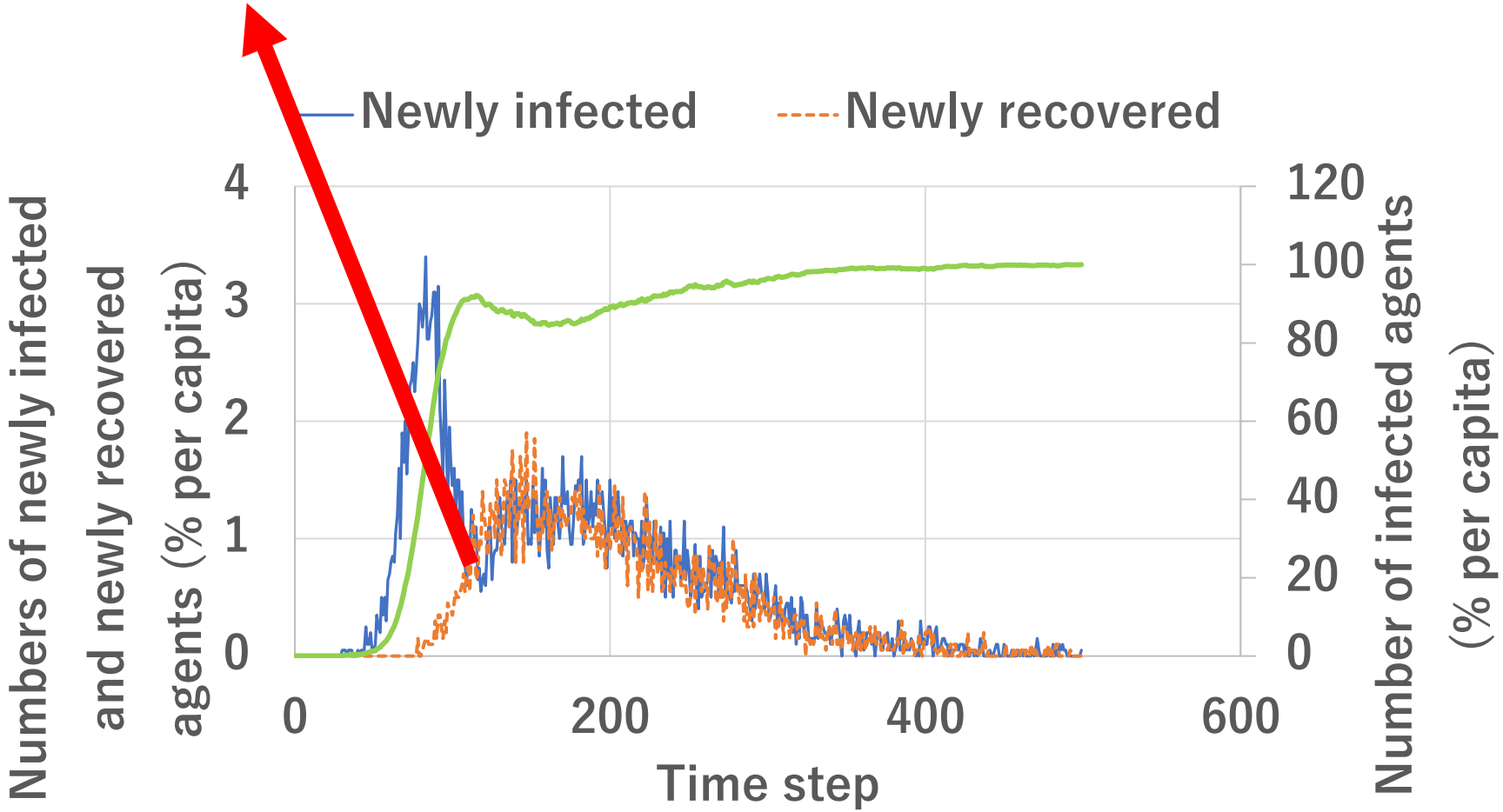


Fig. Relationship between the number of infected agents and the average number of infected neighbors.

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

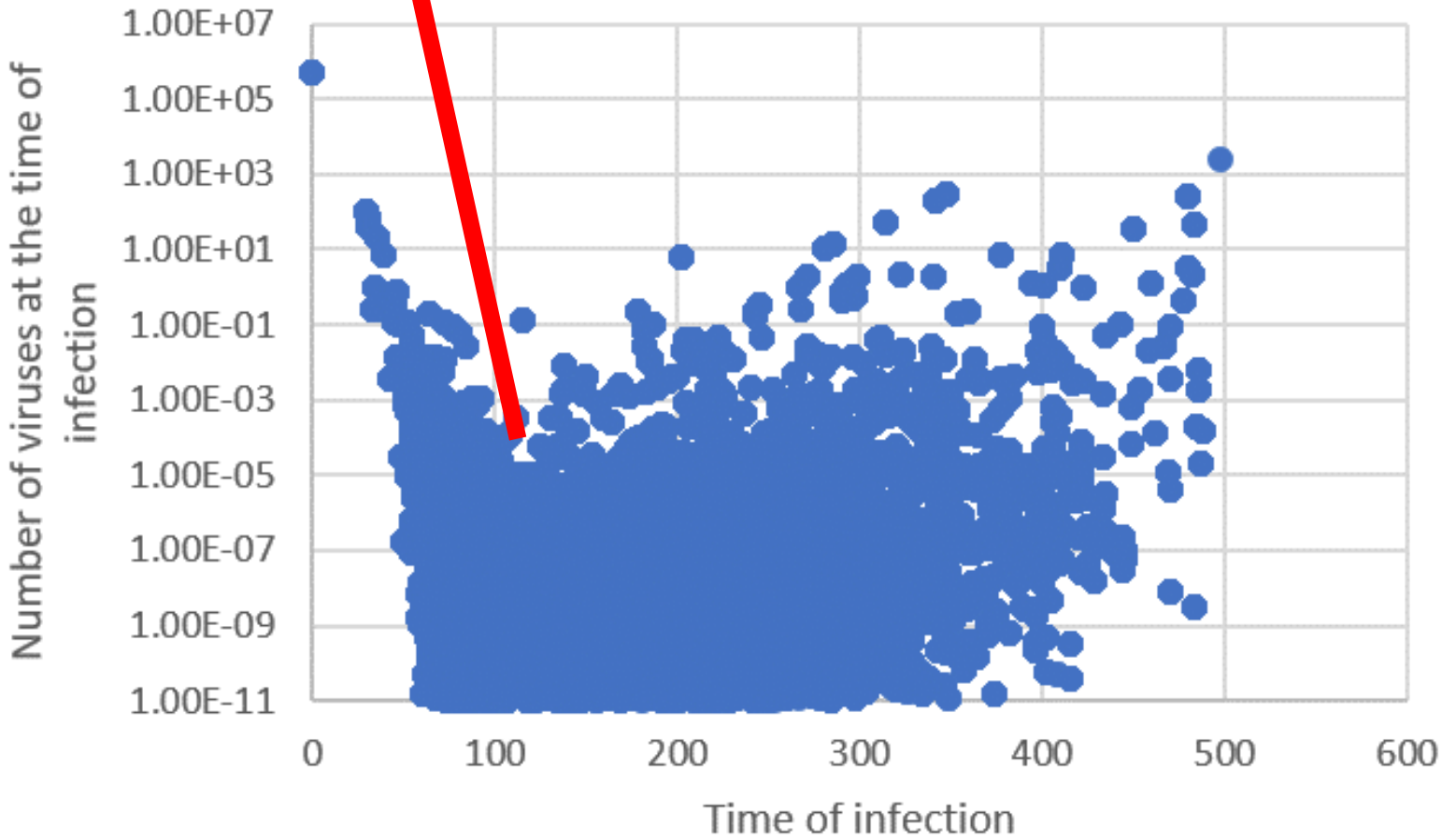
Agent with weak immunity was infected



Virus replication rate 2.0

Agent with weak immunity was infected

Virus replication rate 2.0



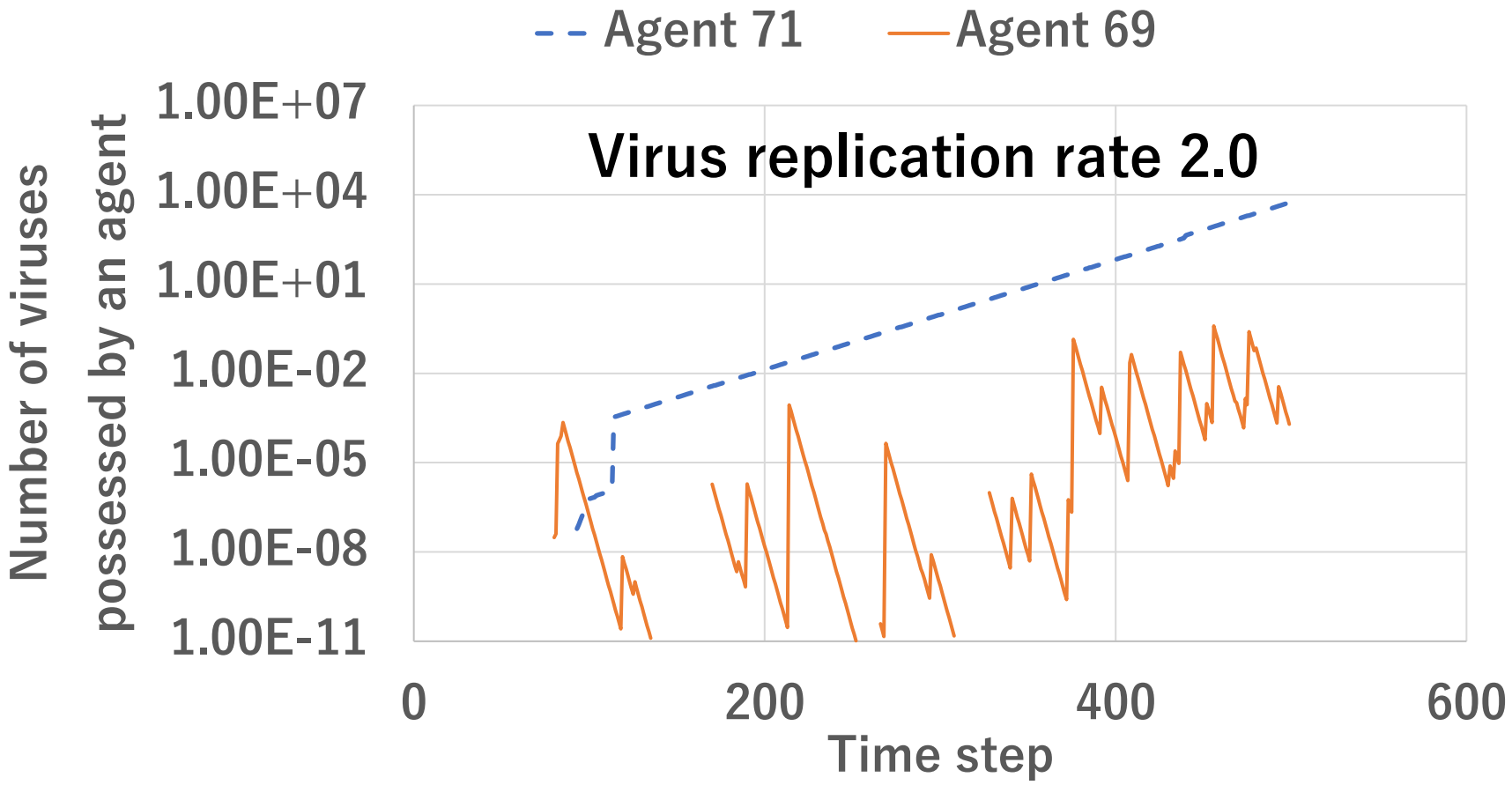
Agent71: effect of immunity ＜effect of virus replication

First infected at t=92,　Reinfected at t=113

The number of viruses indefinitely increases inside his body, unless isolated.

Agent 69: effect of immunity ＞ effect of virus replication

If not infected by Agent 71.



3.1.5 Regulation of the movement

It is effective thorough out the whole stage of pandemic.

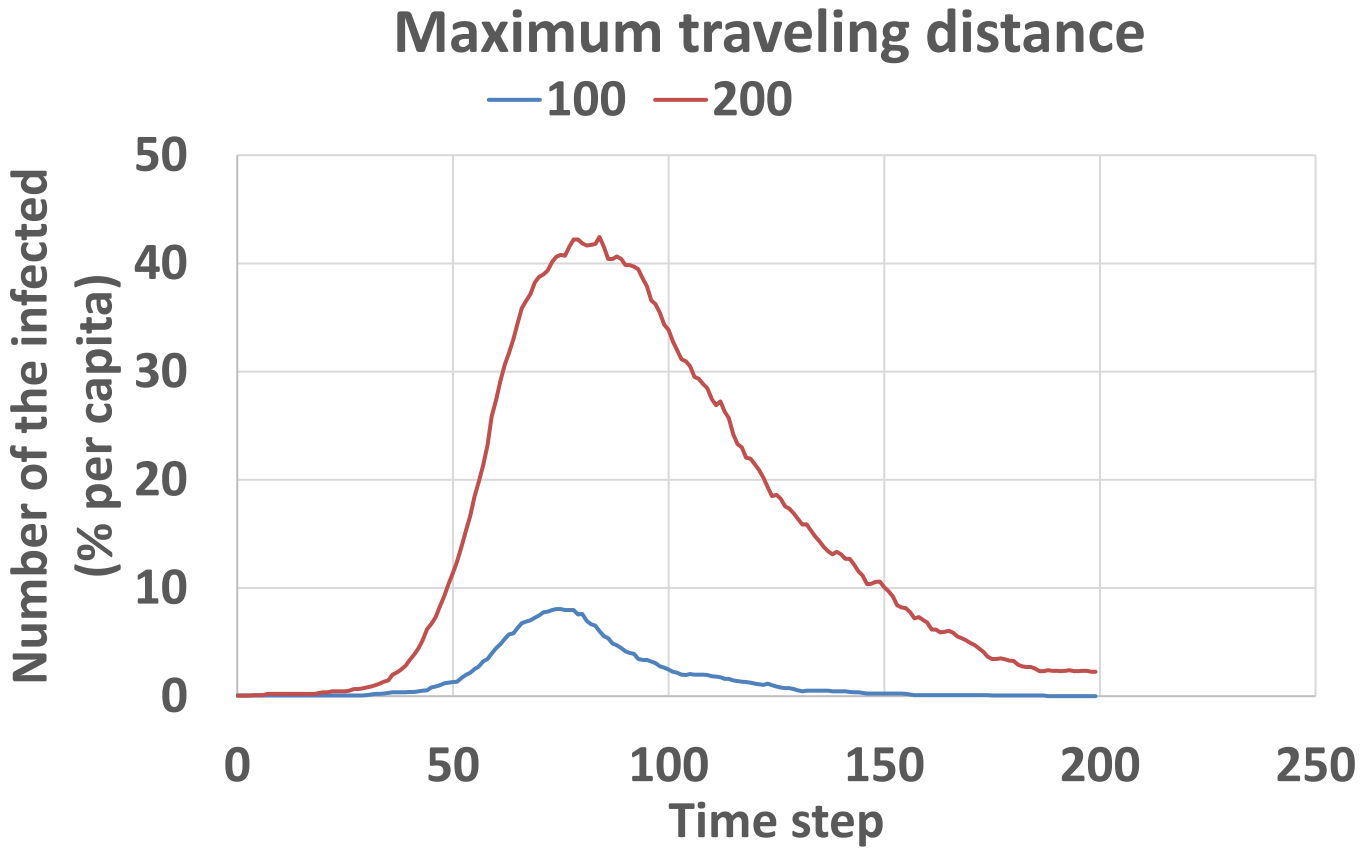
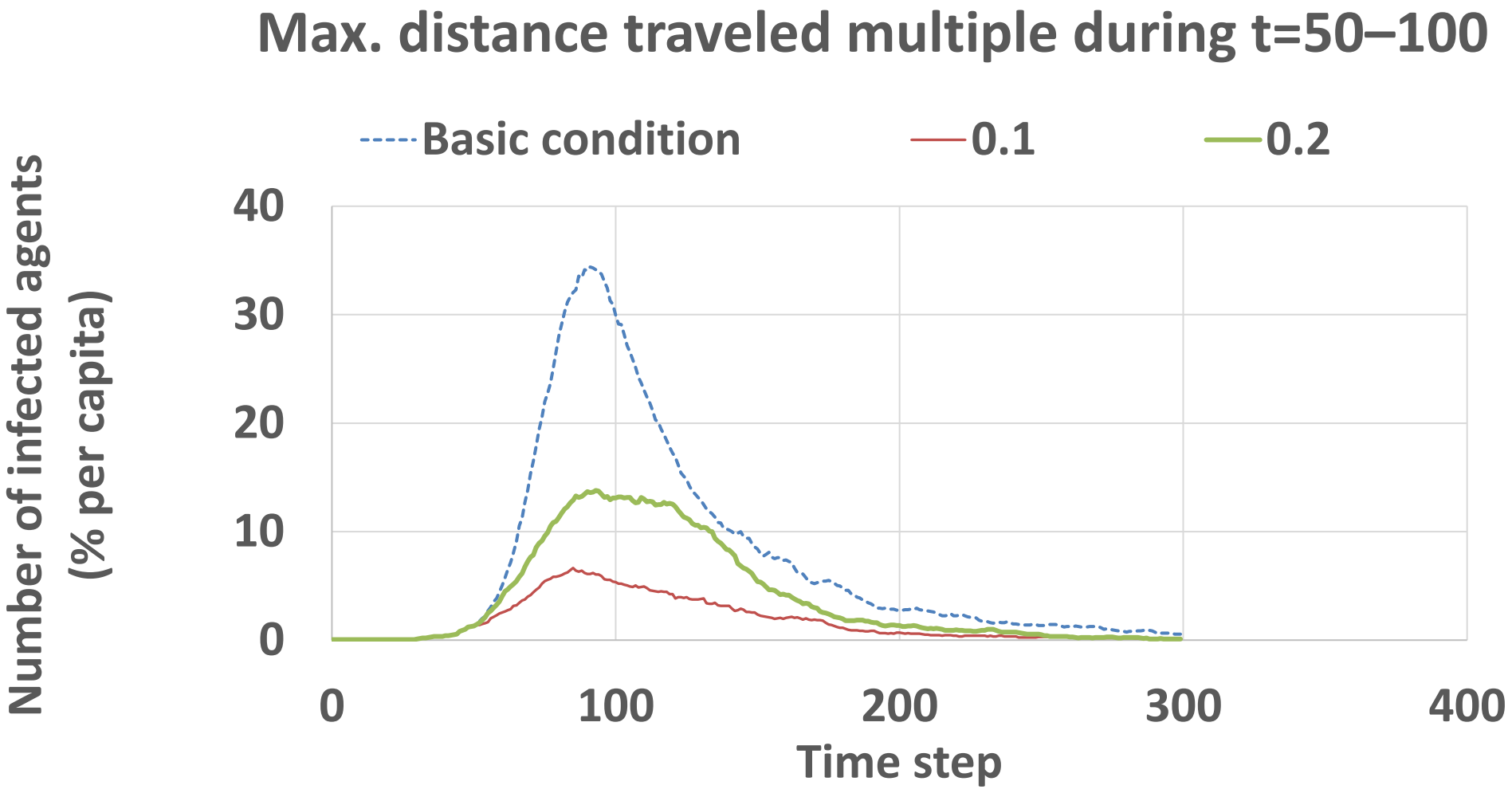


Fig. Effect of the maximum traveling distance on the total number of infected agents (virus replication rate: 1.6).

3.3 Temporal regulation of movement

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



3.4 Infection behavior when antibodies entirely do not exist.

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.

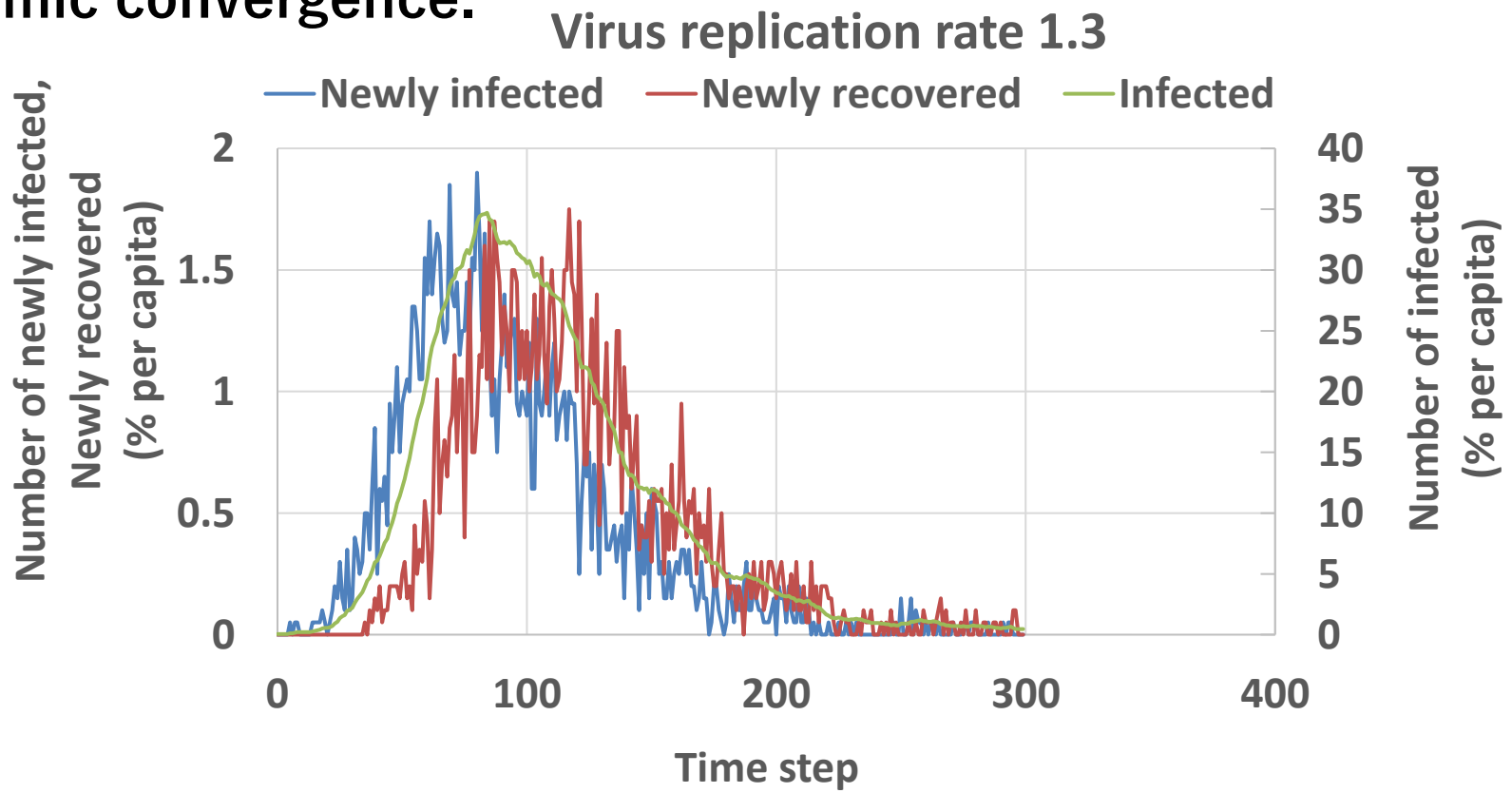


Fig. 27 An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case without antibodies.

What happens if assumption for virus decreasing 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".)

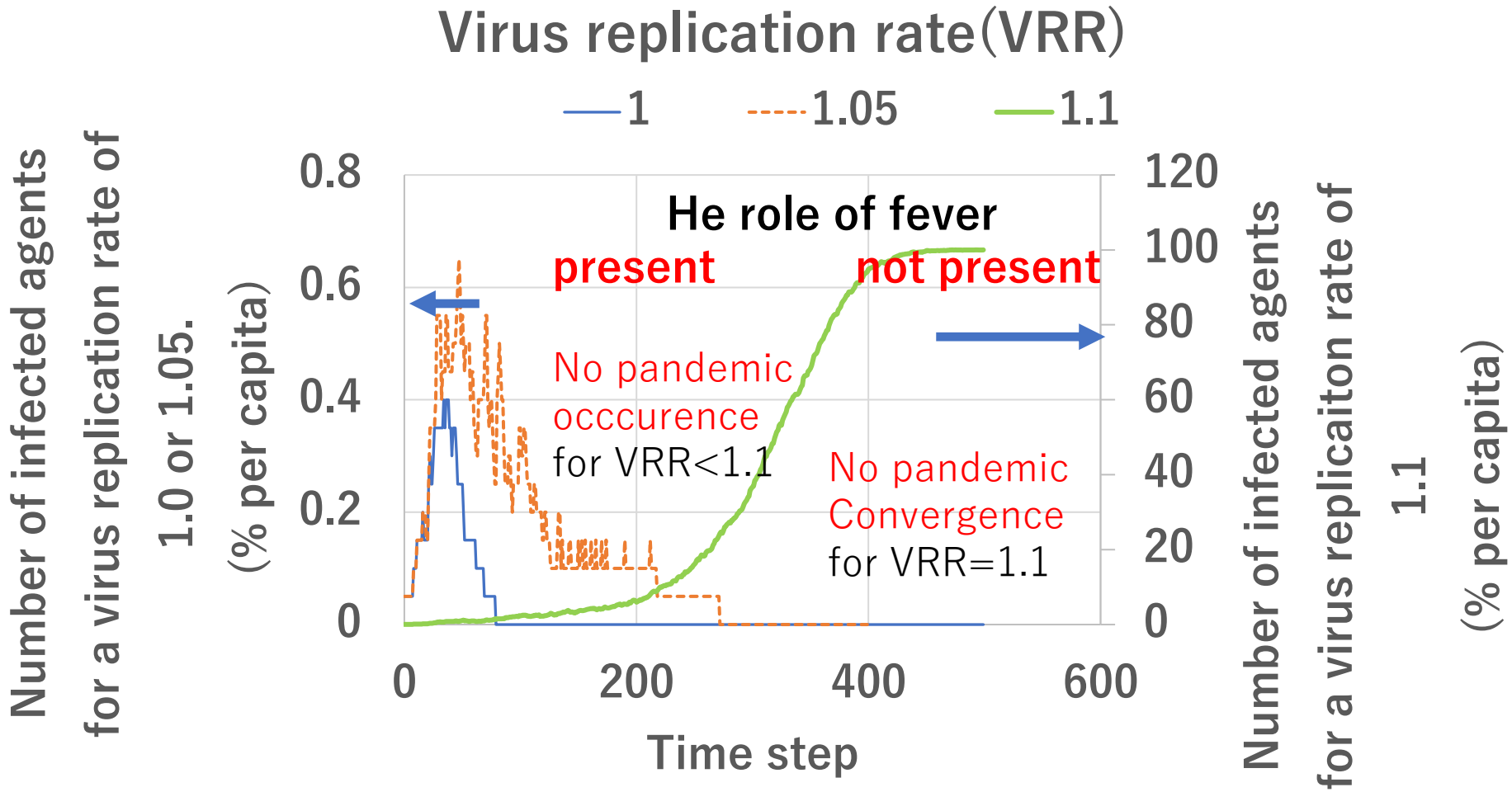
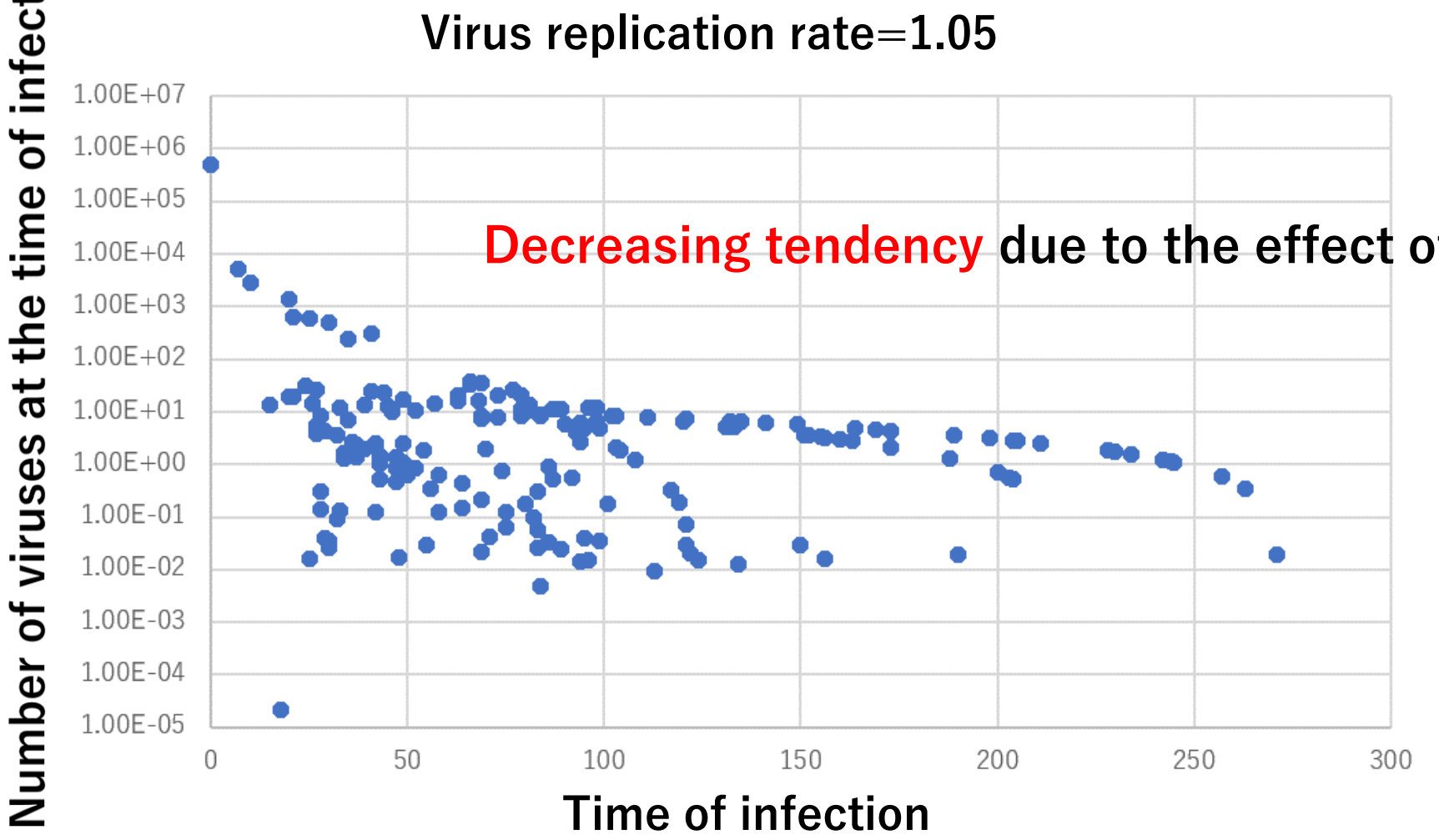


Fig. The behavior of the pandemic when the role of fever is not present.

Virus releasing rate is assumed proportional to the number of viruses

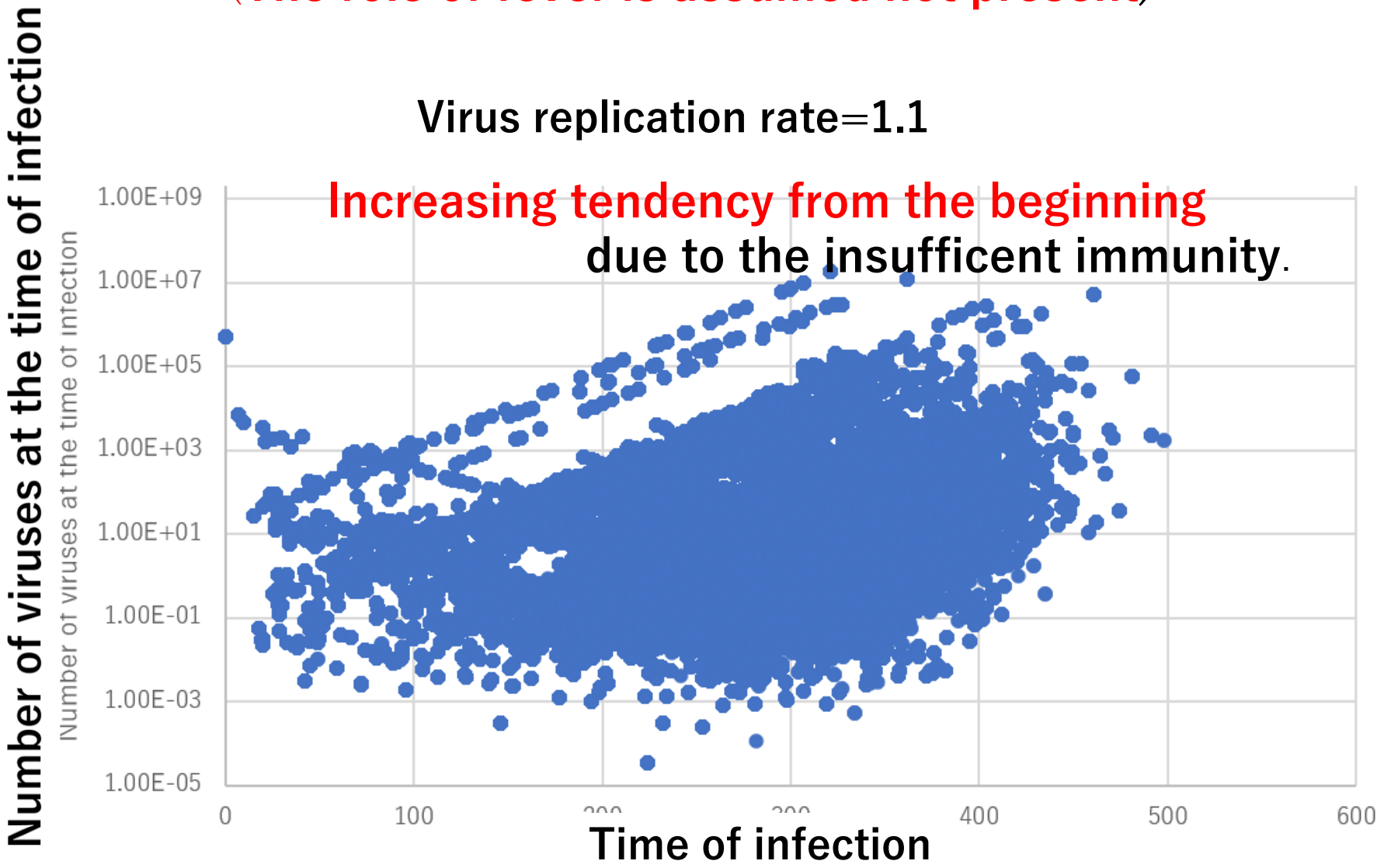
(The role of fever is assumed present)



Decreasing tendency due to the effect of immunity.

Virus releasing rate is assumed constant.
(The role of fever is assumed not present)

Virus replication rate=1.1



4. Discussions

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 converge 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 reproduced,, i.e. the pandemic never converges or never occur, depending on the certain limit of virus replication rate.

5) The role of antibody is increasing 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 .**