

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

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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.

$$t - t_{infected}^i > t_{antibody_emerging}^i \quad \text{and} \quad N_{VP}^i(t) > N_{VP}^i(t_{infected}^i) * Multiple_{antibody_emergence}^i \quad (3)$$

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

$t_{antibody_emerging}^i$: Elapsed period for antibody emergence of agent i after infection

$Multiple_{antibody_emergence}^i$: 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.

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

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

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 viruses 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 dimensional space | defined at every step for each agent |
| Distance of agent's move | $[0, \text{maximum distance}]$ uniform random number |
| Direction of agent's move | $[0, 2\pi]$ uniform random number |
| Agent as an object in the neighbour | defined at every step 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.

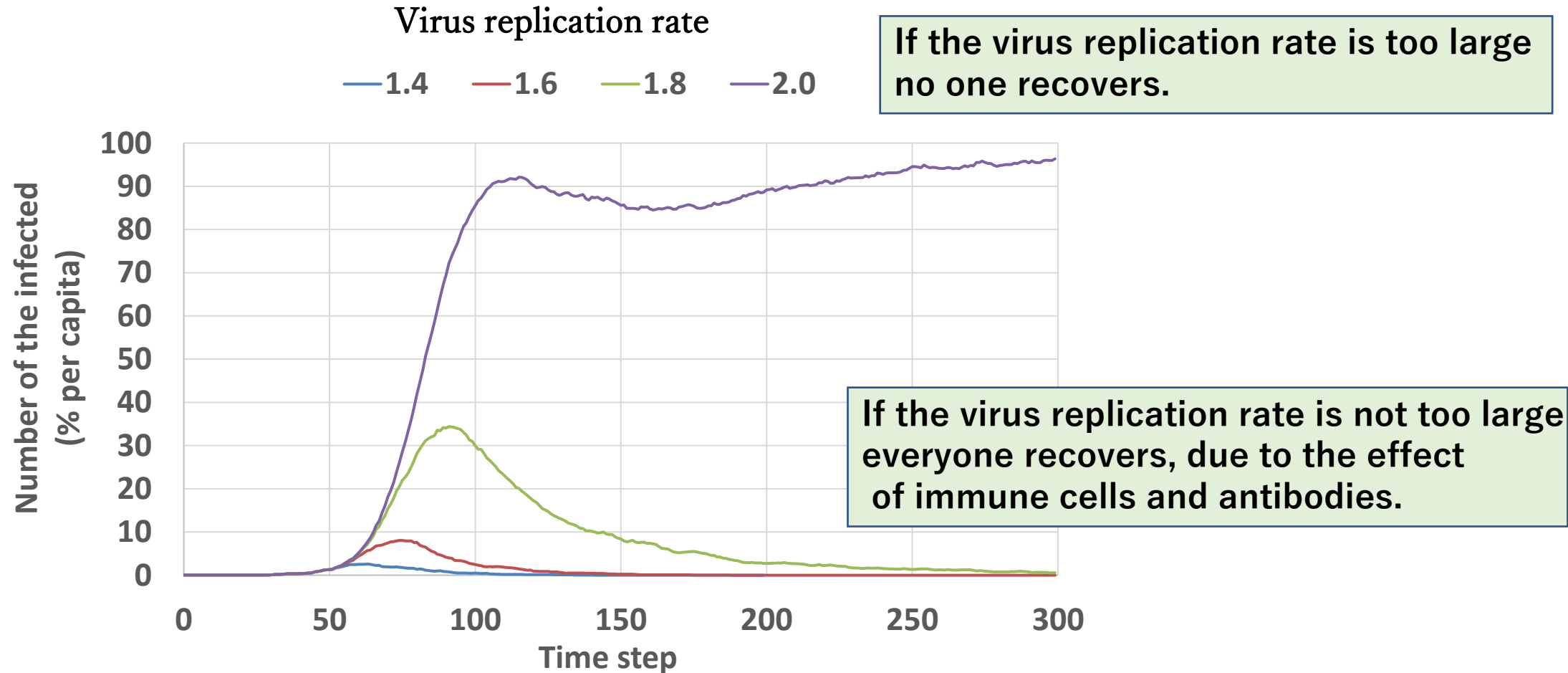
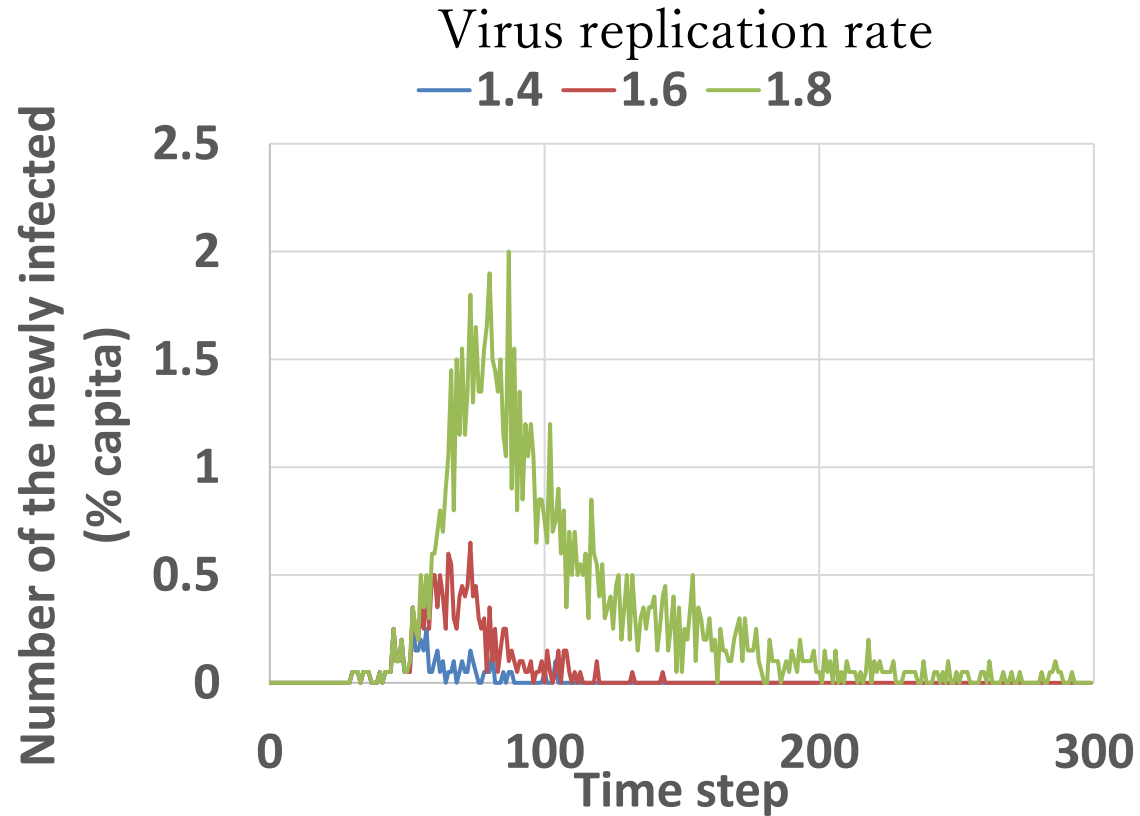


Fig. Effect of the virus replication rate on the number of infected agents.

Newly infected agents



Newly recovered agents

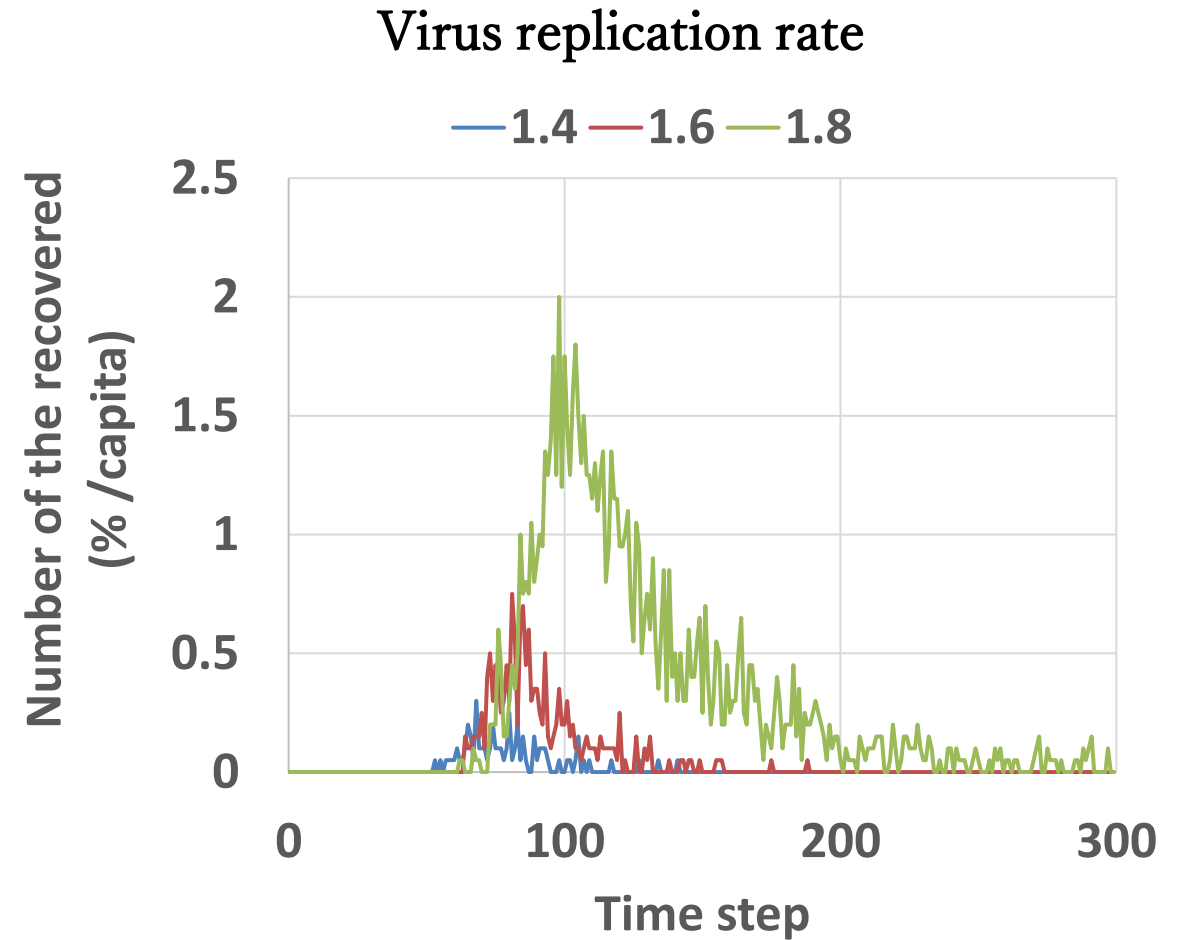


Fig. Effect of virus replication rate on the number of newly infected agents. And the number of newly recovered agents.

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

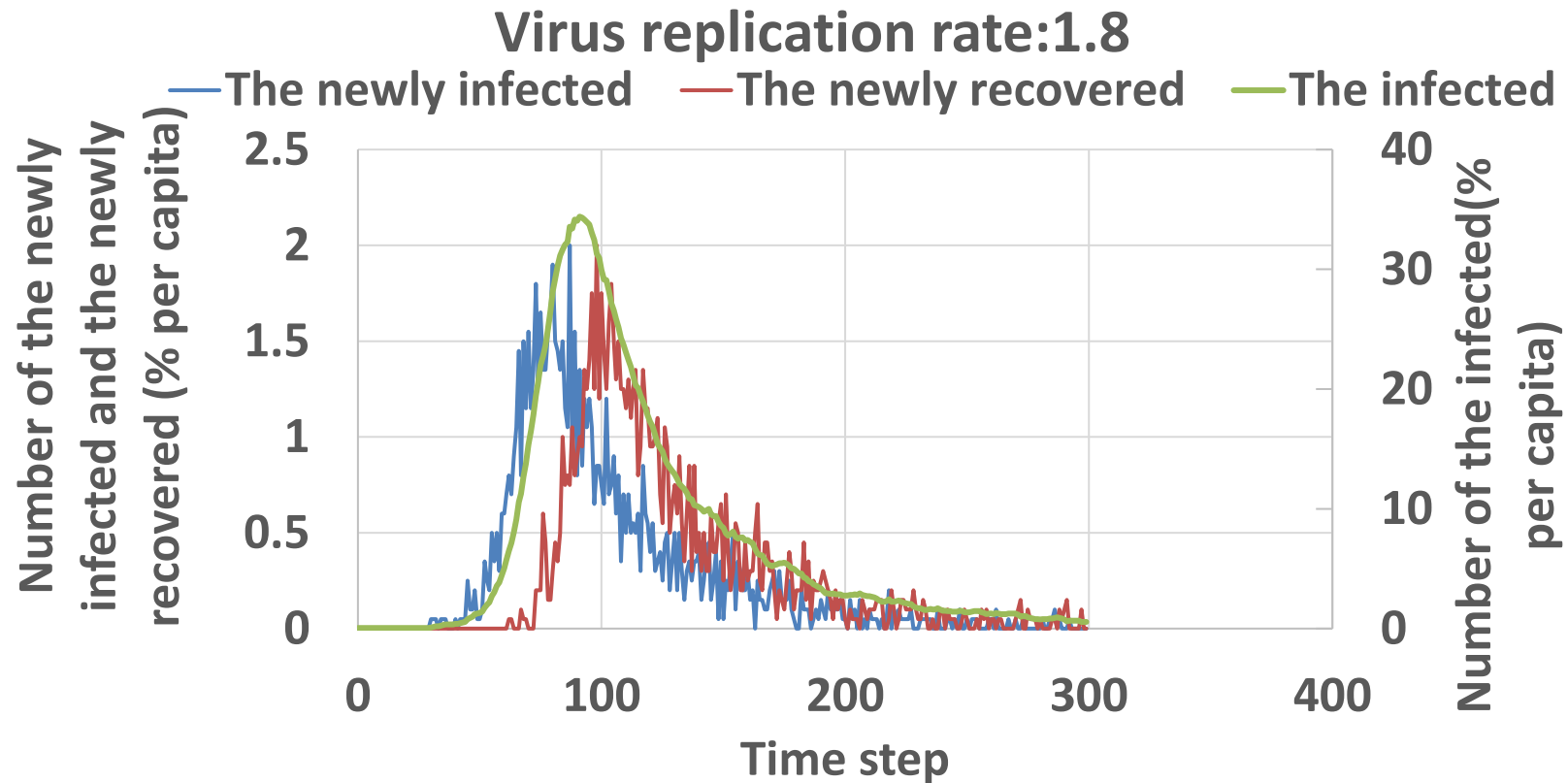


Fig. Changes in the numbers of newly infected, newly recovered, and total infected agents.

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

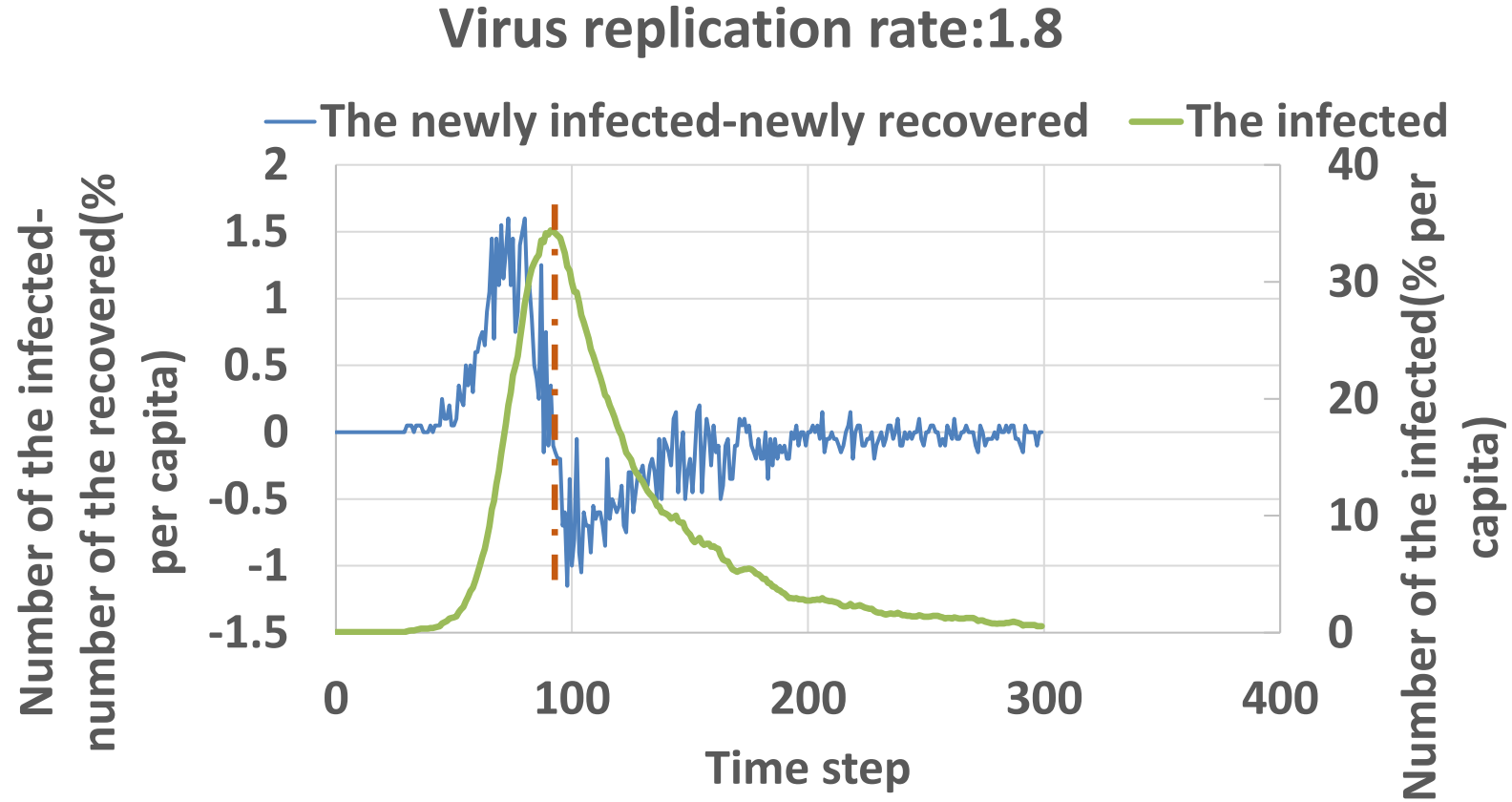


Fig. Change in the total number of infected agents and the difference between the numbers of newly infected and newly recovered agents.

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

Newly Infected vs. Newly Recovered in Japan

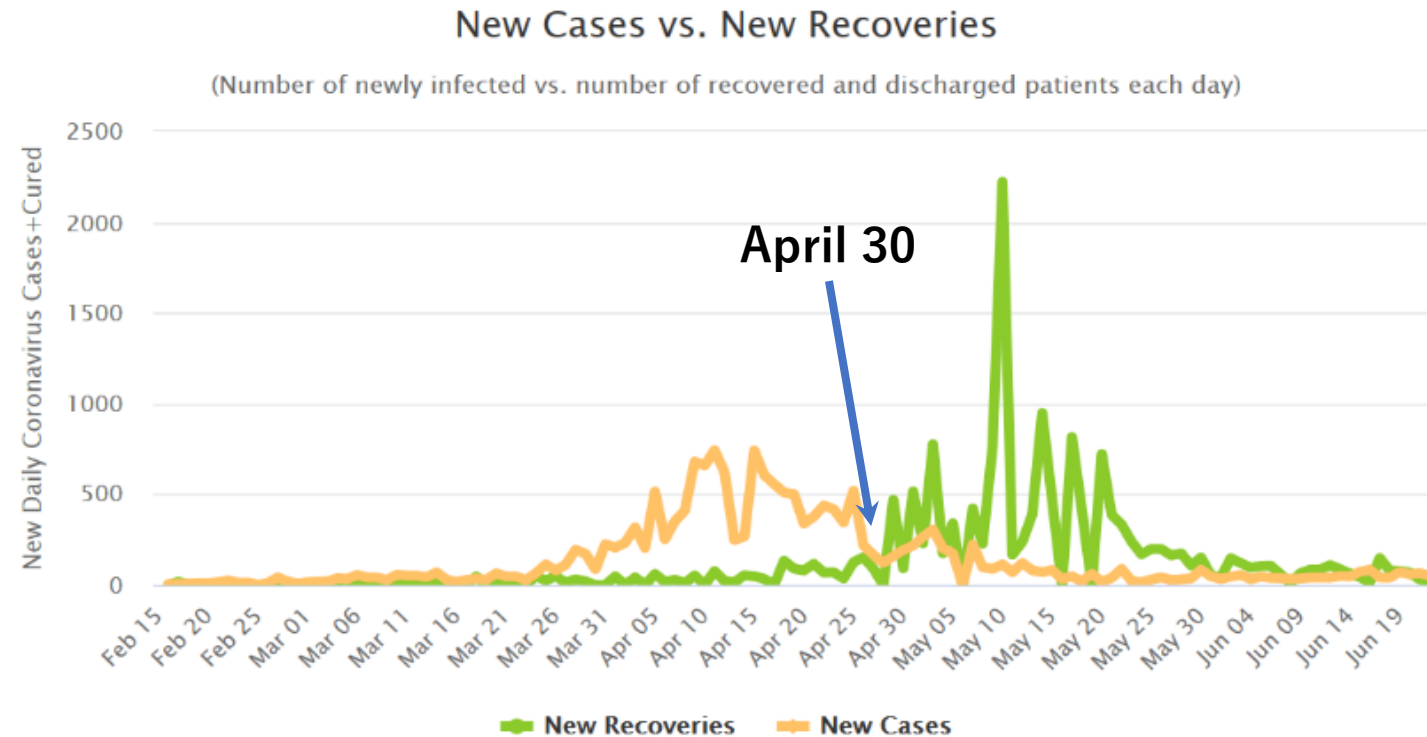


Figure 17. Changes in the numbers of newly infected and recovered people in Japan as of June 20, 2020.¹⁷⁾

Active Cases in Japan

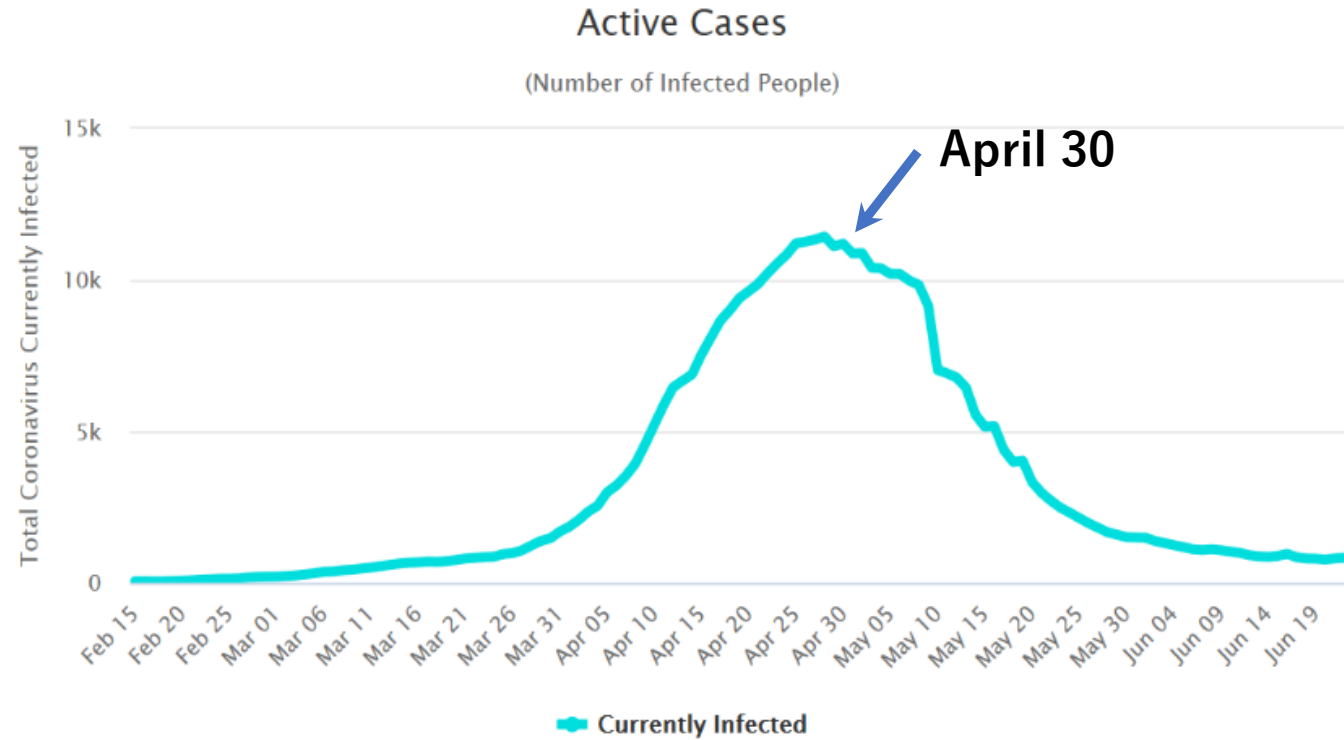


Fig. 18 Change in the number of currently infected people in Japan as of June 20, 2020¹⁷⁾.

3.2 Mechanism of the pandemic convergence.

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

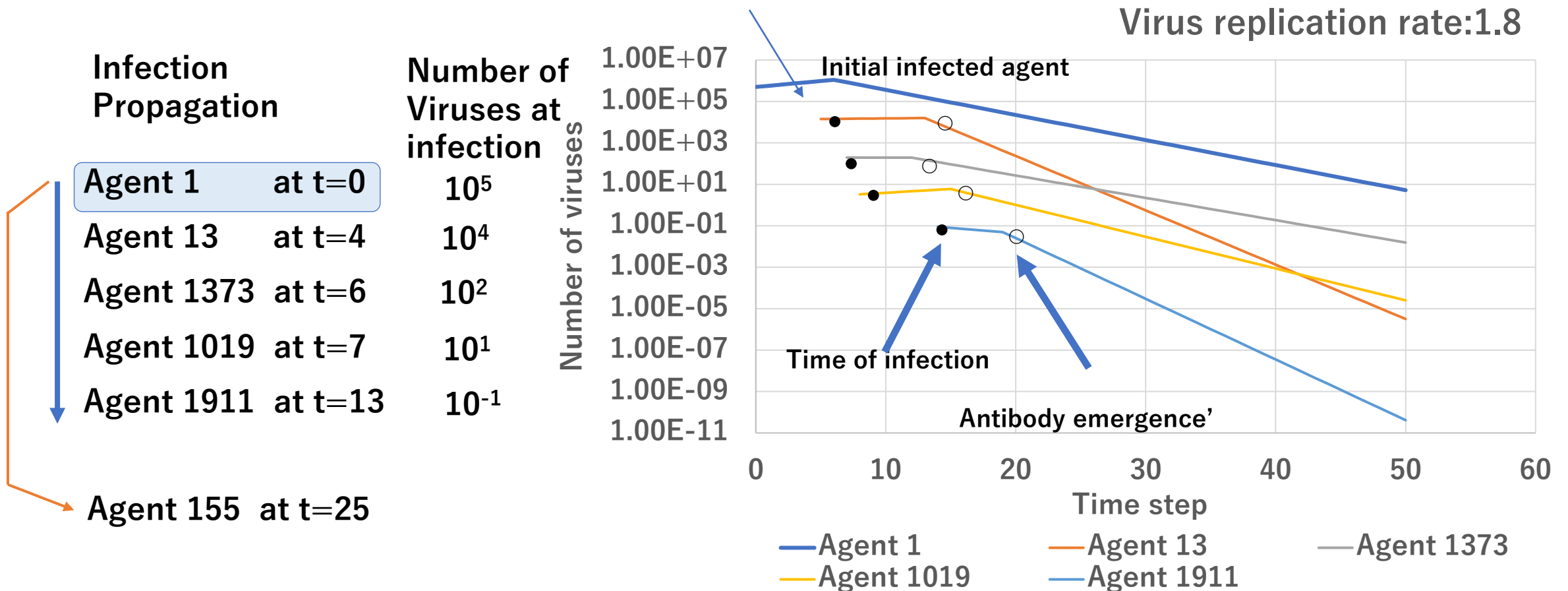


Fig. Change in the number of viruses of each agent during the beginning of infection spread.

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

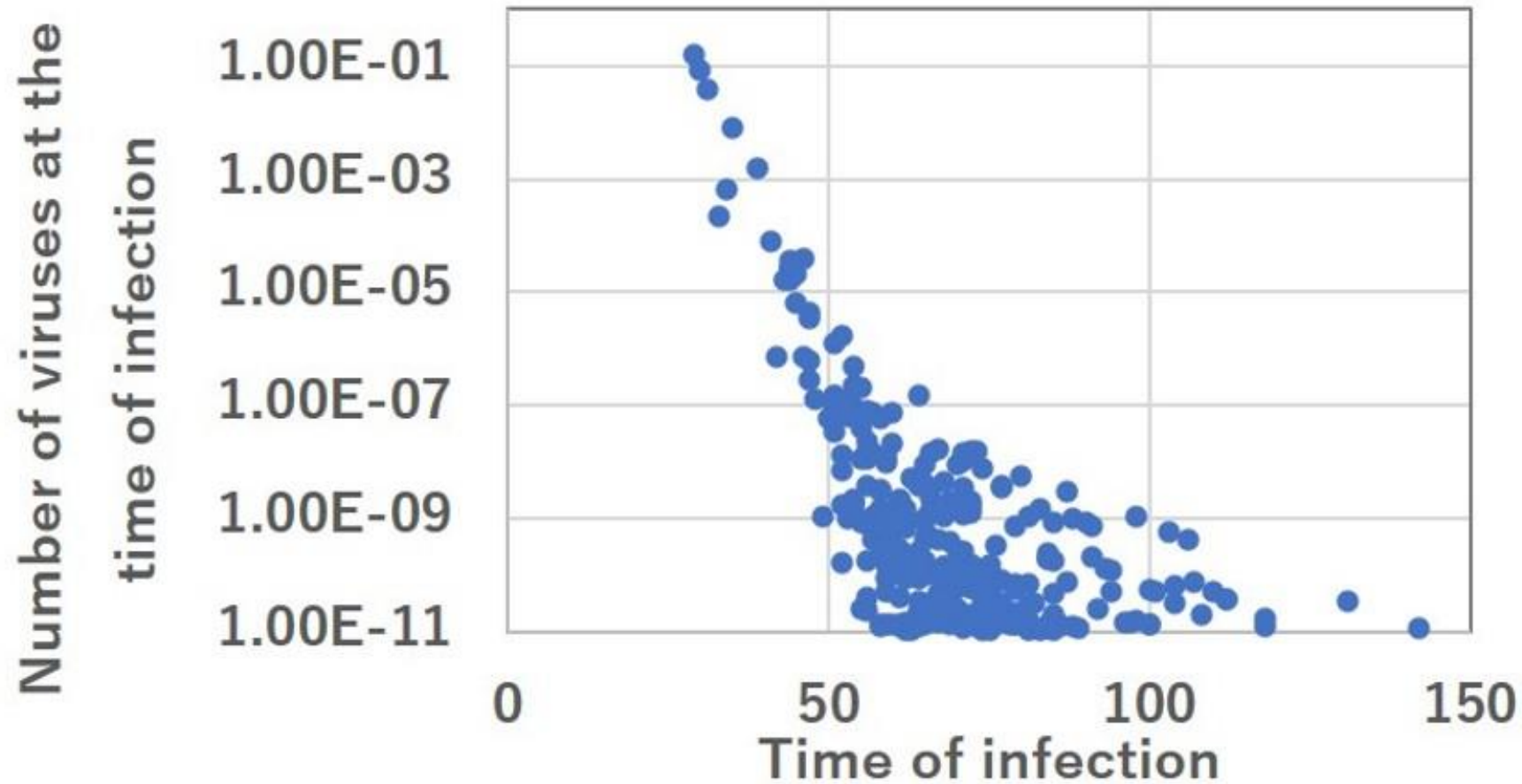


Fig. Change in the number of viruses at the time of infection during infection spread and convergence.

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

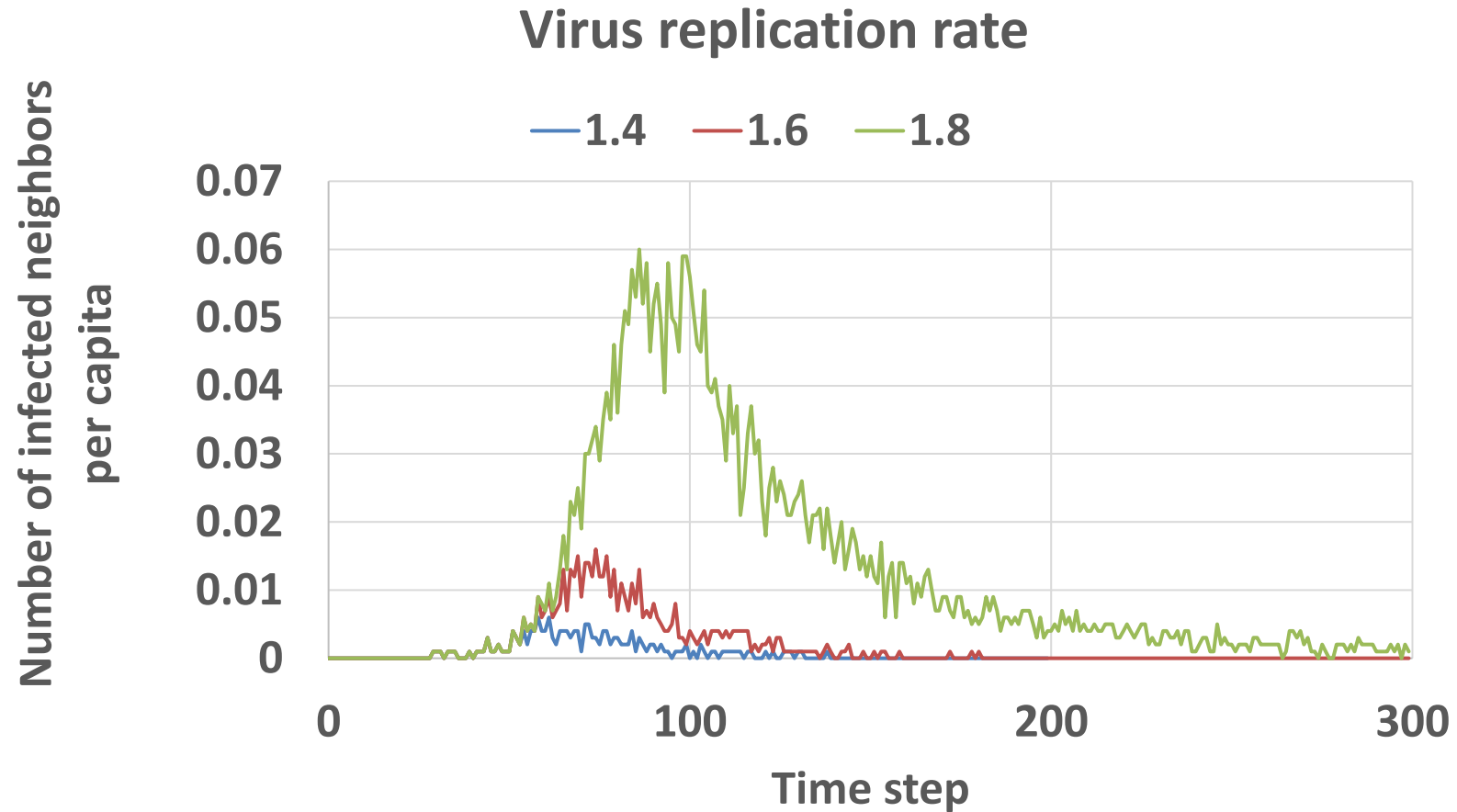


Fig. Effect of virus replication rate on the average number of infected neighbors.

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

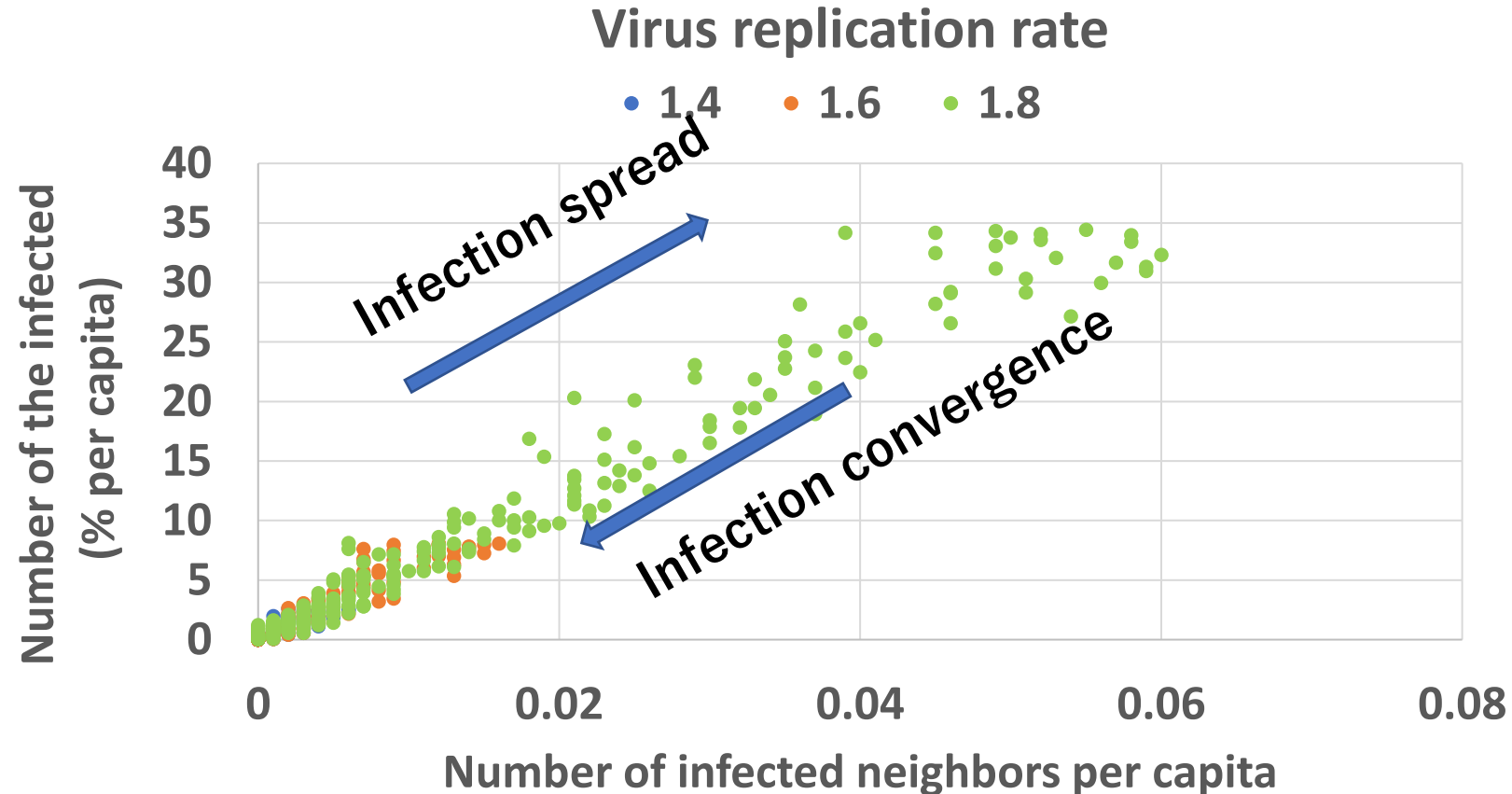
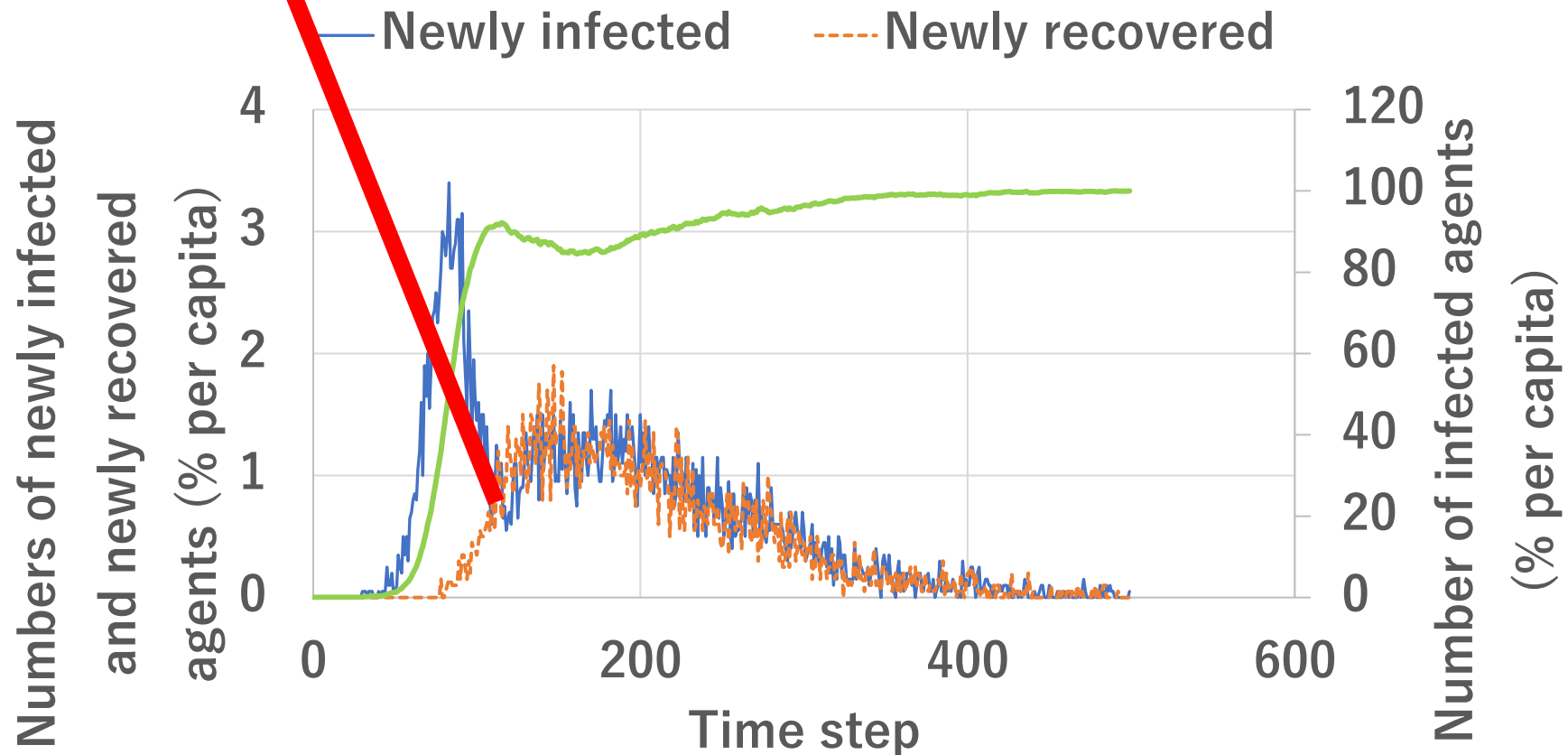


Fig. Relationship between the number of infected agents and the average number of infected neighbors.

3.3 Mechanism that the pandemic does not converge. The behavior of Infection spread and recovery when the pandemic dose not converge.

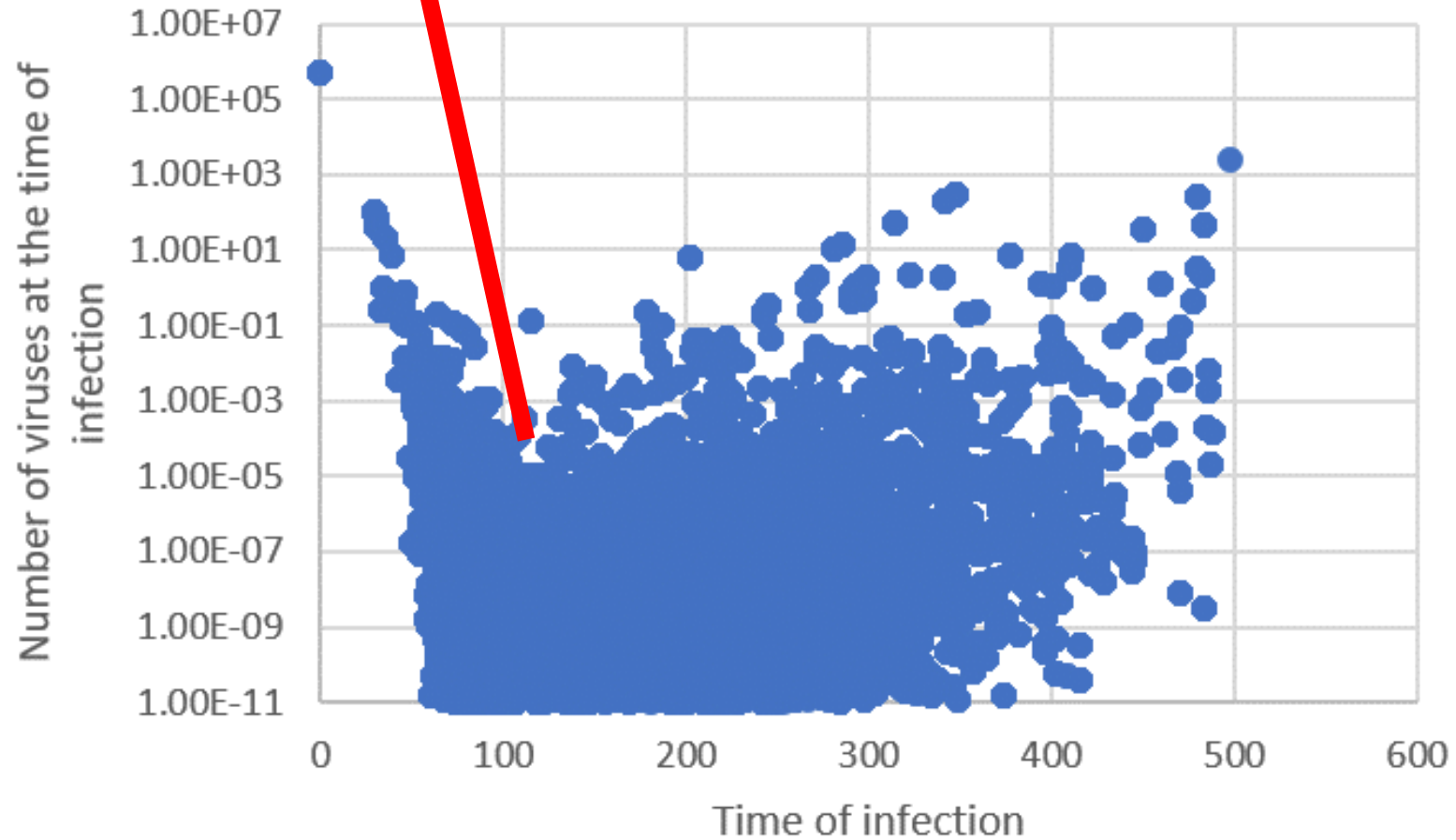
Agent with weak immunity was infected |



Virus replication rate 2.0

Agent with weak immunity was infected |

Virus replication rate 2.0



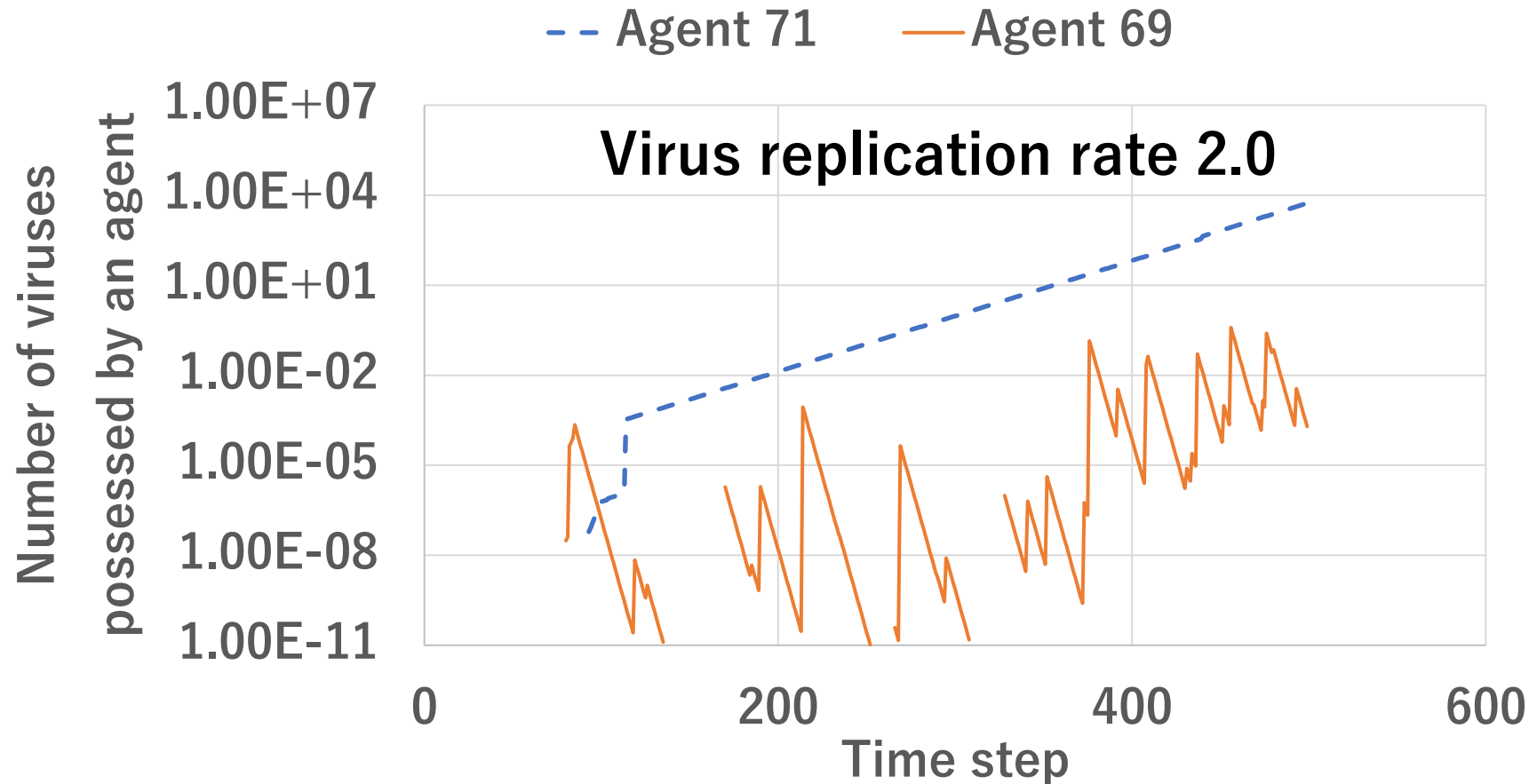
Agent71: effect of immunity < effect of virus replication

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.



3.4 Effect of countermeasures on the pandemic behavior.

3.3.1 Regulation of the movement

It is effective thorough out the whole stage of pandemic.

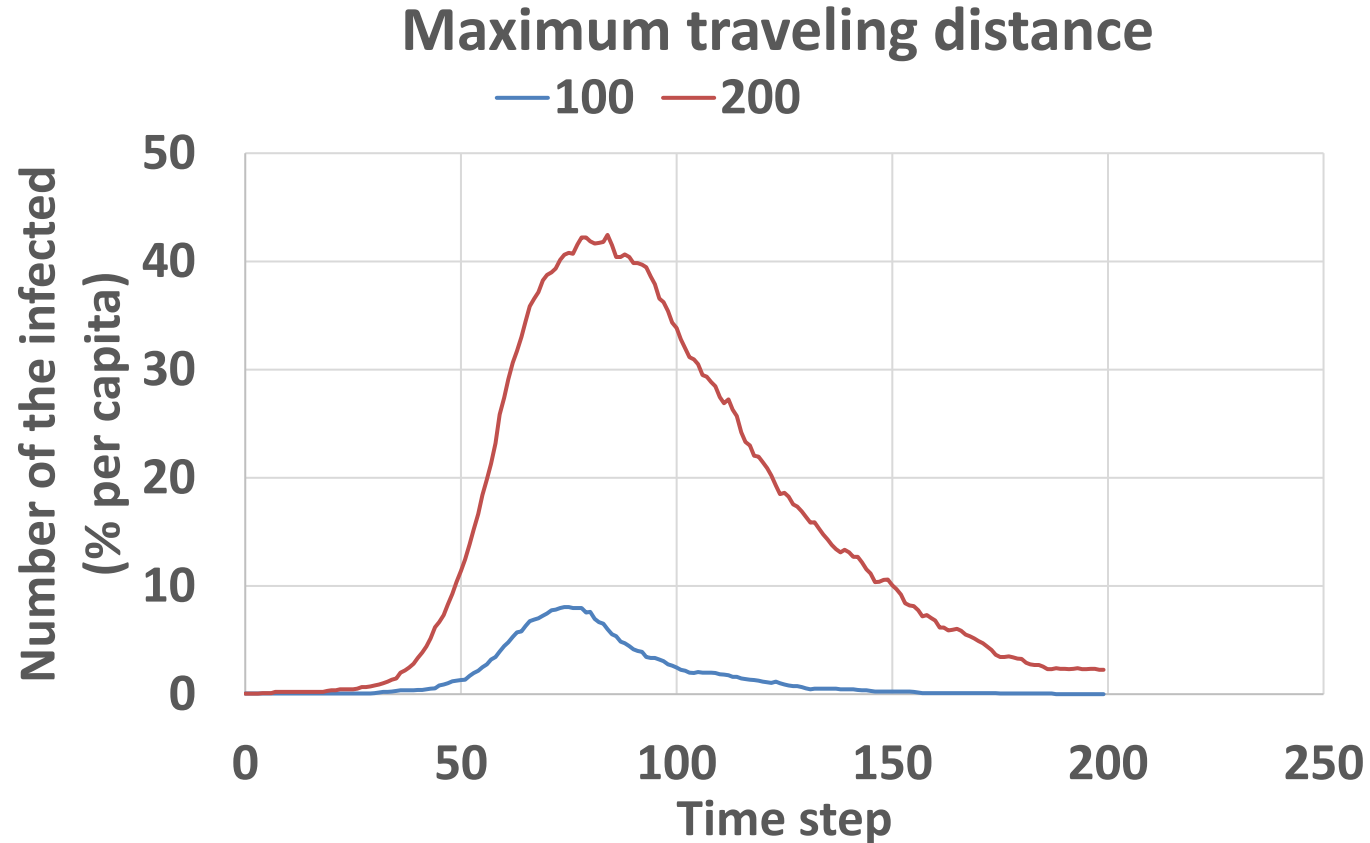
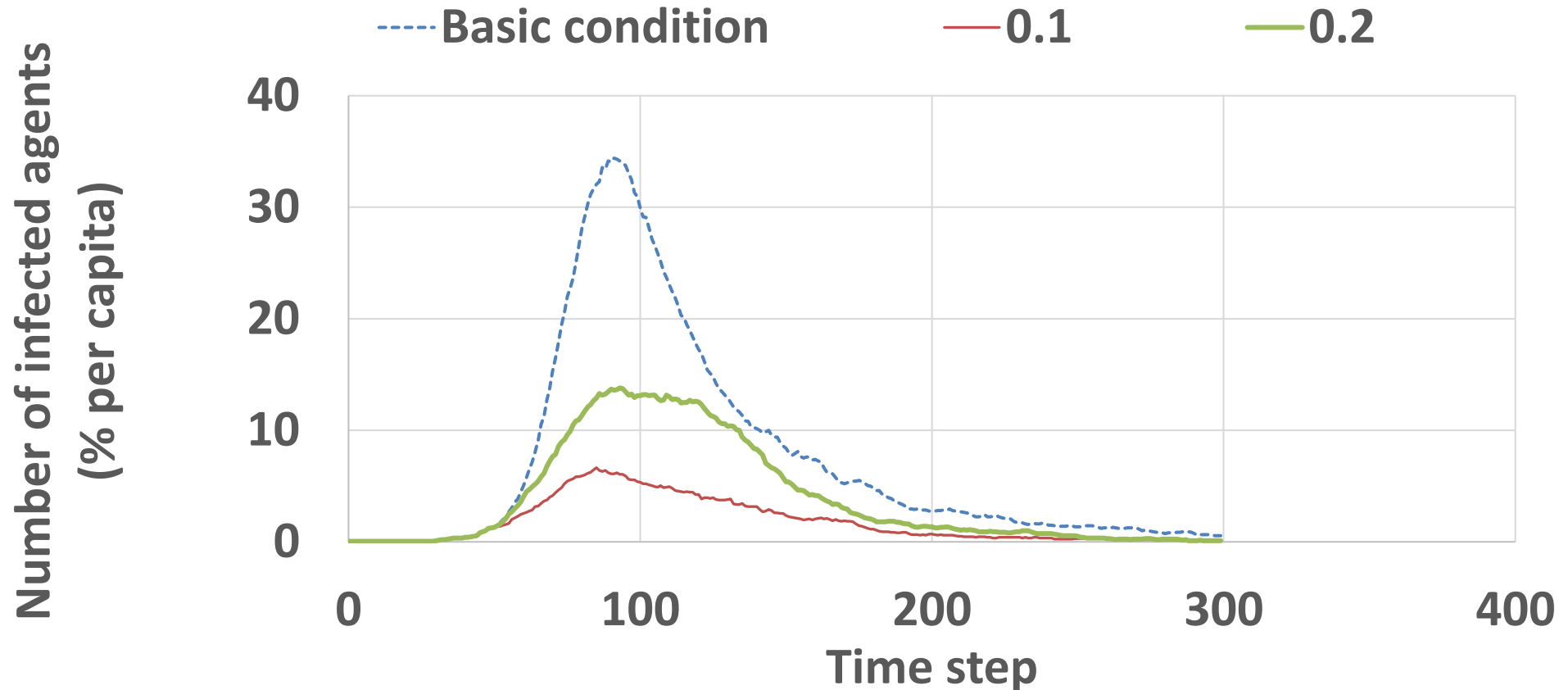


Fig. Effect of the maximum traveling distance on the total number of infected agents (virus replication rate: 1.6).

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.

Max. distance traveled multiple during $t=50-100$



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.

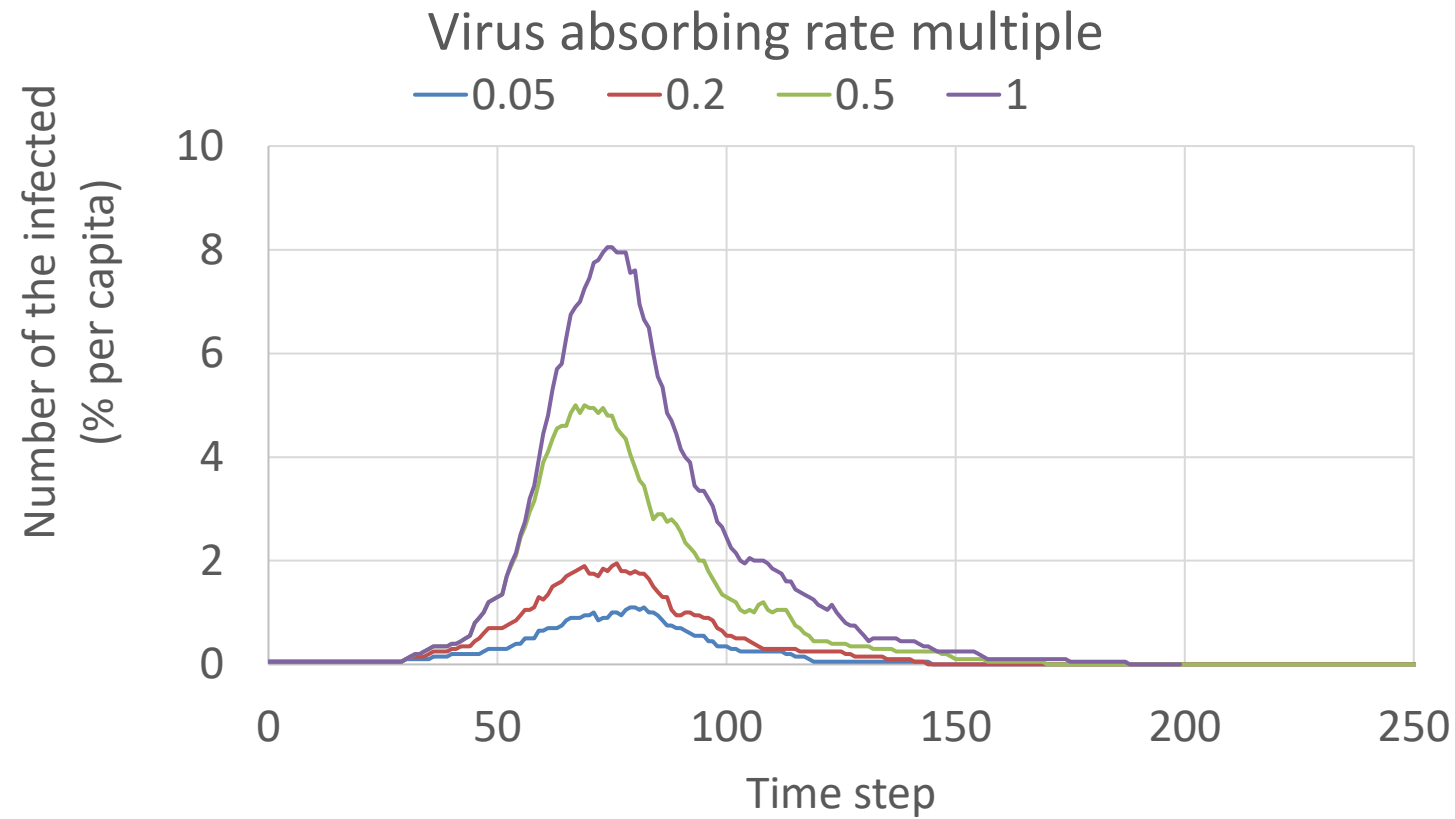


Fig. 16 Effect of the virus absorbing rate on the number of infected agents.

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.

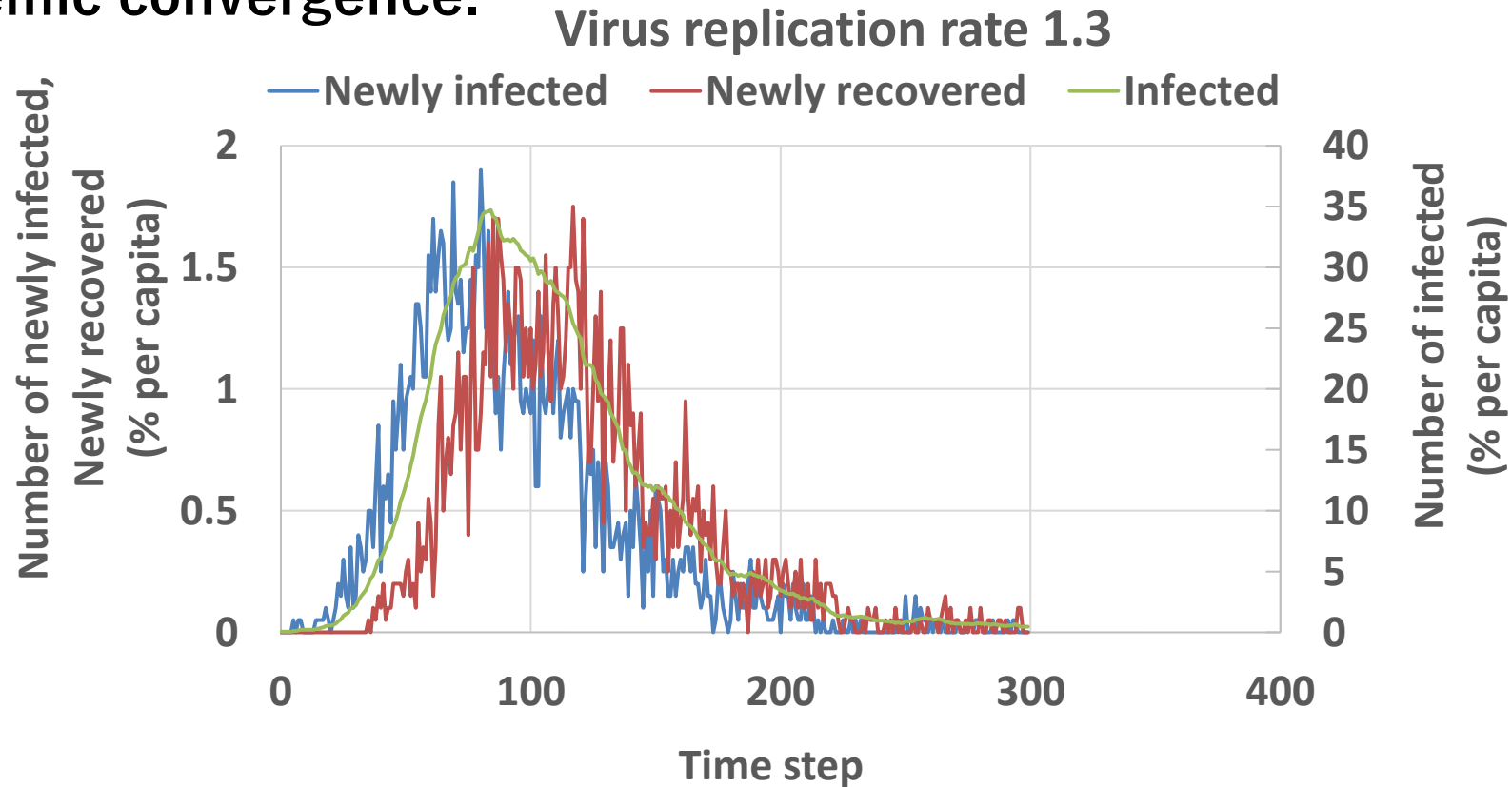
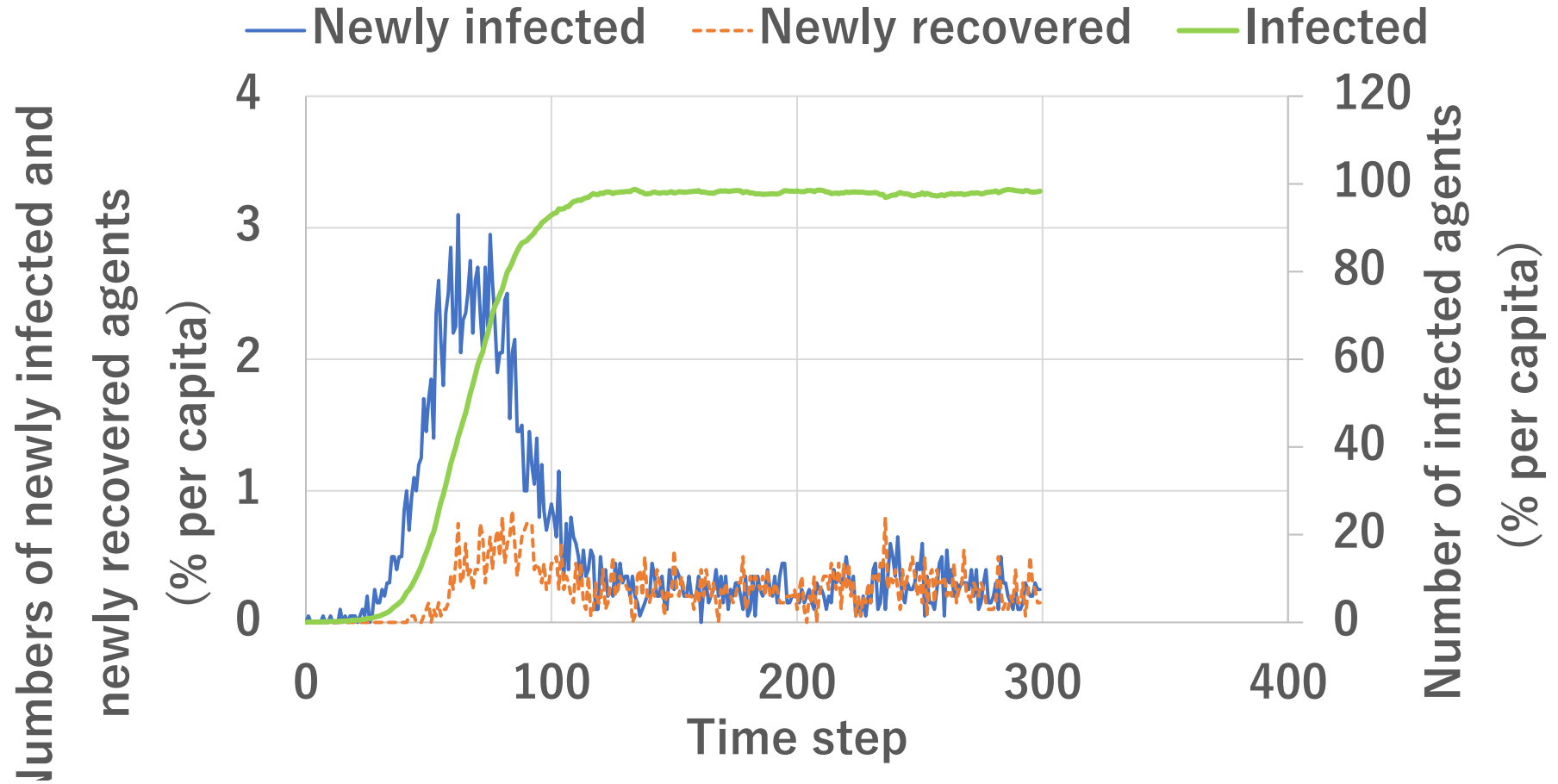


Fig. 27 An example of the calculated numbers of newly infected, newly recovered, and total infected agents in the case without antibodies.

Virus replication rate: 1.4



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.

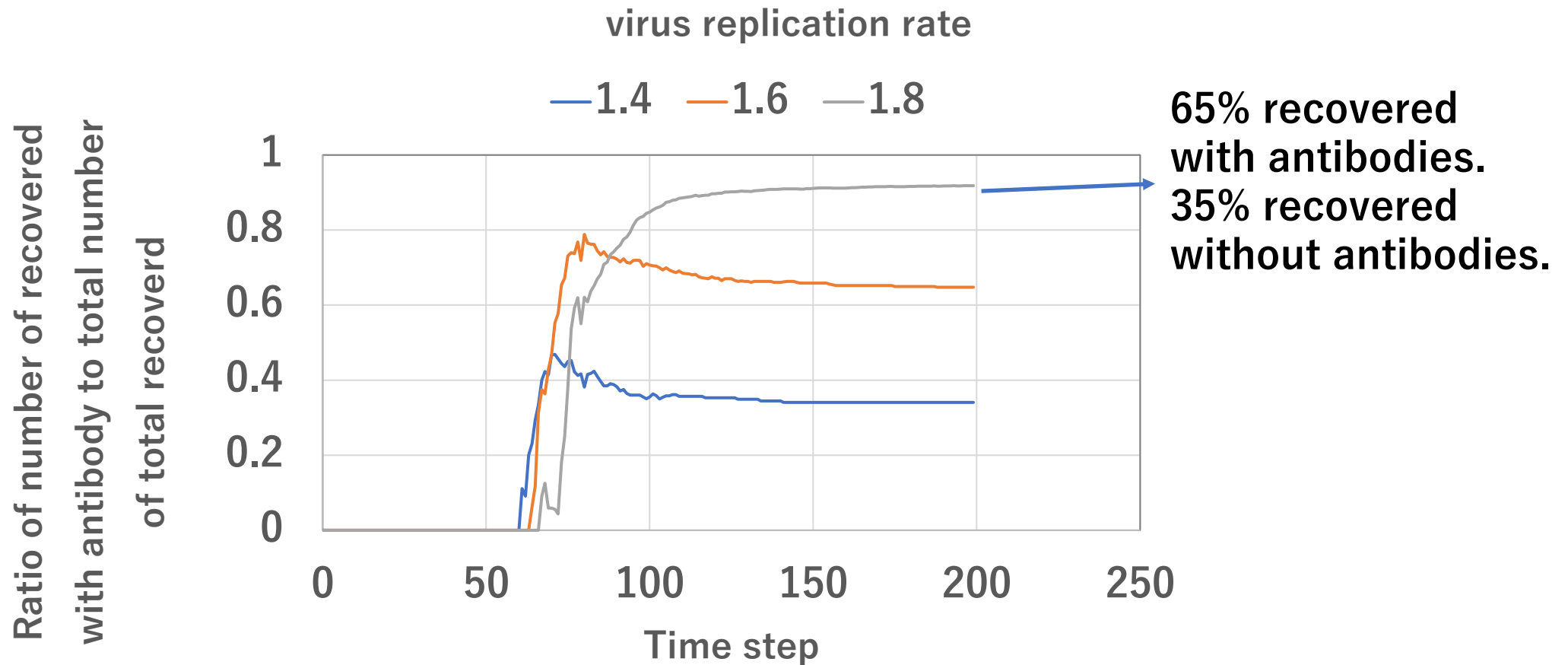


Fig. Effect of virus replication rate on the ratio of the number of recovered agents with antibodies to the total number of recovered agents.

3.6 Effect of the role of fever on the pandemic behavior

What happens if 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**”.)

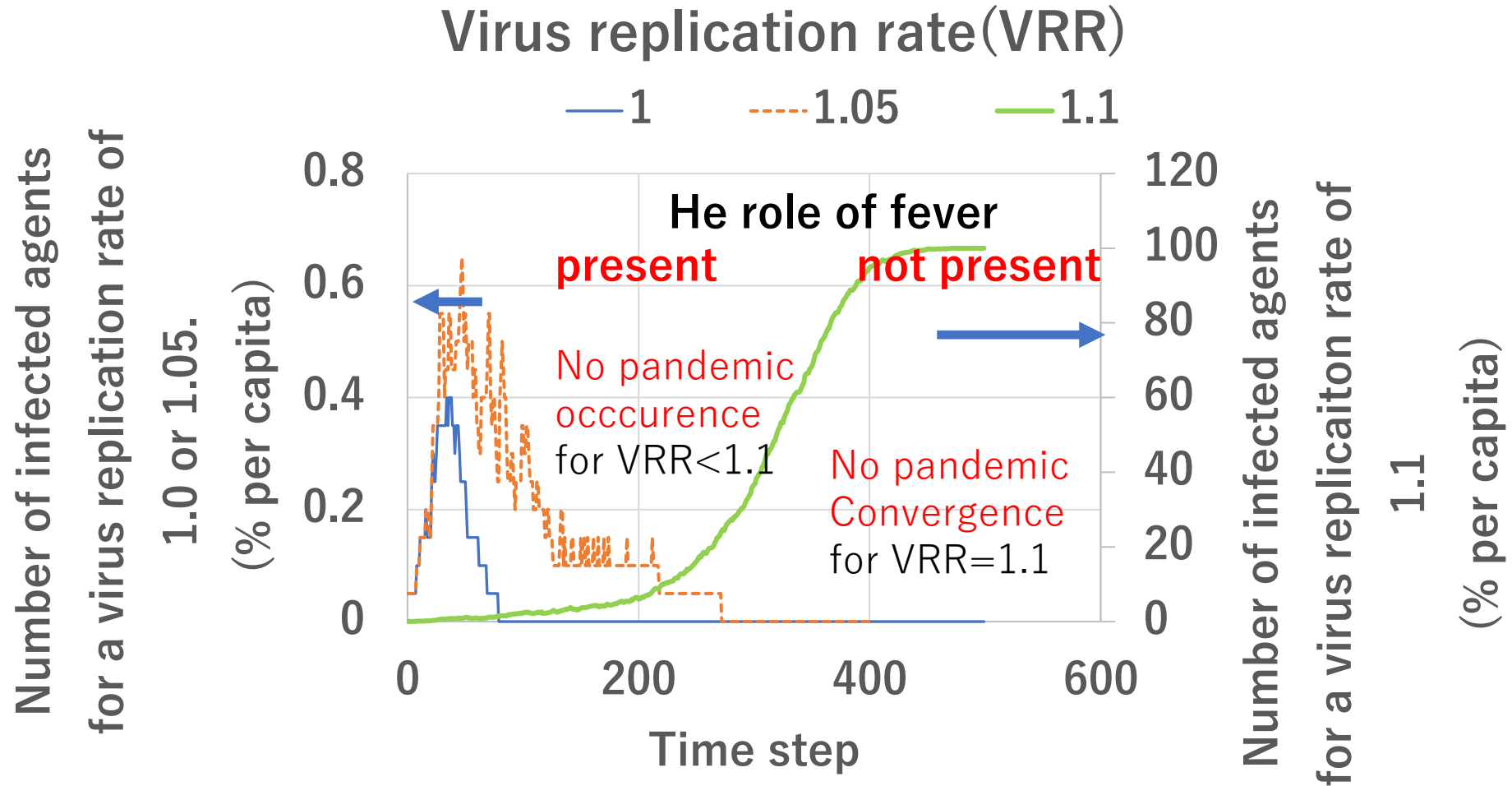
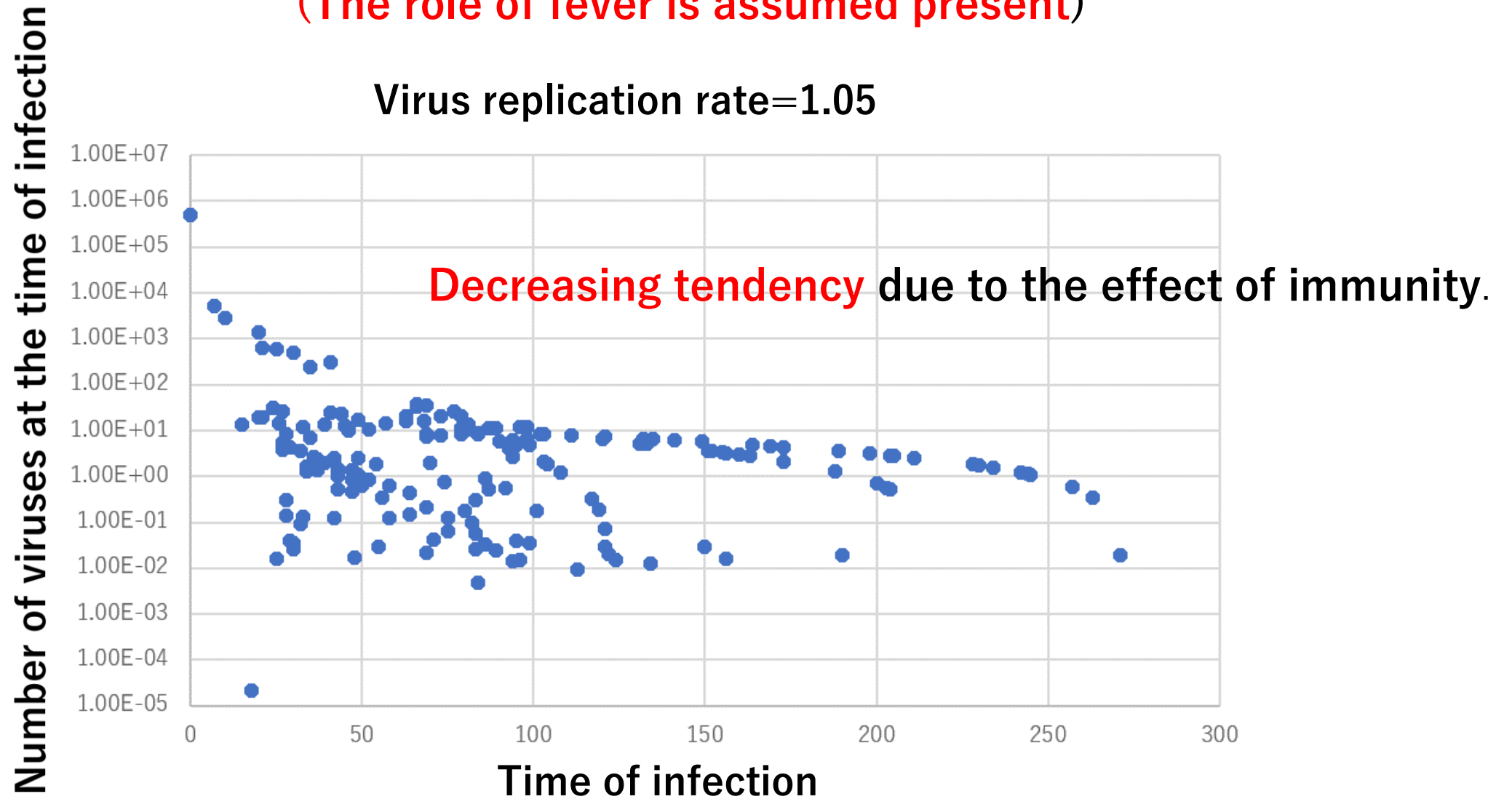


Fig. The behavior of the pandemic when the role of fever is not present.

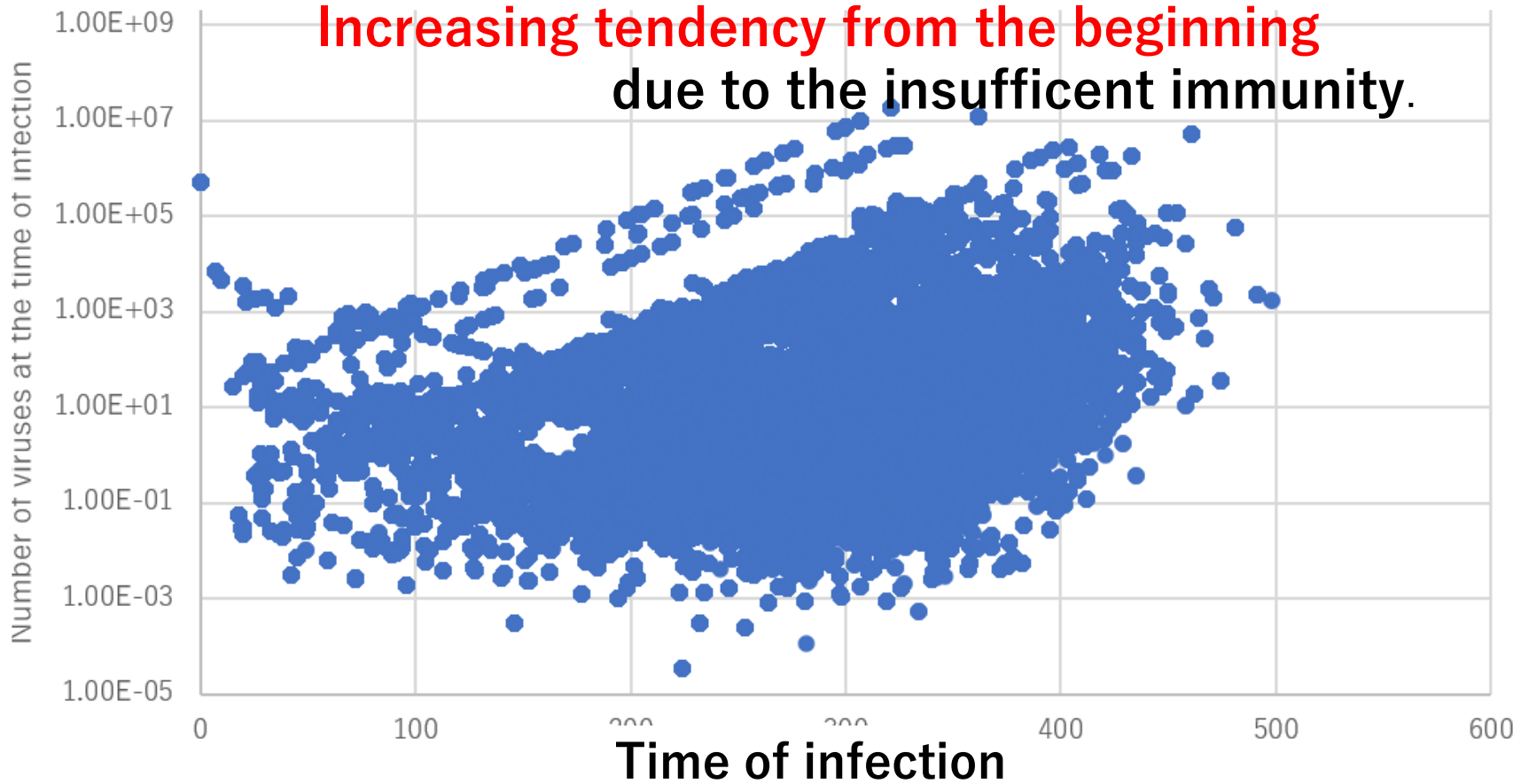
Virus releasing rate is assumed proportional to the number of viruses
(The role of fever is assumed present)



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

Virus replication rate=1.1

Number of viruses at the time of infection



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 be 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 severely infected individuals or refuse their entry at the national border or at the commercial 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 movement on the basis 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.⁸⁰

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 mechanisms of the pandemic occurrence and convergence were elucidated, based on which countermeasures are proposed which are considered effective.**
- 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.**
- 5) I hope this methodology will help understanding the causal mechanism of various phenomena .**

3.3 Temporal regulation of movement followed by temporal mitigation

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

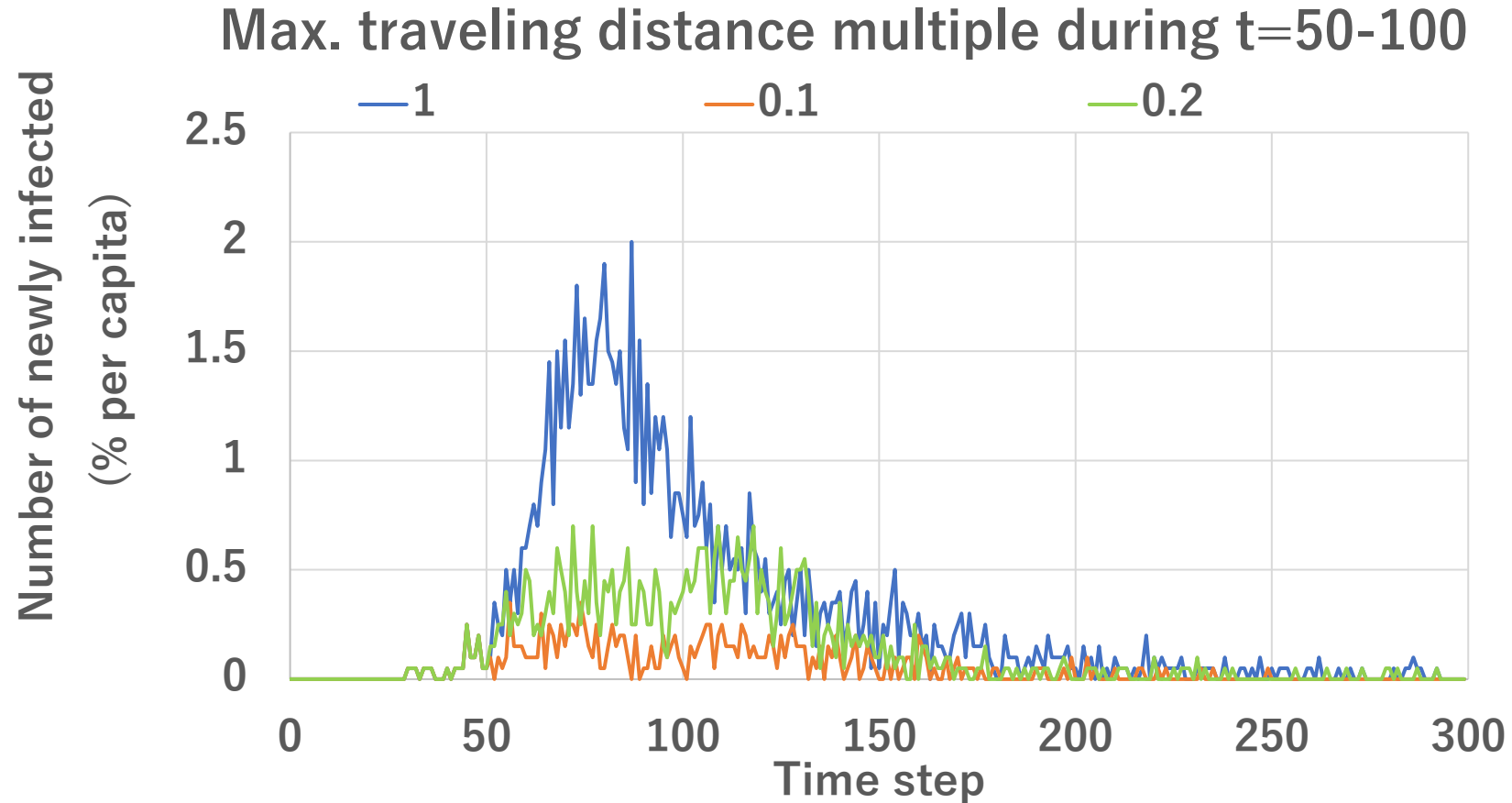


Fig. Effect of temporary regulation of traveling distance and its release on the number of infected neighbors (virus growth rate: 1.8).

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.

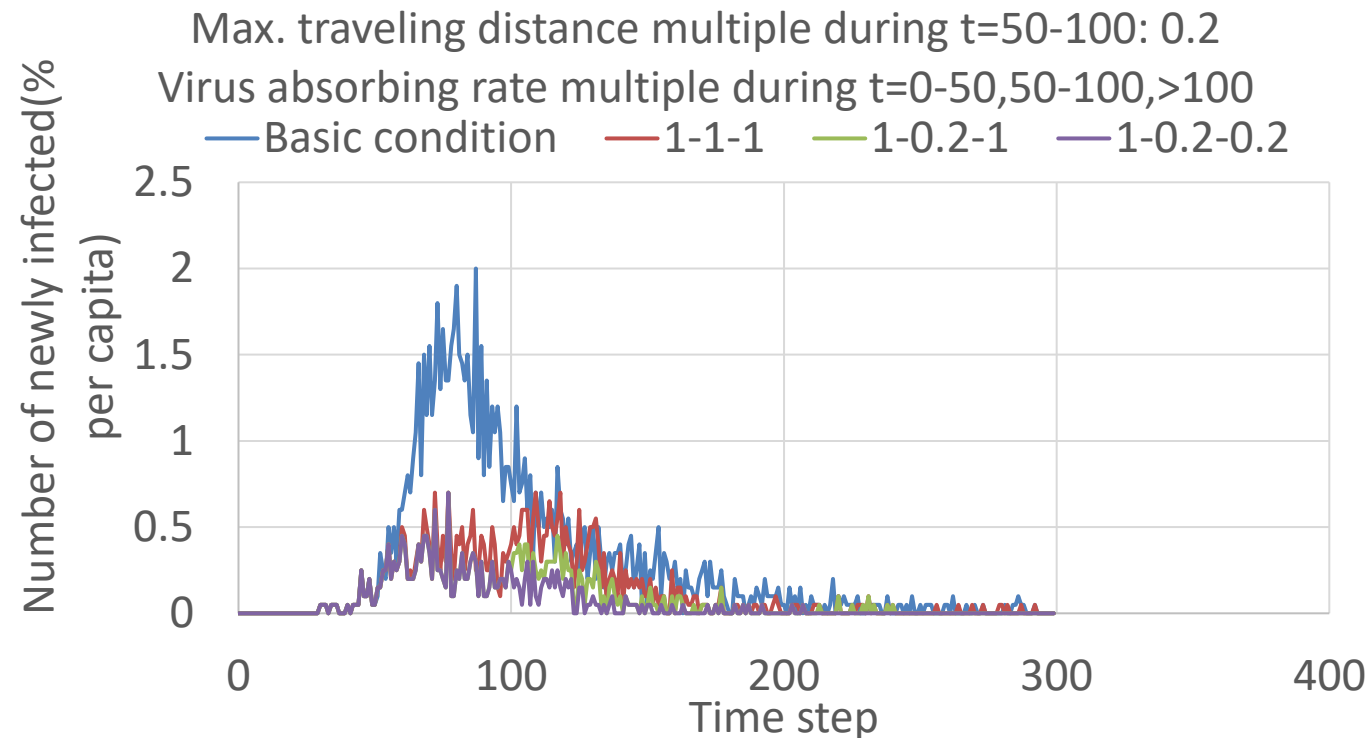
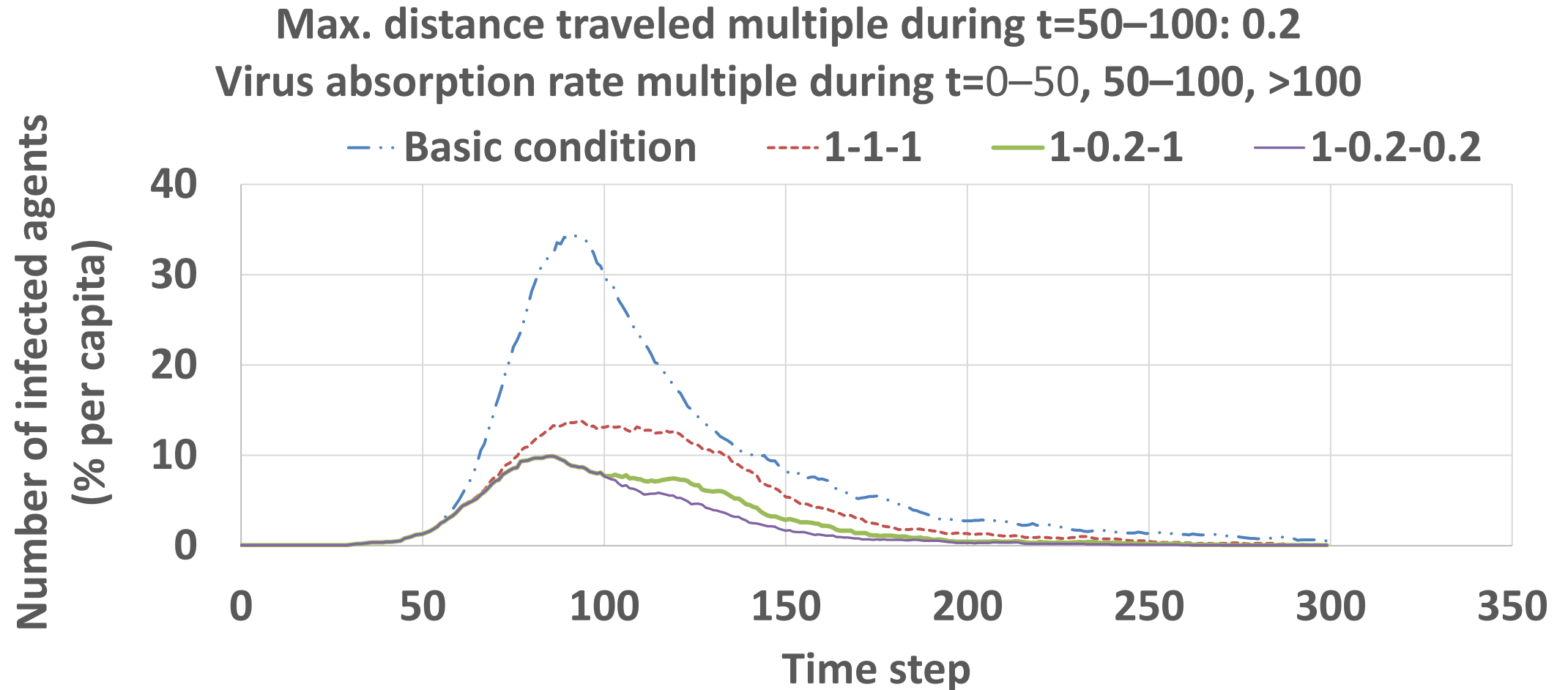


Fig. 24. Effect of the virus absorbing rate on the number of newly infected agents when movement regulation is applied.

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 wave is not remarkable, if the new infected person does not enter into the system from outside



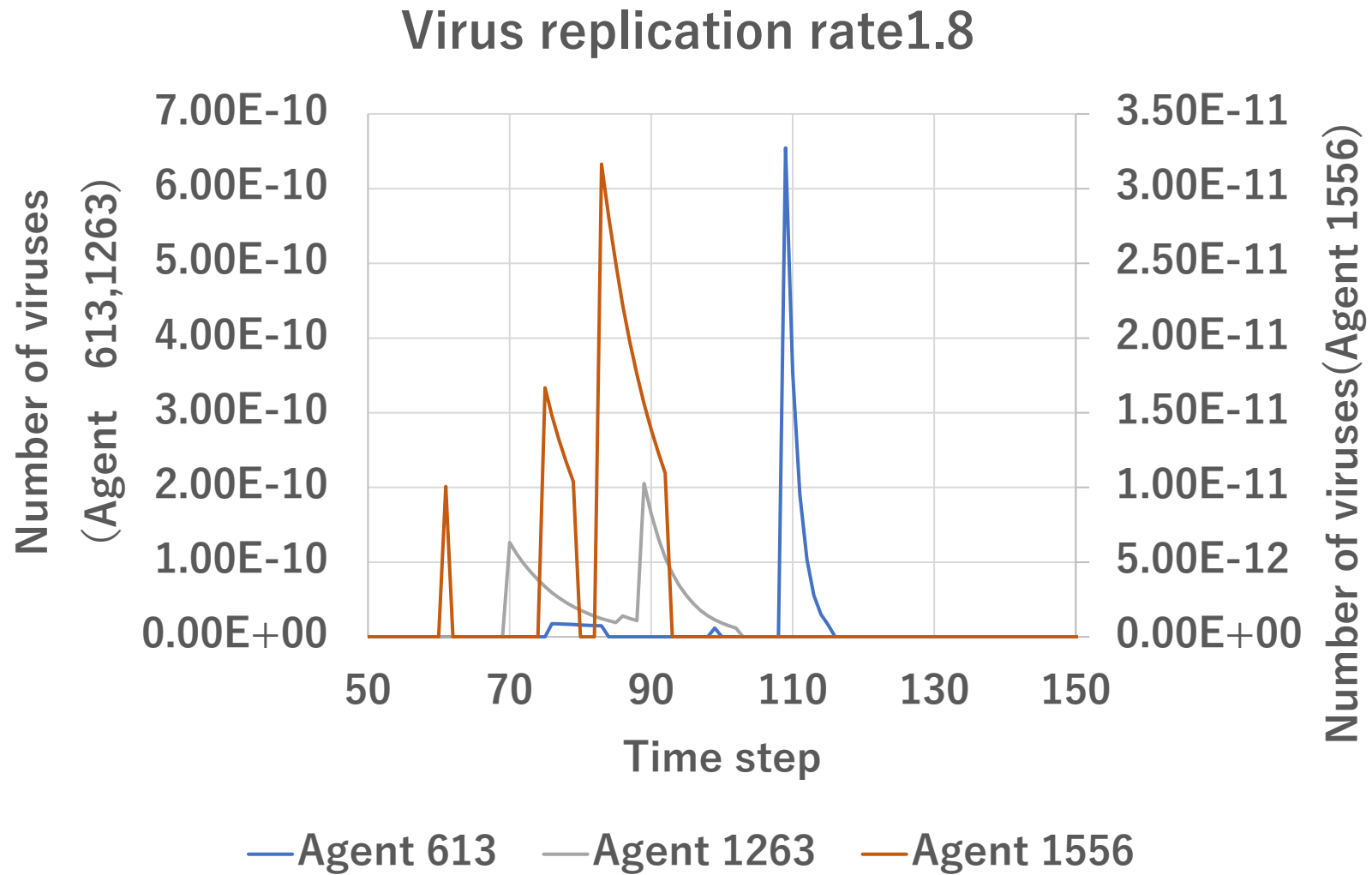


Fig. Examples of cases of multiple infections