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Analysis of the effectiveness of control strategies against bioterrorist smallpox attacks by using Individual Based Model

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We carried out simulations of various scenarios for bioterrorist attacks using smallpox occurring in a virtual area set up on the basis of the census of Okayama-city, Japan, which predict the effect of control strategies against bioterrorism and the loss scale. On simulating a smallpox epidemic, we followed the method of the Individual Based Model stochastically, which can treat the population in the virtual area as individuals. Individuals have personal information, behavior patterns, and interactions among social groups. We took into consideration the influence of residual immunity due to past vaccination. We considered Traced Vaccination (TV) and Mass Vaccination (MV) strategies against bioterrorism. We investigated the effect of TV and MV strategies on the suppression of smallpox epidemics. Consequently, the TV strategy was found to have higher effectiveness than the MV strategy.

Key words: *smallpox, bioterrorism, Individual Based Model, Traced Vaccination, Mass Vaccination*

1 Introduction

In recent years, a lot of terrorist attacks have occurred around the world. The weapons for the use of bioterror are easily and inexpensively manufactured, so that bioterrorism is regarded as a significant threat. The World Health Organization (WHO) shows smallpox as one of the biological weapons with the highest infectiousness and mortality rate (Center for Disease Control, 2001). WHO declared that smallpox was eradicated from the world in 1980. In Japan, smallpox was eradicated in 1956. Consequently, regular vaccination for smallpox finished in Japan in 1976, therefore the population of non-immune younger people has increased since then (Ministry of Health, Labour and Welfare, 2006). Although it is said that variola (smallpox) virus exists only in laboratories in the USA and Russia, it is predicted that variola virus may escape from these laboratories in the future (Fenner *et al.*, 1988). We carried out simulations of various scenarios for bioterrorist attacks using smallpox occurring in a virtual area set up on the basis of the census of Okayama-city, Japan, which predict the effect of control strategies against bioterrorism and the loss scale.

Fennner *et al.* (1988) reviewed the symptoms and the history of eradication of smallpox. For control strategies against bioterrorism, Kaplan *et al.* (2003) carried out a comparative study among Traced Vaccination (TV) and Mass Vaccination (MV) strategies by a deterministic model. Nishiura *et al.* (2004) investigated the influence of residual immunity on a smallpox epidemic initiated by bioterrorists. Longini *et al.* (2007) analyzed various scenarios in cooperation with historical research resulting in severity based on an Individual Based Model (IBM).

In simulating smallpox epidemics stochastically in this article, we followed the IBM method, which can treat the population as individuals. Every individual has personal information about age, home address, behavior patterns

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such as movement between home and workplace, and interaction among social groups. The course of a smallpox epidemic is simulated by the processes of infection, severity, death, and vaccination of each individual followed from probability distributions (See next section). We considered TV and MV strategies against bioterrorism. TV, which is recommended by the Centers for Disease Control and Prevalence (CDC) in the United States, traces and vaccinates persons who came into contact with patients (Center for Disease Control, 2001). On the other hand, MV doses all persons in a certain area with vaccine irrespective of contact with patients. We also considered the influence of three stage residual immunity due to past vaccination. In Japan, the majority of people born after 1977, between 1970 and 1976, and before 1969 have been vaccinated zero, once, and more than two times, respectively. In this article, we introduce a virtual area where the age structures, the number of social settings, *etc.* are referenced from the census of Okayama-city, Japan. We arranged 10 scenarios with the execution of TV, MV, and both TV and MV simultaneously with three lengths of necessary tracing time for TV, two kinds ranges for MV-blocks, and two kinds of behavior patterns of patients.

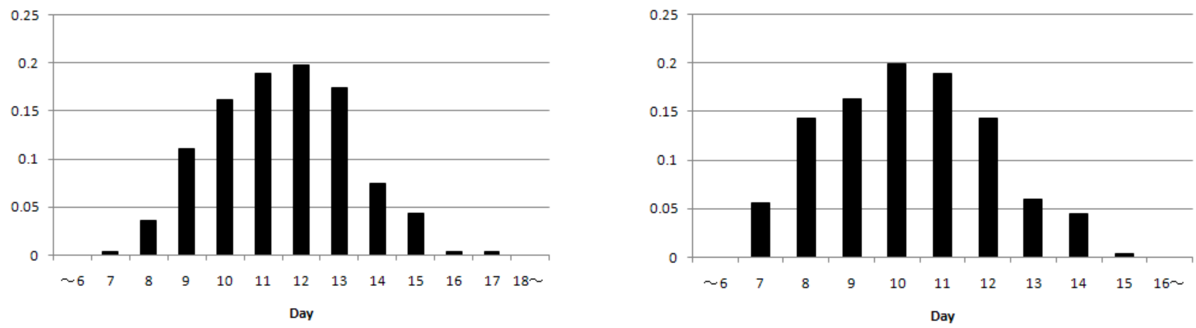
We compared the spread of smallpox epidemics over 10 scenarios for the five index patients introduced at the beginning of each trial with the average number of total infections, deaths, doses of vaccine, and percentage of eradication of the virus within 100 days in 100 simulations. The simulation results showed that the TV strategy reduced the average number of total infections and deaths to 30% and 10% compared with a no-control scenario, and can eradicate the smallpox epidemic within 100 days in all 100 trials. While the MV strategy reduced the average number of total infections and deaths only to 73% and 69% compared with the no-control scenario, and eradicated the outbreak within 100 days in only 59 trials. This result showed a higher effectiveness of the TV strategy on the suppression of a smallpox epidemic caused by a bioterrorist attack.

2 Materials and Methods

2.1 Natural history of smallpox

The progression stages of smallpox are separated into five stages, which are, susceptible, incubation, fever, rash, and recover, according to the symptoms (Fenner *et al.*, 1988). The patients of smallpox are classified into three types: ordinary, modified, and hemorrhagic, according to their severity. The modified type patients who have relaxed symptoms may spread more smallpox infection because of the difficulty in recognizing the infection. Hemorrhagic type patients are recognized as having severe symptoms and high infectiousness and mortality.

The incubation period of smallpox, which is dependent on severity type, lasts 7-17 and 7-15 days with means of 11.48 and 10.24 days for ordinary/modified types and hemorrhagic type, respectively (**Fig. 1**) (Fenner *et al.*, 1988). Fever and rash periods last 1.5-4.5 and 4.5-12.5 days, respectively (Fenner *et al.*, 1988). The infectiousness of smallpox is dependent on both severity type and infection stage (Fenner *et al.*, 1988). Hemorrhagic type patients have the highest infectiousness, and the modified type patients have the lowest infectiousness. Smallpox



(a) (b)

Fig. 1 The distribution of incubation

(a) ordinary and modified types, (b) hemorrhagic type (Fenner *et al.*, 1988).

patients in the early rash period have the highest infectiousness, and those in the period just before rash appearance have the lowest infectiousness (Fenner *et al.*, 1988). Fatality occurs in patients 7-17 days after fever, and other smallpox patients recover after the rash period has finished (Fenner *et al.*, 1988).

2.2 Infection model of smallpox

In the model, the population in the model for transmission of smallpox are divided into six epidemiological classes, that is, susceptible, incubation, fever, rash, death, and recover. The susceptible class is subdivided into three subclasses based on residual immunity: individuals in subclasses A, B, and C have been vaccinated zero, once, and more than two times, respectively. The model scheme for the transmission dynamics of smallpox is shown in **Fig. 2**. The individuals born after 1977, between 1970 and 1976, and before 1969 belong to subclasses A, B, and C, respectively (Nishiura *et al.*, 2004). The fever and the rash periods were estimated at 3 and 11 days, respectively (Longini *et al.*, 2007). The days from infection to death for ordinary and modified type patients were distributed uniformly across 7-14 days. All hemorrhagic type patients end in death on the 11th day after infection (Longini *et al.*, 2007). Mortalities of ordinary, modified, and hemorrhagic types patients were assumed as 0.3, 0.1, and 1.0, respectively (Longini *et al.*, 2007). The infectiousness of smallpox, which is dependent on both severity types and progress in infection is tabulated in **Table 1**. We introduce the Base ratio and multipliers to express infectiousness on the 2nd day of the fever stage, and the relative infectiousness of ordinary and the others type patients (**Table 1**).

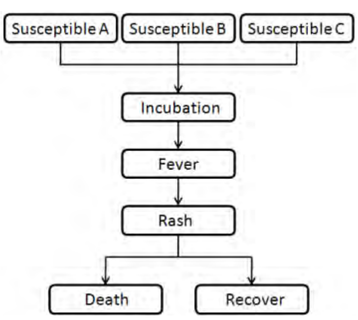


Fig. 2 The model scheme for transmission dynamics of smallpox.

Table 1 The infectiousness of smallpox (Burke *et al.*, 2006).

Infectious parameter	Value
Base	0.07
Ordinary multiplier	1.00
Modified multiplier	0.33
Hemorrhagic multiplier	5.00
Days (+ incubation period)	**Value**
~1	0.0
2	1.0*base*multiplier
3	2.0*base*multiplier
4～9	4.0*base*multiplier
10～14	2.0*base*multiplier
15～	0.0

2.3 Efficacy of vaccination

The efficacy of the vaccine for smallpox, which is dependent on both susceptible subclasses and elapsed time from infection is tabulated in **Table 2** (Fenner *et al.*, 1988). Vaccination for individuals in the susceptible and incubation classes within 4 days from infection is extremely effective, while vaccination for individuals in incubation or fever classes within 5-7 days after infection is imperfect and vaccination for those after 8 days from infection ineffective, respectively. The additional death rate caused by vaccine is estimated at 10^{-6} (Fenner *et al.*, 1988). The residual immunity for individuals by the number of vaccinations is estimated in **Table 3**.

2.4 Population structure of the targeted area

In this article, we simulated a situation of a smallpox epidemic in a city with a population of 10,000 attacked by smallpox, where the demographic data was referenced from the census data of Okayama-city, Japan (Okayama-City, 2007). The age distributions of males and females are shown in **Fig. 3** (Okayama-City, 2007). The ratio of males and females was assumed to be equal. Each individual is classified into one of four roles, namely, worker, student, health care worker (HCW), or non-worker. The ratio of the above roles in the census data are 68%, 10%, 2%, and 20%, respectively (**Table 4**) (Okayama-City, 2007). We assumed that there were three

Table 2 Efficacy of vaccination.

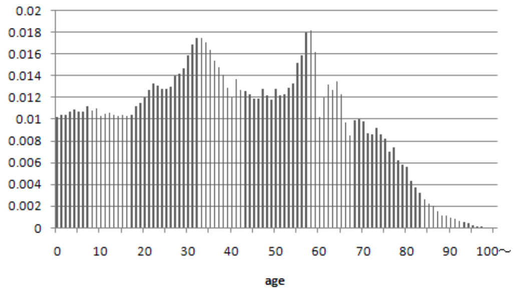
Time of vaccination	Residual immunity subclass	Efficacy of vaccination	Proportion
Susceptible	A	full protection	97%
		modified	3%
	B	full protection	99%
		modified	1%
	C	full protection	100%
4 days after infection	A	full protection	90%
		modified	10%
	B	full protection	95%
		modified	5%
	C	full protection	100%
5-7 days after infection	A	ordinary	38%
		modified	60%
		hemorrhagic	2%
	B	full protection	10%
		ordinary	20%
		modified	70%
	C	full protection	20%
		ordinary	10%
		modified	90%
From 8th day after infection		ineffectiveness	

Table 3 The effectiveness of vaccination due to residual immunity.

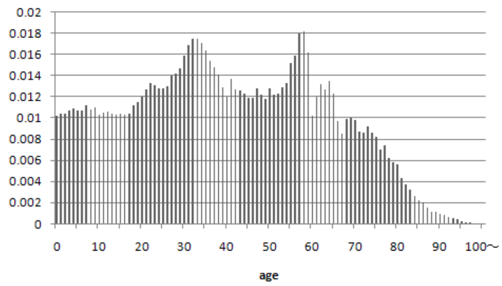
Susceptibility class	Full protection	Ordinary	Modified	Hemorrhagic
A	0%	95%	0%	5%
B	0%	66%	30%	4%
C	10%	30%	57%	3%

kinds of households: single, couple, and couple with a child, and the ratio of households was also referenced from the census data, as shown in **Table 5**.

The numbers of social settings in the targeted area were also determined from the census data (**Table 6**) (Okayama-City, 2007). We assumed that all workers, students, and HCWs go back and forth between home and workplace, school, or hospital each day, respectively, and that non-workers spend the whole day in home. We assumed that the infectiousness of smallpox was proportional to the relative force of infection in each social setting as compared with the force of infection in hospital (**Table 7**) (Halloran *et al.*, 2007).



(a)



(b)

Figure 3 Age structure in the targeted area [9]. (a) male, (b) female.

Table 4 Roles.

Role	Age	Ratio [a]
Worker	16～	68%
Student	5～	10%
HCW	22～	2%
Non-worker	～4 , 16～	20%
Total	-	100%

[a] Refer to (Okayama-City, 2007)

Table 6 Number of social settings in the targeted area.

Social setting		Number [a]
School	Kindergarten	8
	Elementary	9
	Junior high	4
	High	3
	College	1
Workplace		450
Hospital		1

[a] Refer to (Okayama-City, 2007)

Table 5 Structure of household.

Size	Age	Ratio [a]
Single	18~	35%
Couple	20~	20%
Couple with a child	couple：20~ child :（average of age of couple）－（age of child）≥20	45%
Total	-	100%

[a] Refer to (Okayama-City, 2007)

Table 7 Relative force of infection per social setting.

Social setting	Relative force of infection
Household	0.9
School	0.8
Workplace	0.7
Hospital	1.0

2.5 Control strategies

The scenarios were framed by both Traced Vaccination (TV) and Mass Vaccination (MV) strategies. In the TV strategy, persons who came into contact with patients are traced (Center for Disease Control, 2001), but the tracing of contacts of contacts of patients was not considered (secondary contacts). The advantage of the TV strategy is its capability to vaccinate persons who have a chance of infection. However, it has the disadvantage of the time and labor consumed in tracing. On the other hand, in the MV strategy, people in the area of an outbreak of smallpox patients are vaccinated. In this article, it is assumed that a targeted area is divided equally into several MV-blocks, and that the execution of the vaccination program in another MV-block begins after completion of vaccination of all people in the current MV-block. The advantage of the MV strategy is that it is capable of vaccinating a large number of people. However, it demands a lot of vaccines for complete use of the MV strategy. It is assumed that the number of doses of vaccine that can be administered per hour in MV strategy is in proportion to the number of HCWs. For full details of the tracing time required, tracing rate, the number of doses of vaccine per hour for the MV strategy, and coverage for MV refer to Scenarios.

2.6 Scenarios

2.6.1 Baseline scenario

We carried out simulations on the basis of various scenarios. The base scenario was as follows.

Ten index patients are introduced into a social setting chosen at random. The behavior patterns of patients are set in **Table 8**, which is referenced from Longini *et al.* (2007). On the second day of fever, 47.5% of ordinary type patients withdraw to home, and another 47.5% go to hospital, and remaining 5% maintain normal behavior. On the other hand, 25% of modified type patients withdraw to home, another 25% go to hospital, and remaining 50% maintain normal behavior, but all hemorrhagic type patients go to hospital. On the fourth day of fever, all patients visit a hospital. When an index patient visits a hospital, all HCWs in the hospital are vaccinated according to priority. A one-third of HCWs are occupied in dosing persons. One HCW can dose 6 persons per hour. Any patients who visit to hospital are quarantined. There is no limit in the quarantining capacity.

2.6.2 Scenarios

We prepared the following 10 scenarios.

(1) Baseline scenario.

(2) Scenario (1) plus TV strategy. In this scenario, we assume that the necessary trace time is 24 hours, trace rates in household and social settings are 0.9 and 0.7, respectively. TV strategy starts five days after the first patient was identified by HCWs.

(3) Only the necessary trace time changes from 24 hours to 48 hours compared with scenario (2).

(4) Only the necessary trace time changes from 24 hours to 72 hours compared with scenario (2).

(5) Pattern 1 and pattern 2 in **Table 8** are simultaneously delayed for 1 day compared with scenario (2).

(6) Pattern 1 and pattern 2 in **Table 8** are simultaneously delayed for 2 days compared with scenario (2).

(7) Scenario (1) plus MV strategy. In this scenario, a targeted area is divided into five MV-blocks. The coverage of MV is set at 0.8, and the number of doses of vaccine per hour for MV is assumed to be five times that in scenario (1).

(8) The division number of blocks in the targeted area changes 5 with 10 compared with scenario (7).

(9) The coverage of MV changes from 0.8 to 0.5 compared with scenario (7).

(10) Both TV and MV are performed simultaneously using the conditions of scenario (3) and scenario (8)

Table 8 Behavior patterns of patients (Longini *et al.*, 2007).

Type	2nd and 3rd day of Fever (Pattarn1)		4th day of Fever（Pattarn2）
	Action	**Probability**	
Ordinary	Go to hospital	47.5%	All patients go to hospital
	Withdraw to home	47.5%	
	Normal behavior	5%	
Modified	Go to hospital	25%	
	Withdraw to home	25%	
	Normal behavior	50%	
Hemorrhagic	Go to hospital	100%	

3 Results

We carried out 100-trial simulations for 100 days for the 10 Scenarios. **Table 9** shows the average numbers of total infections, total deaths, total doses of vaccine with 95% confidence interval, and the eradication percentage within 100 days in the 10 scenarios. **Fig. 4** shows the transition of smallpox incidence and the 95% confidence intervals.

4 Discussions

We carried out simulations of various scenarios of a bioterrorist attack using smallpox occurring in a virtual area (population size 10,000) set up on the basis of the census of Okayama-city, Japan, which predict the effect of control strategies against bioterrorism and the loss scale.

Firstly, we investigated the effect of TV and MV strategies (scenarios (2) and (7)) on the suppression of a smallpox epidemic by comparison with a no-control baseline (scenario (1)). In the no-control baseline scenario (1), we showed that the average number of total infections and deaths amount to 933.1 and 241.5, respectively, and that only 45% of trials resulted in eradication within 100 days. The TV (scenario (2)) reduced the average number of total infections and deaths to 30% and 10% compared with the no-control scenario (scenario (1)), and eradicated the smallpox epidemic within 100 days in all 100 trials. While the MV strategy (scenario (7)) reduced the average number of total infections and deaths only to 73% and 69% compared

Table 9 Results of simulations in 10 scenarios.

Scenario	Average number of total infections (95% CI)	Average number of total deaths (95% CI)	Average number of doses of vaccine (95% CI)	Percentage of eradication within 100 days
(1)	933.1 (685.5-1180.6)	241.5 (185.9-297.2)	1067.8 (859.0-1276.5)	48%
(2)	268.0 (193.5-342.5)	24.7 (20.7-28.7)	1233.0 (1024.3-1441.6)	100%
(3)	314.1 (240.7-387.4)	25.1 (20.2-30.0)	1440.7 (1244.6-1656.7)	100%
(4)	406.1 (308.7-503.5)	35.19 (28.5-41.8)	1612.9 (1379.1-1846.8)	100%
(5)	483.6 (388.8-578.4)	47.5 (36.5-58.5)	2361.3 (2126.4-2596.1)	95%
(6)	656.3 (527.7-784.9)	104.0 (84.3-123.6)	2835.3 (2585.1-3085.4)	65%
(7)	680.2 (506.2-854.2)	165.9 (125.1-216.7)	2799.1 (2627.3-2970.9)	59%
(8)	715.2 (525.8-904.6)	189.0 (138.4-239.6)	1855.7 (1667.4-2043.9)	56%
(9)	740.3 (569.4-921.1)	204.7 (156.2-253.3)	2710.6 (2553.2-2868.1)	52%
(10)	267.5 (199.7-335.3)	23.8 (18.9-28.6)	3268 (3001.9-3534.2)	100%

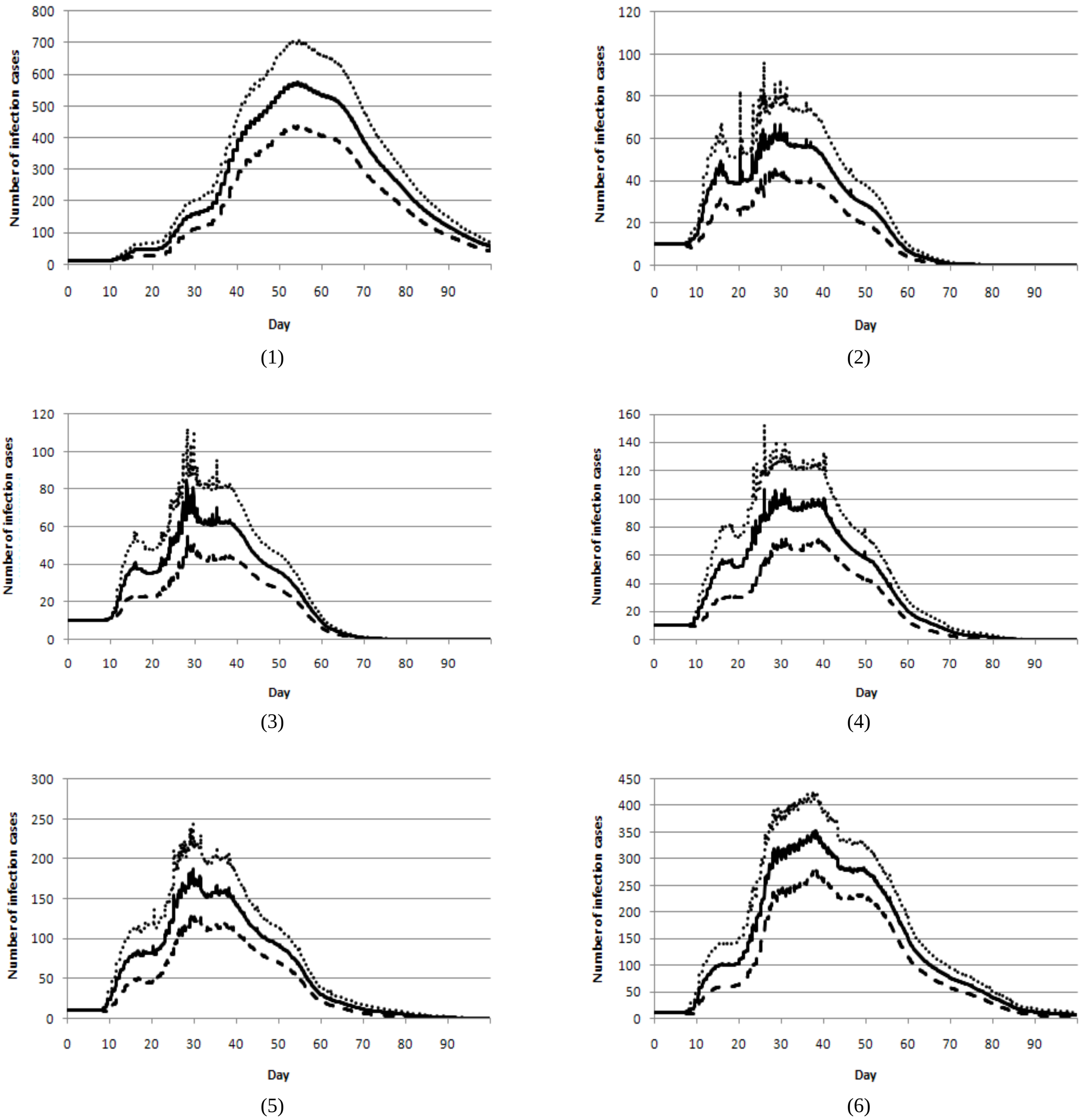


Fig. 4 Transition of smallpox incidence in scenarios

(1)-(10) correspond to scenarios (1)-(10). Solid, dashed, and broken lines show the average number of infections, upper limit, and lower limit of 95% confidence intervals in 100 simulations.

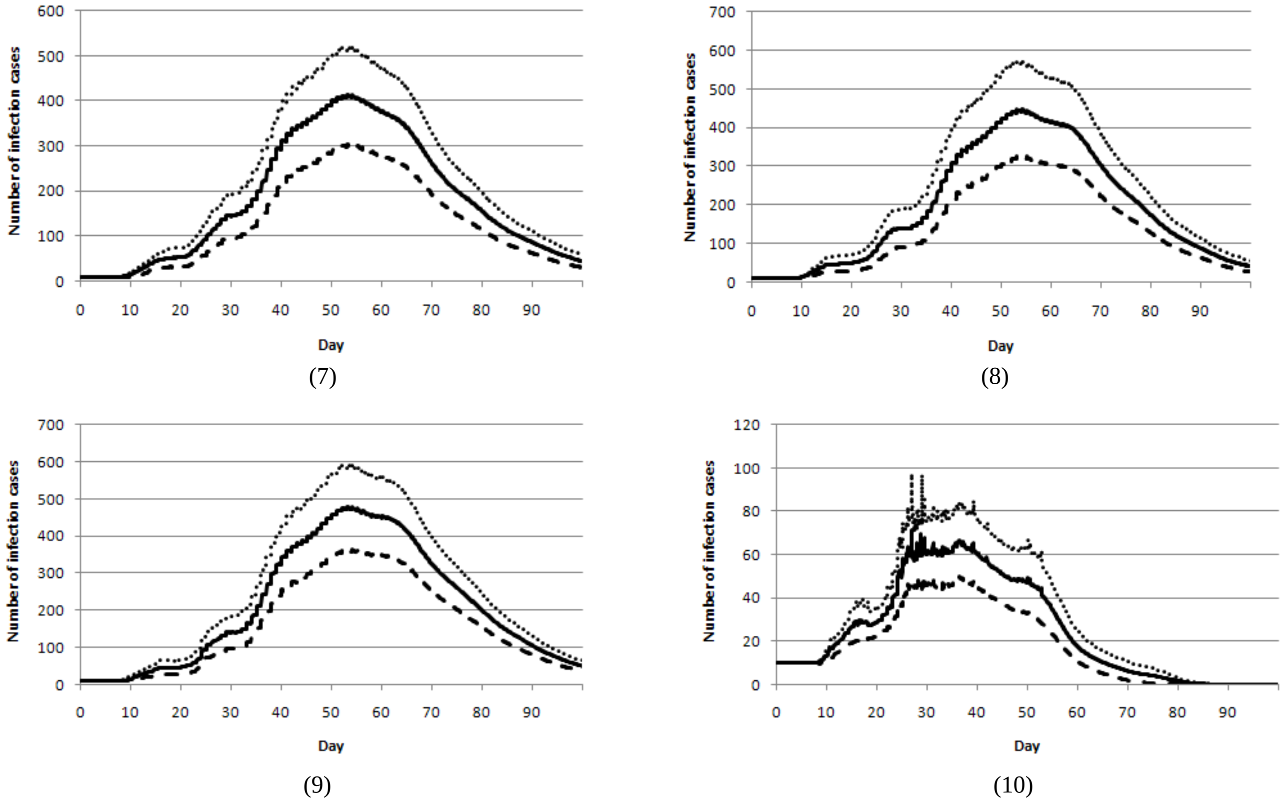


Fig. 4 (continued)

with the no-control scenario (scenario (1)), and eradicated the outbreak within 100 days in only 59 trials. Therefore, it is confirmed that only quarantining patients (scenario (1)) is incapable of suppressing the smallpox epidemic, whereas the TV strategy (scenario (2)) has high effectiveness in suppressing the outbreak, and that the TV strategy has higher effectiveness than the MV strategy.

Secondly, we investigated the influence of the span of necessary tracing time for TV on suppression of the smallpox epidemic (scenarios (2)-(4)). The average numbers of the total infections for necessary tracing times of 48 and 72 hours (scenarios (3) and (4)) increased to 314.1 (117%) and 406.1 (150%) compared with 268.0 in the scenario for 24 hours (scenario (2)), although both TV strategies with 48 and 72 hours tracing times (scenarios (3) and (4)) obtained eradication of the outbreaks within 100 days (100%). Consequently, it is desirable that for an effective TV strategy tracing is begun within 48 hours.

Thirdly, we investigated the influence of the size of MV-blocks on suppression (scenarios (7) and (8)). In MV with an area that is divided into five MV-blocks (scenario (7)) the average number of total infections and deaths was reduced to 95% and 91% compared with MV with ten MV-blocks (scenario (8)), and could eradicate the smallpox epidemic within 100 days in 59 trials, while the ten-blocks MV strategy (scenario (8)) achieved this in only 56 trials. Therefore, there is little difference in suppression between the two sizes of MV-blocks.

Fourthly, we investigated the influence of coverage of MV on suppression of the outbreaks (scenarios (7) and (9)). MV with 50% coverage (scenario (9)) increased the average number of total infections and deaths to 108% and 123% compared with MV with 80% coverage (scenario (7)), and it could eradicate the smallpox epidemic within 100 days in only 52 trials, while the MV strategy with 50% coverage (scenario (9)) could eradicate it within 100 days in only 59 trials. A large amount of time is consumed in vaccinating in a block because of the low coverage for MV. Therefore, a low coverage MV strategy (scenario (9)) prolongs the term of a smallpox epidemic.

Fifthly, we compared the effect of TV and simultaneous TV and MV strategies on suppression of the outbreak (scenarios (2) and (10)). The simultaneous performance of TV and MV (scenario (10)) had about the same results on the average numbers of total infections and deaths and the same result (100%) on the eradication probability within 100 days as the performance of only TV. However, these analogous results should be attributed to the lower effectiveness of the MV strategy. We may expect a better result if the effectiveness of the MV strategy can be improved. The number of total doses of vaccine in scenario (10) is about 2000 more than in scenario (2). Although deaths due to side effects of the vaccine occur rarely, even with a small fatality rate (10^{-6}) this effect will become significant when MV is operated for a larger population. Hence, only TV that vaccinates contacts is recommended as a control strategy, unless the effectiveness of the MV strategy can be further improved.

Finally, we investigated the influence of behavior pattern of patients on suppression of the outbreak (scenarios (2), (5), and (6)). The delay case for 1 day of behavior pattern of patients in **Table 8** (scenario (5)) increases the average number of total infections and deaths 180% and 190% compared with the no-delay case (scenario (2)), and could eradicate the smallpox epidemic within 100 days in 95 trials. While the delay case of behavior patterns of patients in **Table 8** for 2 days (scenario (6)) increased the average number of total infections and deaths to 240% and 420% compared with the no-delay case (scenario (2)), and could eradicate the smallpox epidemic within 100 days in only 65 trials. Quick hospitalization of patient is proven to have a good influence on the control smallpox epidemics, because infections increase less rapidly under effective quarantine conditions.

The comparative studies in scenarios (1)-(10) demonstrate the high effectiveness of the TV strategy and the lower effectiveness of the MV strategy. We show that the TV strategy has an advantage with regard to side effects of the vaccine, because TV (scenario (2)) reduces the required number of total doses of vaccine by half compared with the MV (scenario (7)). There were two reasons why the MV strategy was less effectiveness. Firstly, if patients leave a MV-block before MV is carried out, the smallpox epidemic could leak out. As a countermeasure, MV-blocks can be fixed by the prospect of behavior patterns of patients. Secondly, it takes too much time to vaccinate all persons in a MV-block. As a consequence of a precondition in the model that vaccination moves to the next block only after vaccination of all persons in the present block is finished, there is prevalence for the infection to spread out before vaccination. To avoid excessively strict preconditions, we set a time limit on vaccination in a MV-block when vaccination in MV is dosed.

We adopted IBM in order that individuals have personal information about age and address, behavior patterns such as movement between home and workplace, and interaction among social groups, which can make the model realistic. However, a behavior pattern that consists of a movement between home and workplace and a visit to hospital is monotonic. It will be necessary to introduce more complicated behavior patterns to make the model more realistic. In the model, the incubation period and the infectiousness depend on three severity types: ordinary, modified, and hemorrhagic types, and also the infectiousness and the severity depend on the residual immunity due to past vaccination, where there are three stages in residual immunity. However, it is not yet clear how much residual immunity remains (Nishiura *et al.*, 2006). Further refinement of this research is being developed from our basic research.

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