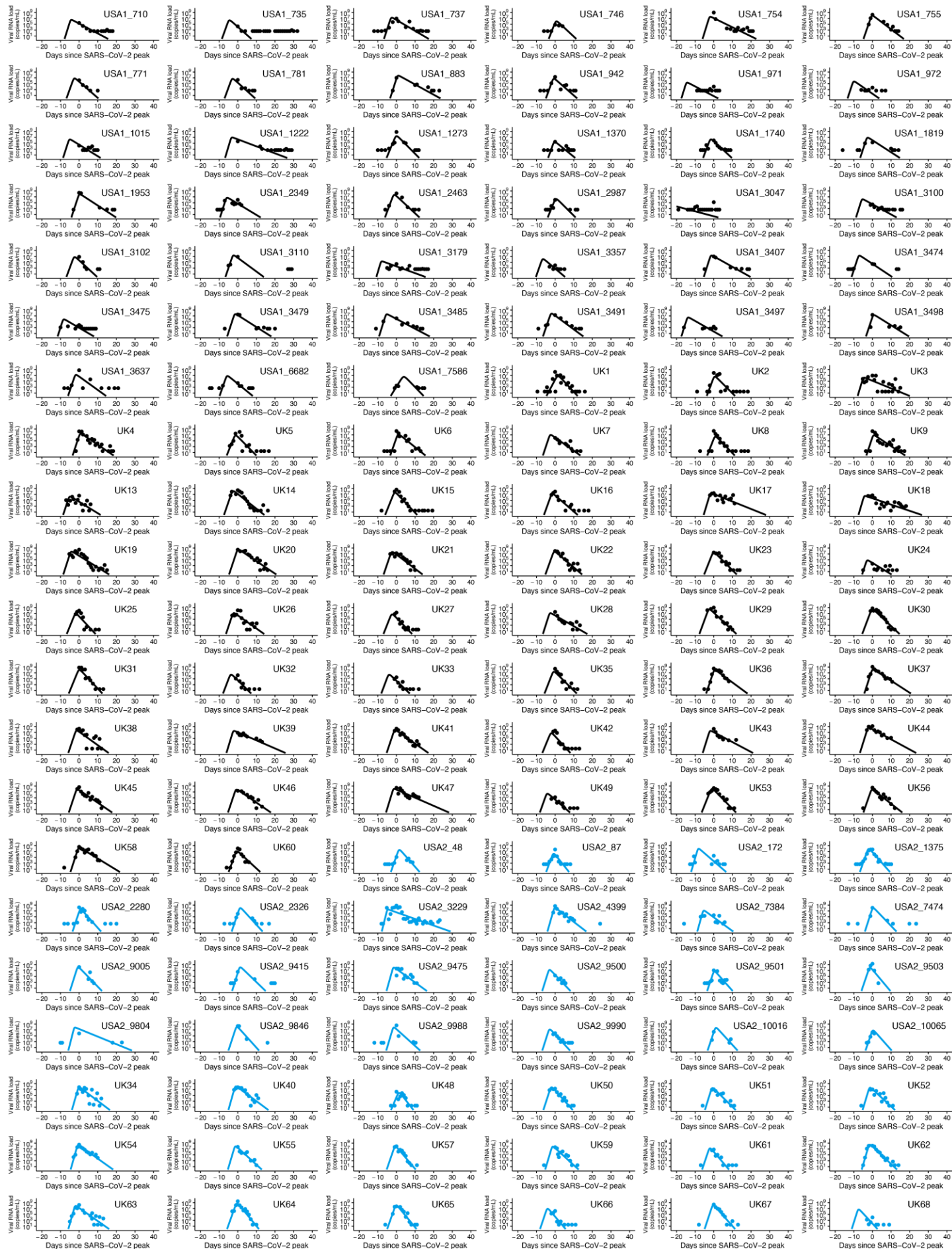


Supplementary Information

Isolation may select for earlier and higher peak viral load but shorter duration in SARS-CoV-2 evolution

Junya Sunagawa^{1,†}, Hyeongki Park^{2,†}, Kwang Su Kim^{2,3,4,†}, Ryo Komorizono⁵, Sooyoun Choi^{2,4}, Lucia Ramirez Torres², Joohyeon Woo², Yong Dam Jeong^{2,4}, William S Hart⁶, Robin N. Thompson^{6,7,8}, Kazuyuki Aihara⁹, Shingo Iwami^{2,10,11,12,13,14,‡,*} and Ryo Yamaguchi^{1,15‡,*}

¹Department of Advanced Transdisciplinary Sciences, Hokkaido University, Sapporo, Hokkaido, Japan. ²interdisciplinary Biology Laboratory (iBLab), Division of Biological Science, Graduate School of Science, Nagoya University, Nagoya, Japan. ³Department of Scientific Computing, Pukyong National University, Busan, South Korea. ⁴Department of Mathematics, Pusan National University, Busan, South Korea. ⁵Laboratory of RNA Viruses, Department of Virus Research, Institute for Life and Medical Sciences (LiMe), Kyoto University, Kyoto, Japan. ⁶Mathematical Institute, University of Oxford, Oxford, United Kingdom. ⁷Mathematics Institute, University of Warwick, Coventry, United Kingdom. ⁸Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research, University of Warwick, Coventry, United Kingdom. ⁹International Research Center for Neurointelligence, The University of Tokyo Institutes for Advanced Study, The University of Tokyo, Tokyo, Japan. ¹⁰Institute of Mathematics for Industry, Kyushu University, Fukuoka, Japan. ¹¹Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University, Kyoto, Japan. ¹²Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS), RIKEN, Saitama, Japan. ¹³NEXT-Ganken Program, Japanese Foundation for Cancer Research (JFCR), Tokyo, Japan. ¹⁴Science Groove Inc., Fukuoka, Japan. ¹⁵Department of Zoology & Biodiversity Research Centre, University of British Columbia, Vancouver, British Columbia, Canada.



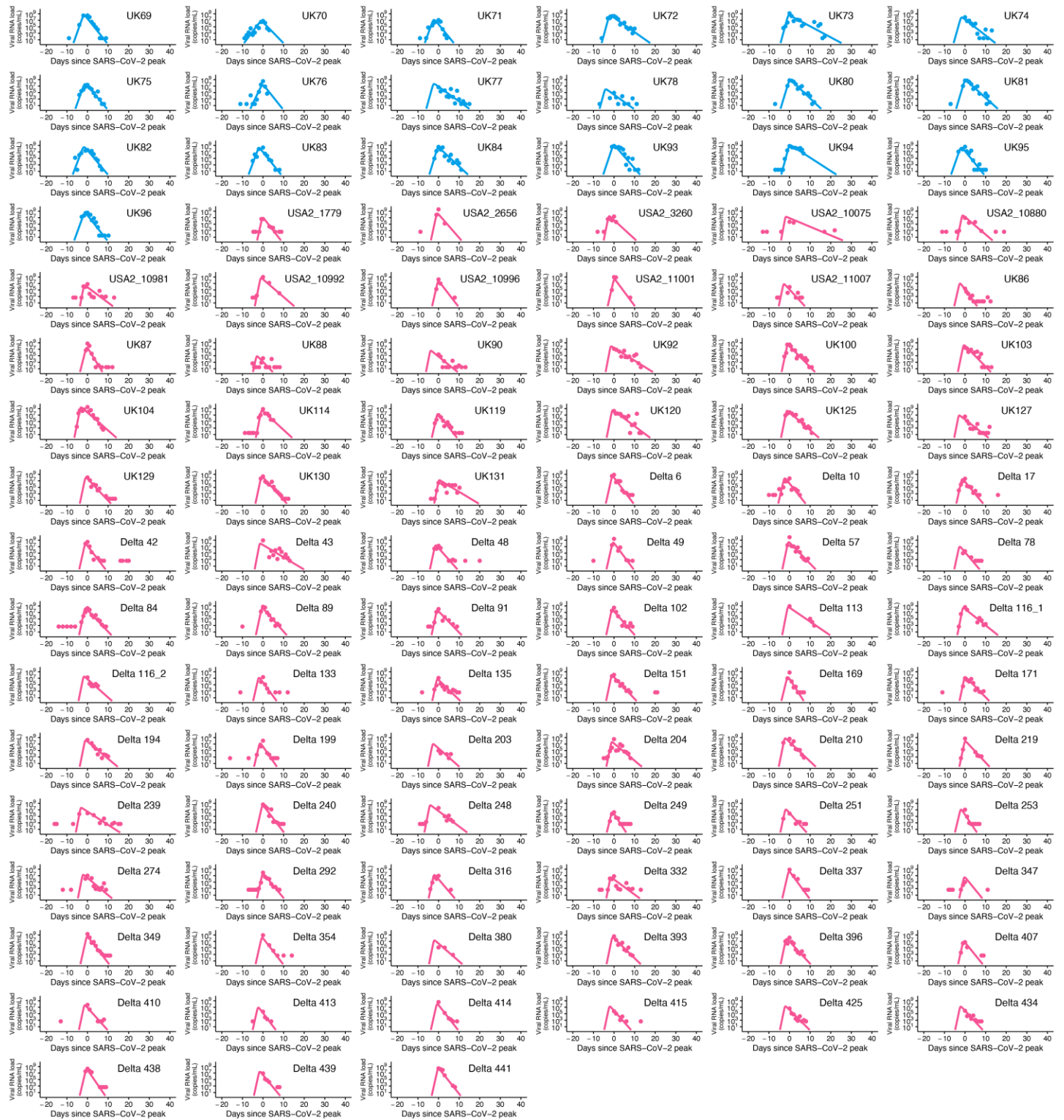


Figure S1. Viral load trajectory for individual patients infected with pre-Alpha, Alpha, and Delta variants. The estimated viral load for each individual patient (solid lines) along with the observed data (closed dots) are depicted using the best-fit parameter estimates. Pre-Alpha, Alpha, and Delta variants are shown in black, blue, and red, respectively. Source data are provided as a Source Data file.

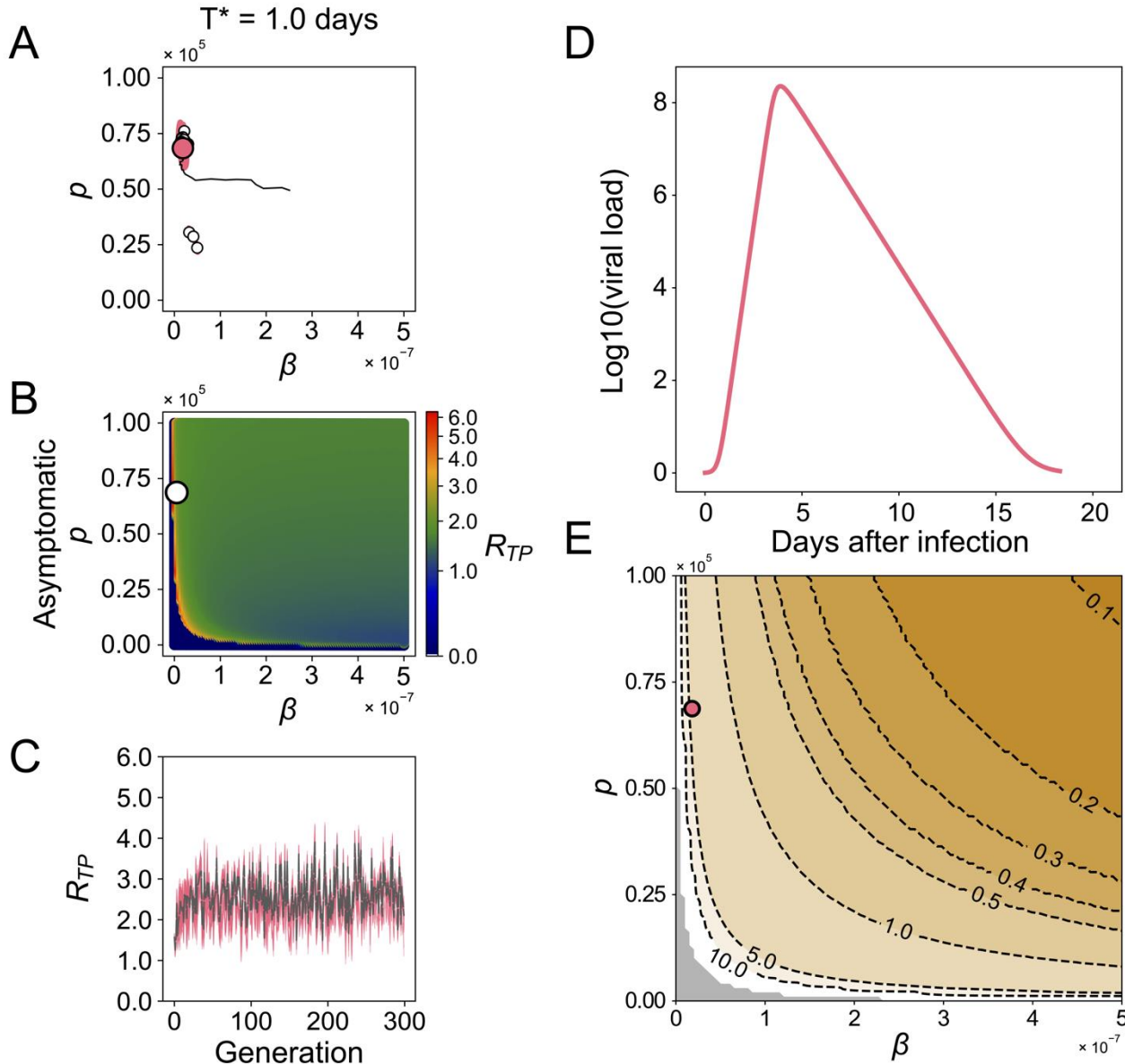


Figure S2. SARS-CoV-2 evolution *in silico* without symptomatic infection ($f = 0$ and $T^* = 1$): **(A)** Genetic algorithm (GA) exploring the evolutionary trajectories on the (β, p) plane until the generation of 300 is applied. Our choice of the incubation period, T^* , does not affect the calculation because no asymptomatic individuals change their transmissibility by isolation (i.e., no individual is applied to isolation). The white dots represent the endpoint of 100 independent simulation runs, and the contour lines are the kernel density estimation of their distribution. The colored dot in the panel is the mean value of the white dots, which represent the optimal set of (β, p) under the parameters we used. The black line is the mean trajectory of the GA through 300 generations. **(B)** The mean transmissibility fitness landscape aggregated from asymptomatic individuals (i.e., no symptomatic individuals due to $f = 0$) is described, using 100 runs of GA. The white dot represents the maximum

value of the mean transmissibility fitness, R_{TP} . **(C)** The trajectories of R_{TP} along the course of GA are calculated. The gray dotted lines are the mean trajectory over 100 trials of colored lines. **(D)** The time-series patterns of viral load with the optimal parameters of (β, p) , which were obtained in (A), are shown. **(E)** The counter plot for the timing of peak viral load (i.e., peak time) is shown. The gray region is the parameter range satisfying $R_{TP} < 1$.

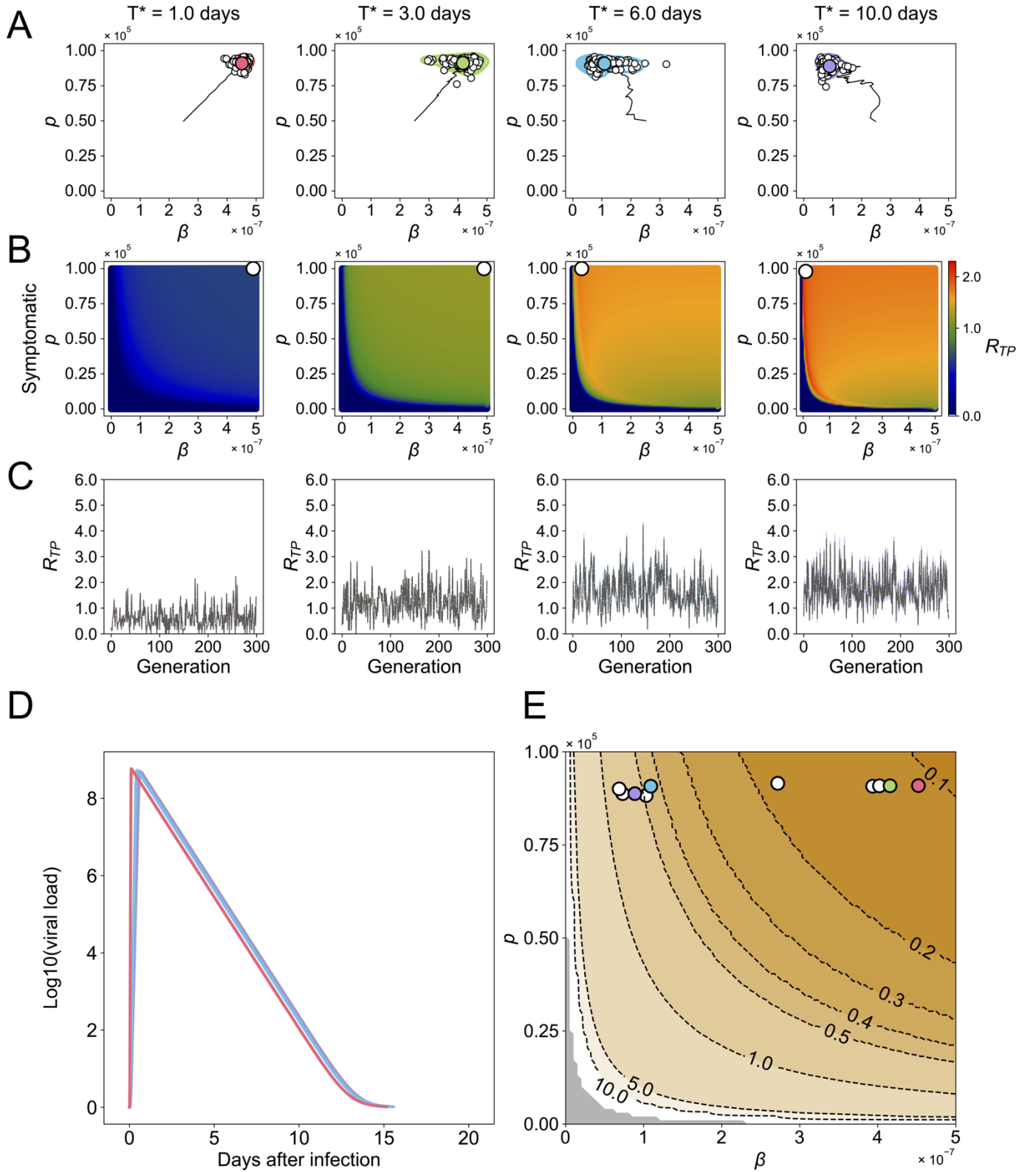


Figure S3. SARS-CoV-2 evolution *in silico* without asymptomatic infection ($f = 1$): (A) GA exploring the evolutionary trajectories on the (β, p) plane until the generation of 300 is applied, depending on different values of the incubation period, T^* . All individuals lose their transmissibility by isolation after the symptom onset ($T^* < t$). The white dots represent the endpoint of 100 independent

simulation runs, and the contour lines are the kernel density estimation of their distribution. The colored dot in each panel is the mean value of the white dots, which represents the optimal set of (β, p) under the parameters we used. The black line is the mean trajectory of the GA through 300 generations. **(B)** The mean transmissibility fitness landscapes aggregated from symptomatic individuals (i.e., no asymptomatic individuals due to $f = 0$) are described, using 100 runs of GA. The white dot represents the maximum value of the mean transmissibility fitness, R_{TP} . **(C)** The trajectories of R_{TP} along the course of GA with different T^* are calculated. The gray dotted lines are the mean trajectory over 100 trials of colored lines. **(D)** The time-series patterns of viral load with the optimal parameters of (β, p) with different T^* , which were obtained in (A), are shown. Each curve is colored accordingly. **(E)** The counter plot for the timing of peak viral load is shown. Each dot is colored accordingly. The gray region is the parameter range satisfying $R_{TP} < 1$.

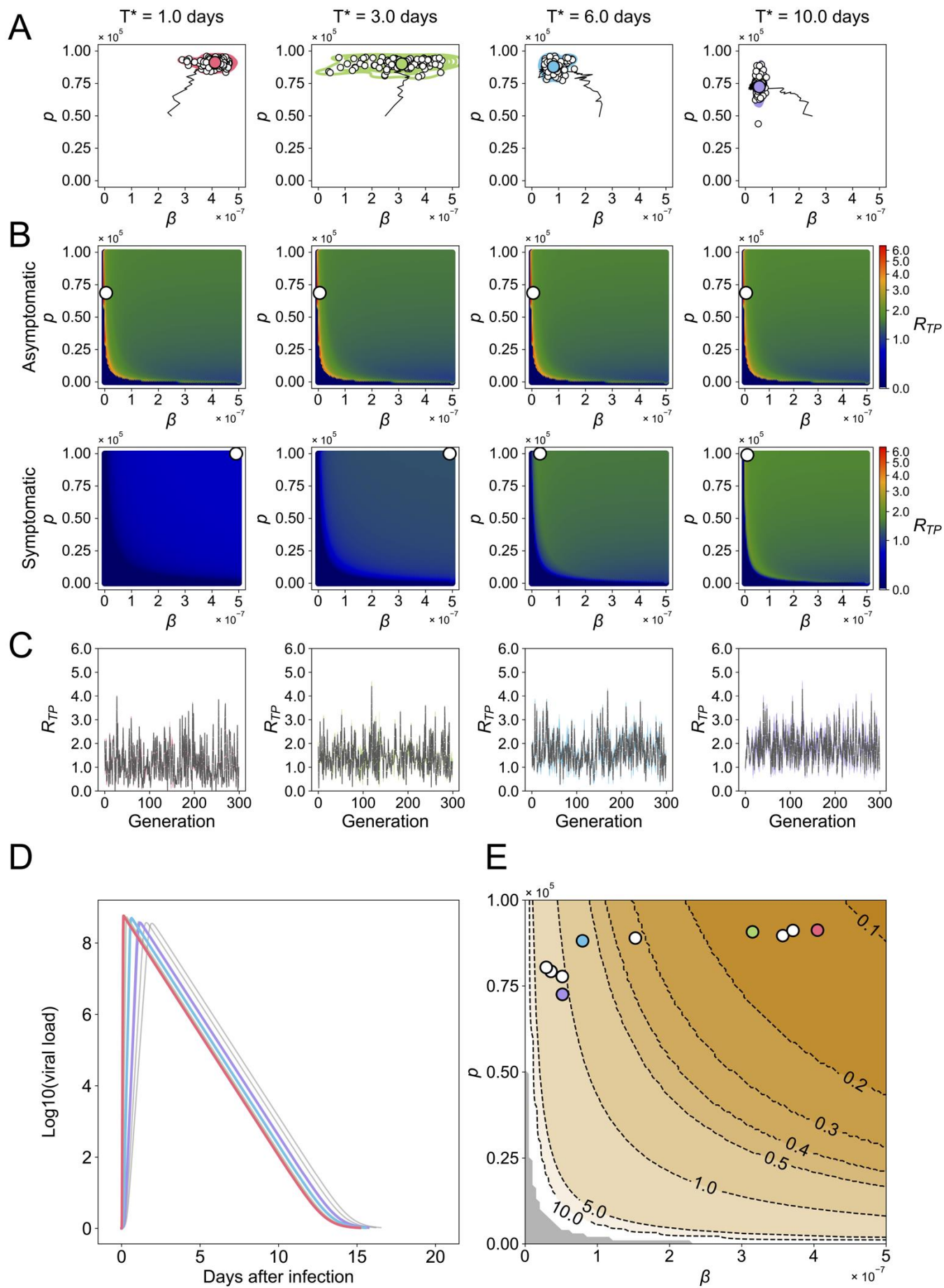


Figure S4-1. Sensitivity analysis of the proportion of symptomatic infection ($f = 0.5$): (A)

Genetic algorithm (GA) exploring the evolutionary trajectories on the (β, p) plane until the generation of 300 is applied, depending on different values of the incubation period, T^* . All individuals lose their transmissibility by NPIs after symptom onset ($T^* < t$). The white dots represent the endpoint of 100 independent simulation runs, and the contour lines are the kernel density estimation of their distribution. The colored dot in each panel is the mean value of the white dots, which represent the optimal set of (β, p) under the parameters we used. The black line is the mean trajectory of the GA through 300 generations. **(B)** The mean transmissibility fitness landscape aggregated solely from the asymptomatic (top row) and symptomatic (bottom row) individuals, respectively, are described, using 100 runs of GA. The white dot represents the maximum value of the mean transmissibility fitness, R_{TP} . **(C)** The trajectories of R_{TP} along the course of GA with different T^* are calculated. The gray dotted lines are the mean trajectory over 100 trials of colored lines. **(D)** The time-series patterns of viral load with the optimal parameters of (β, p) with different T^* , which were obtained in (A), are shown. Each curve is colored accordingly. **(E)** The counter plot for the timing of peak viral load is shown. Each dot is colored accordingly. The gray region is the parameter range satisfying $R_{TP} < 1$.

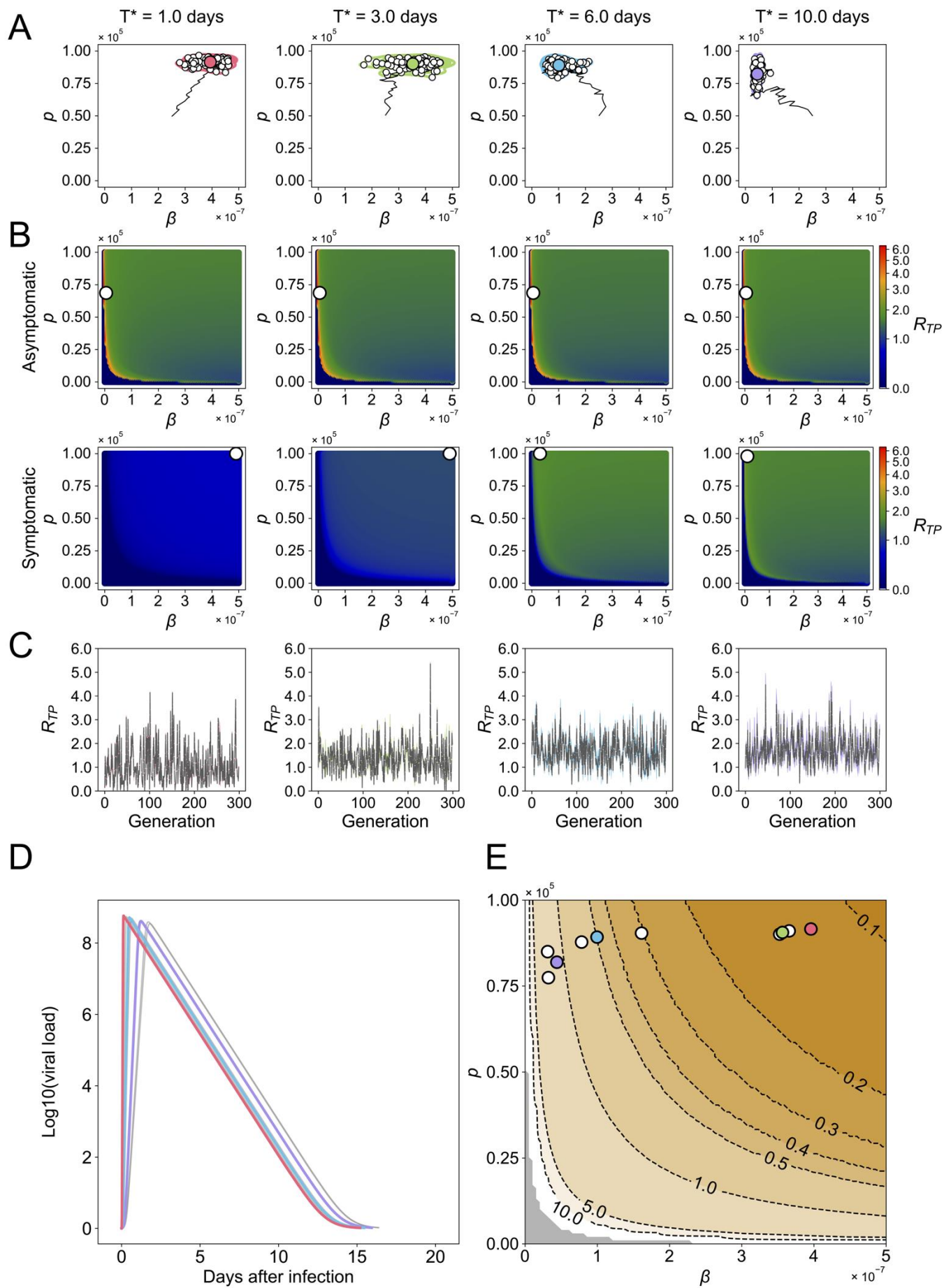


Figure S4-2. Sensitivity analysis of the proportion of symptomatic infection ($f = 0.6$): Same explanation for **(A-E)** is applied as in **Figure S4-1**.

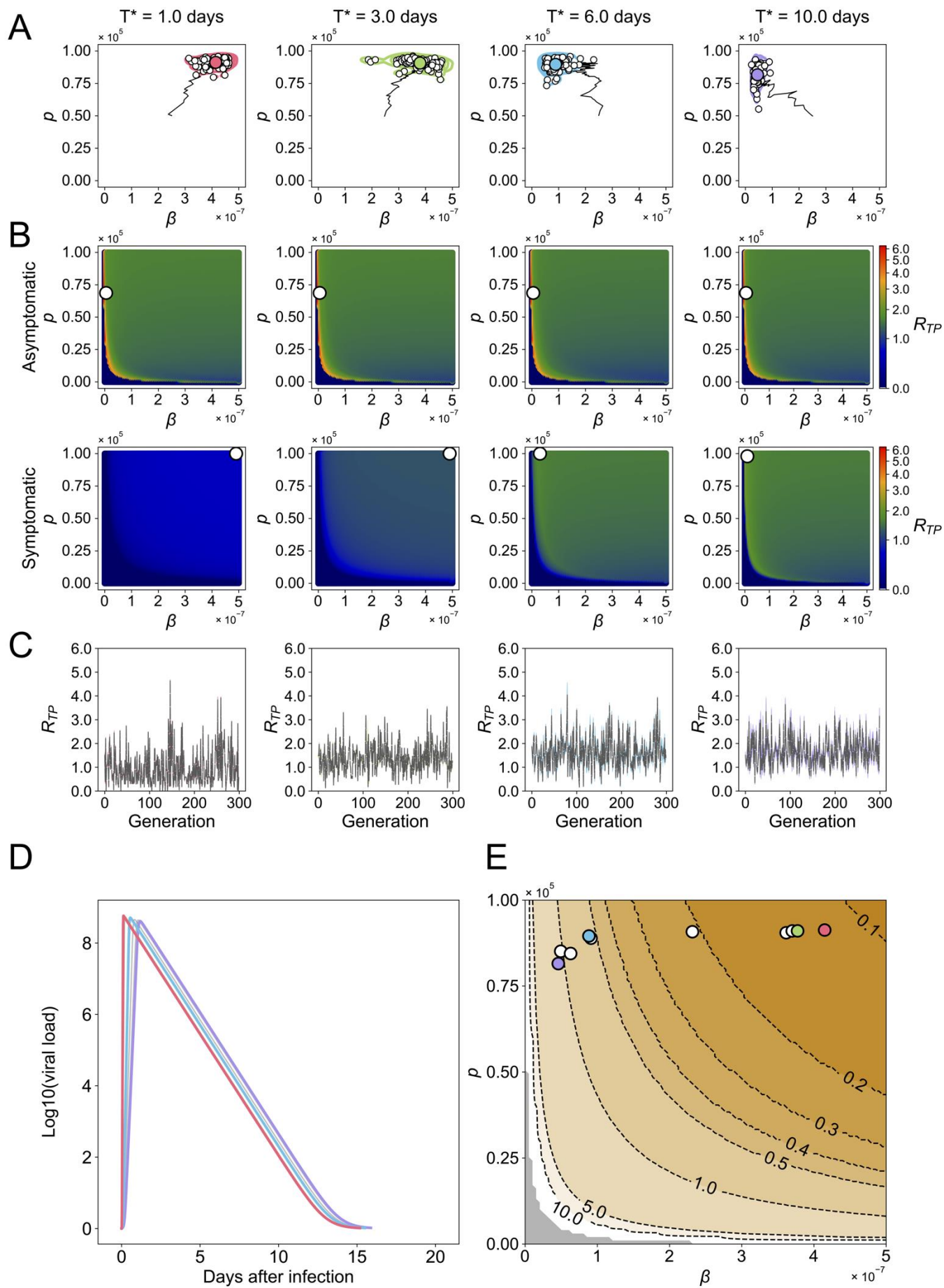


Figure S4-3. Sensitivity analysis of the proportion of symptomatic infection ($f = 0.7$): Same explanation for **(A-E)** is applied as in **Figure S4-1**.

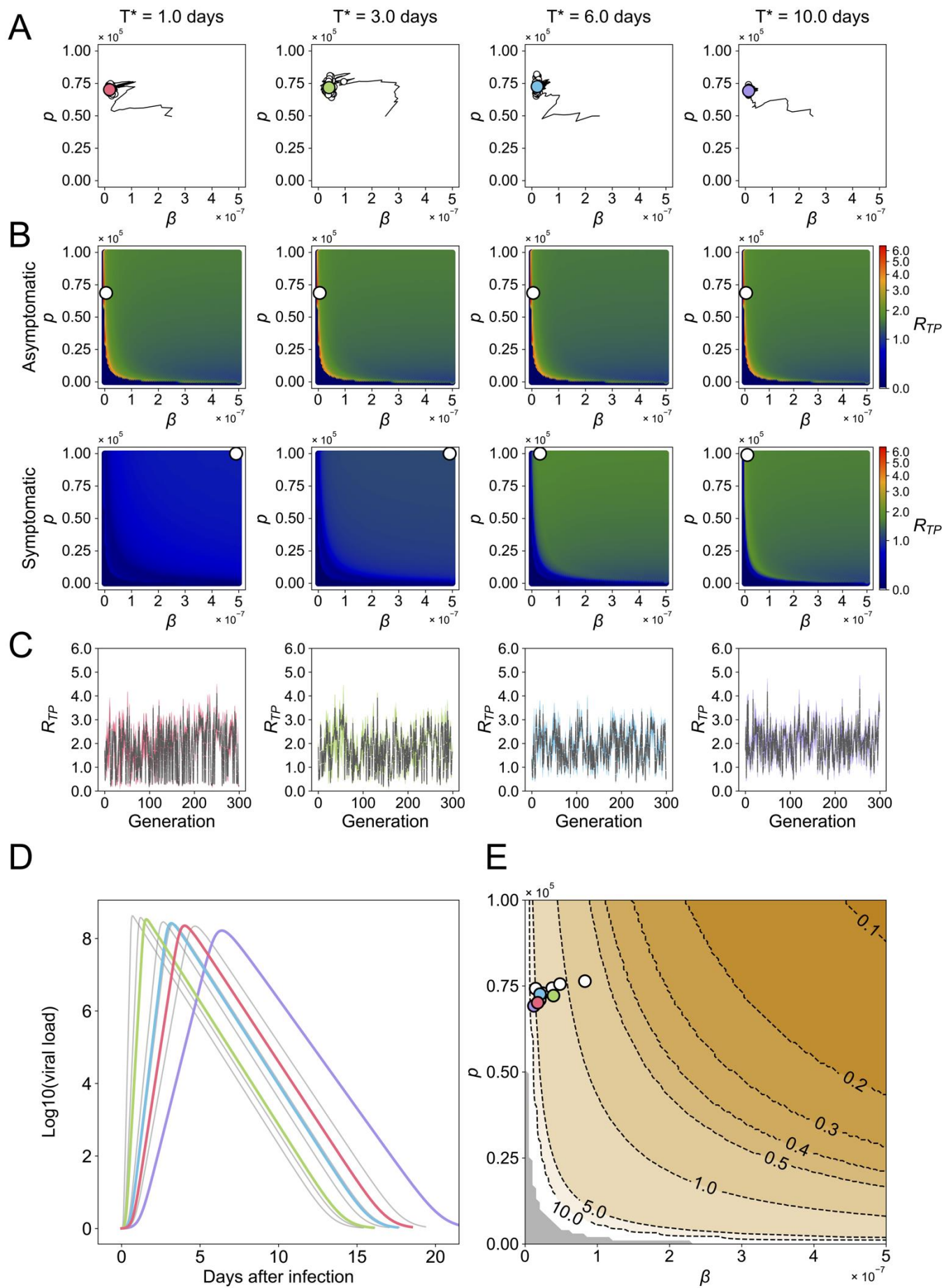


Figure S5-1. Sensitivity analysis of the impact of Incomplete Isolation on Viral Load Dynamics

($f = 0.3$ and $\xi = 0.1$): **(A)** Genetic algorithm (GA) exploring the evolutionary trajectories on the (β, p) plane until the generation of 300 is applied, depending on different values of the incubation period, T^* . All individuals lose their transmissibility by NPIs after symptom onset ($T^* < t$). The white dots represent the endpoint of 100 independent simulation runs, and the contour lines are the kernel density estimation of their distribution. The colored dot in each panel is the mean value of the white dots, which represent the optimal set of (β, p) under the parameters we used. The black line is the mean trajectory of the GA through 300 generations. **(B)** The mean transmissibility fitness landscape aggregated solely from the asymptomatic (top row) and symptomatic (bottom row) individuals, respectively, are described, using 100 runs of GA. The white dot represents the maximum value of the mean transmissibility fitness, R_{TP} . **(C)** The trajectories of R_{TP} along the course of GA with different T^* are calculated. The gray dotted lines are the mean trajectory over 100 trials of colored lines. **(D)** The time-series patterns of viral load with the optimal parameters of (β, p) with different T^* , which were obtained in (A), are shown. Each curve is colored accordingly. **(E)** The counter plot for the timing of peak viral load is shown. Each dot is colored accordingly. The gray region is the parameter range satisfying $R_{TP} < 1$. Additional graphs illustrating dependency on parameter f : see <https://zenodo.org/record/10030531>

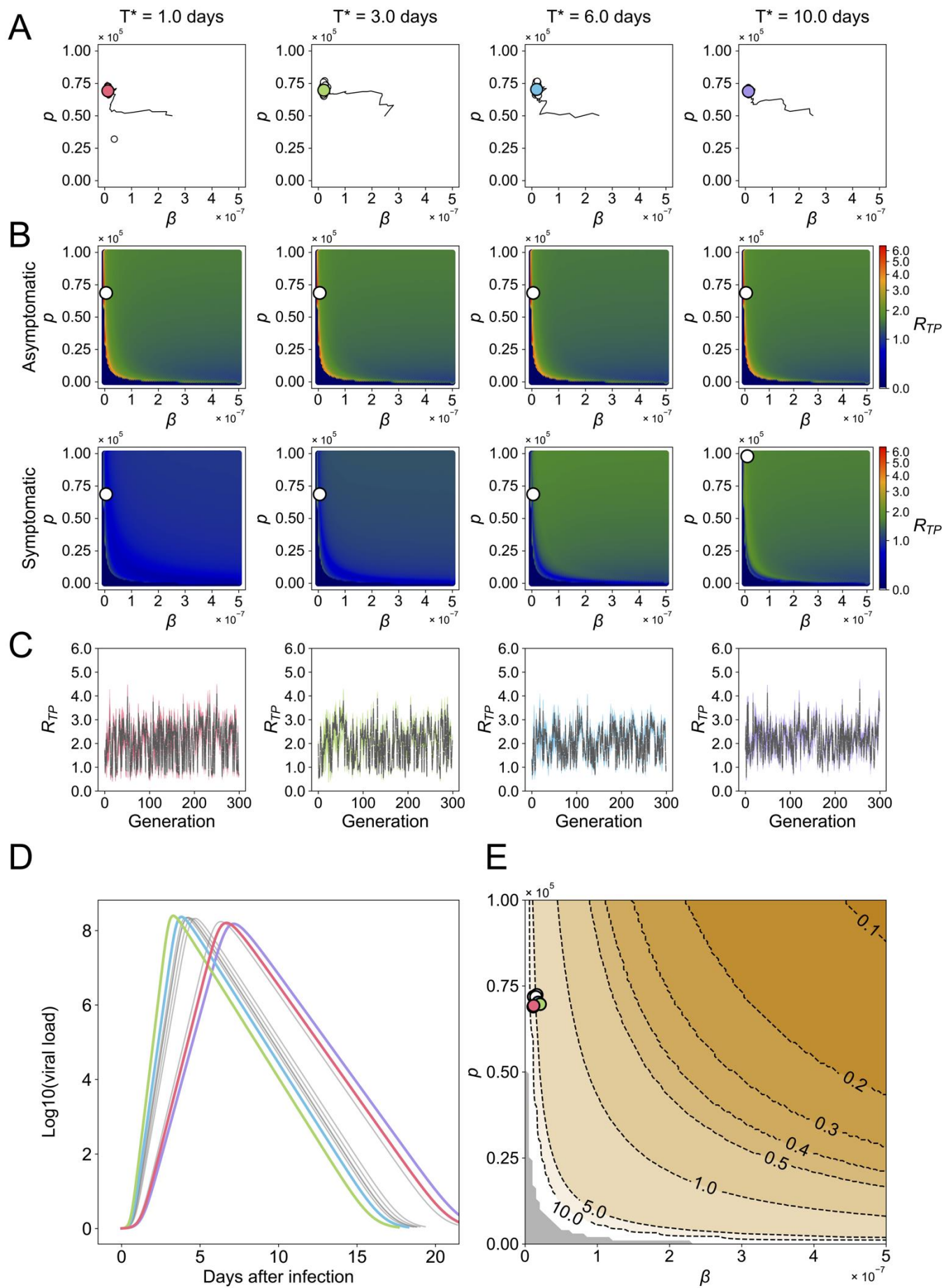


Figure S5-2. Sensitivity analysis of the impact of Incomplete Isolation on Viral Load Dynamics
($f = 0.3$ and $\xi = 0.3$): Same explanation for (A-E) is applied as in **Figure S5-1**.

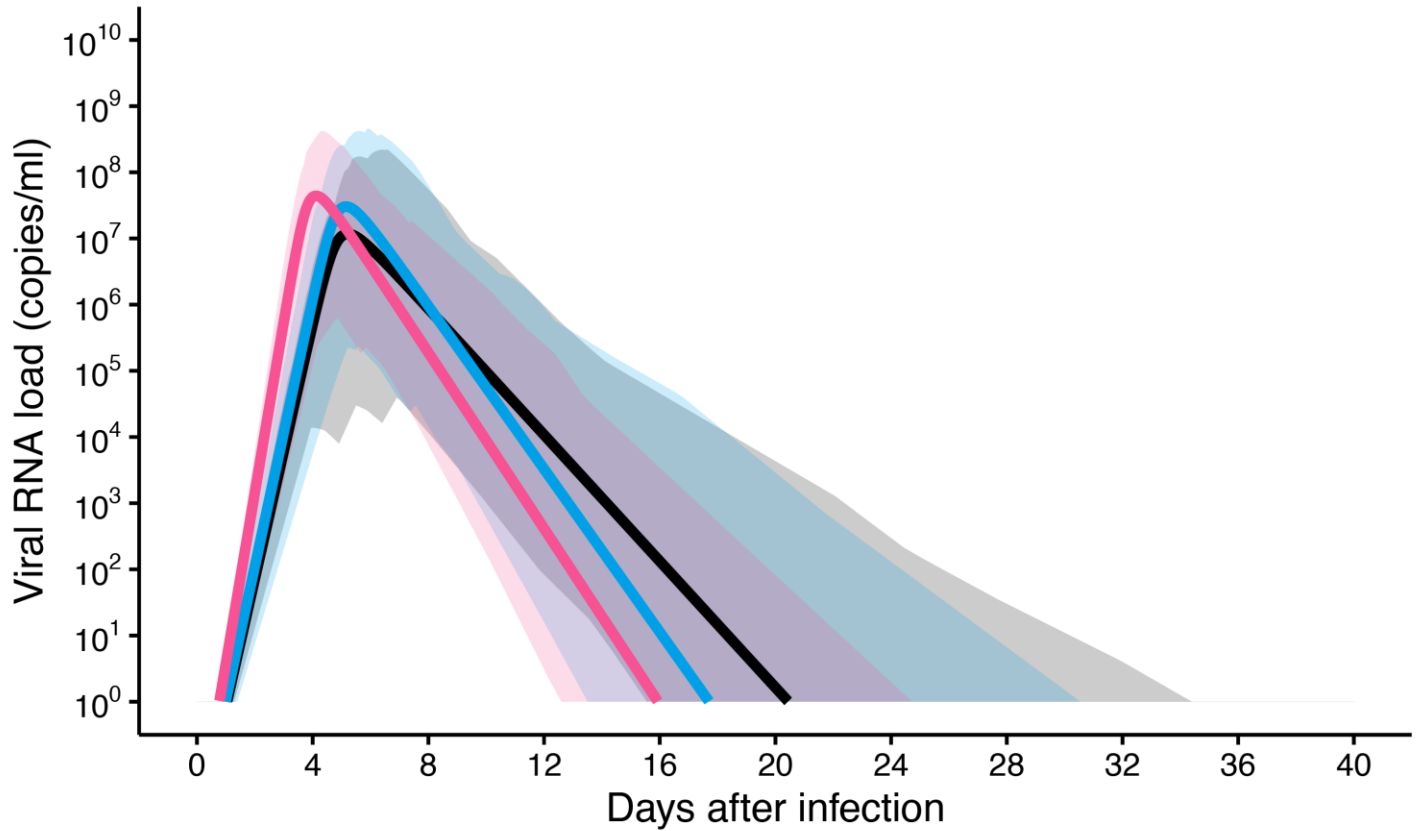


Figure S6. Quantification of SARS-CoV-2 infection dynamics with patients who have prior immunity: The inferred viral dynamics of 293 COVID-19 patients with and without prior immunity. It contains 225 patients without prior immunity (86 with pre-Alpha variant, 59 with Alpha variant and 80 with Delta variant), and 68 patients with prior immunity by vaccination or pre-infection (14 with Alpha variant and 54 with Delta variant). The solid curves correspond to the solution of Eqs.(4-5) using the best-fit population parameters, and the shadow regions are the 95% interquartile range of the predictive interval using the estimated parameters for each patient. The black, blue, and red colors indicate the pre-Alpha, Alpha, and Delta variants, respectively.

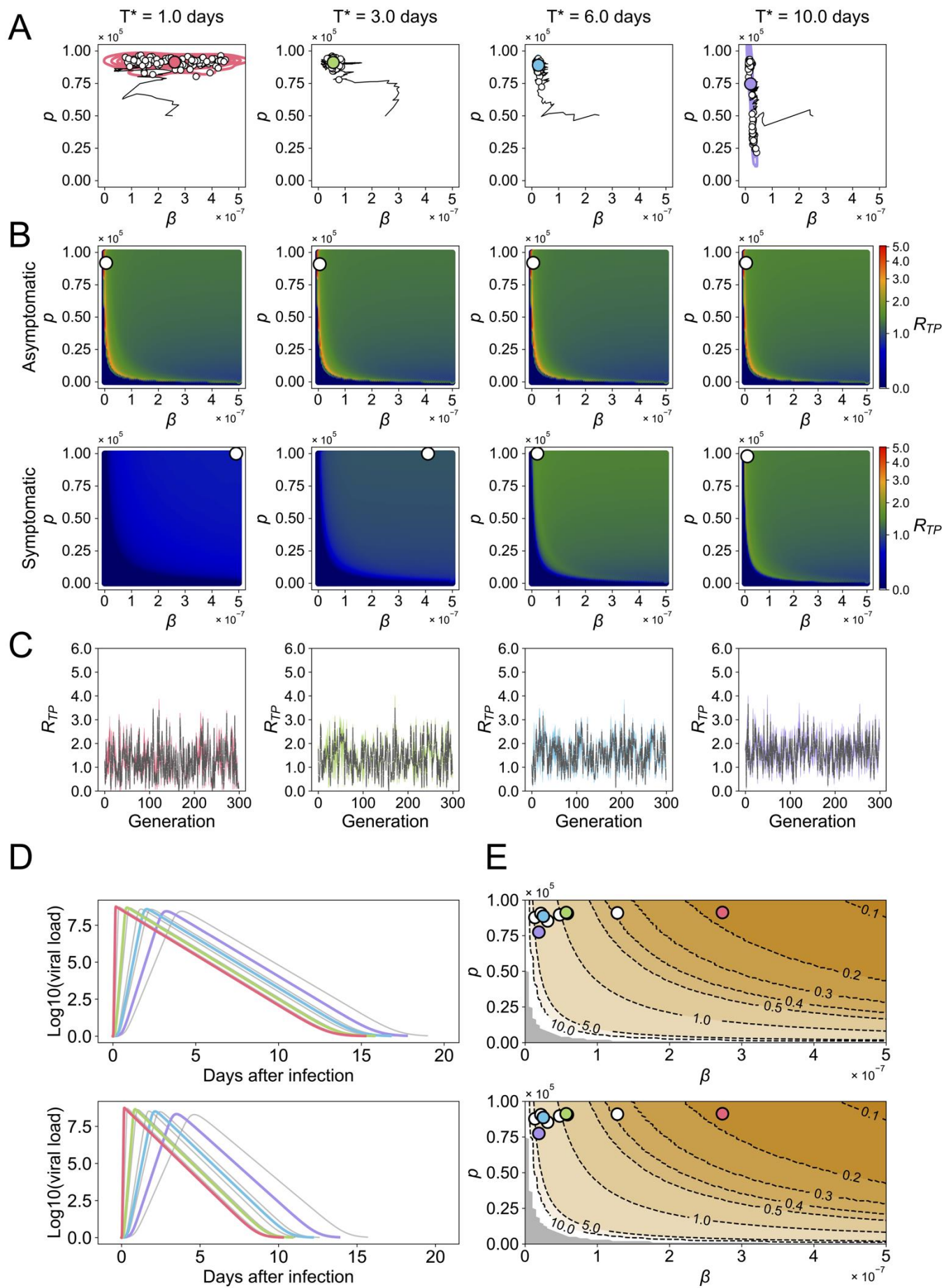


Figure S7-1. Sensitivity analysis of effects of vaccination rates on optimal viral parameters ($f = 0.3$ and vaccination rate = 0.5): **(A)** Genetic algorithm (GA) exploring the evolutionary trajectories on the (β, p) plane until the generation of 300 is applied, depending on different values of the incubation period, T^* . All individuals lose their transmissibility by NPIs after symptom onset ($T^* < t$). The white dots represent the endpoint of 100 independent simulation runs, and the contour lines are the kernel density estimation of their distribution. The colored dot in each panel is the mean value of the white dots, which represent the optimal set of (β, p) under the parameters we used. The black line is the mean trajectory of the GA through 300 generations. **(B)** The mean transmissibility fitness landscape aggregated solely from the asymptomatic (top row) and symptomatic (bottom row) individuals, respectively, are described, using 100 runs of GA. The white dot represents the maximum value of the mean transmissibility fitness, R_{TP} . **(C)** The trajectories of R_{TP} along the course of GA with different T^* are calculated. The gray dotted lines are the mean trajectory over 100 trials of colored lines. **(D)** The time-series patterns of viral load with the optimal parameters of (β, p) with different T^* , which were obtained in (A), are shown. Each curve is colored accordingly. The upper row represents the case for unvaccinated individuals, while the lower row demonstrates the case for vaccinated individuals (with δ increased by 1.5 times). **(E)** The counter plot for the timing of peak viral load is shown. Each dot is colored accordingly. The gray region is the parameter range satisfying $R_{TP} < 1$. The upper and lower rows are the same as in (D). Additional graphs illustrating dependency on parameter f : see <https://zenodo.org/record/10030531>

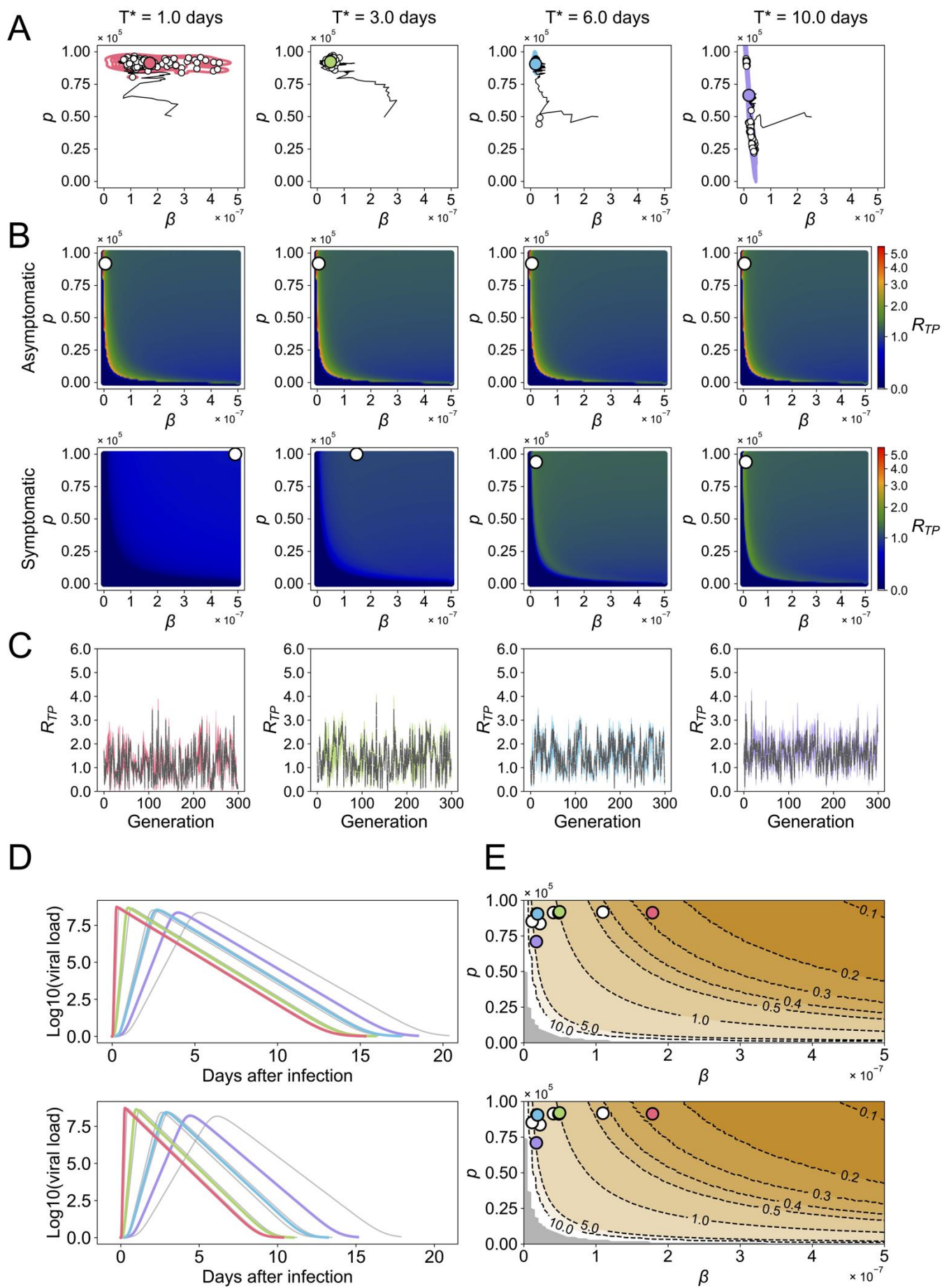


Figure S7-2. Sensitivity analysis of effects of vaccination rates on optimal viral parameters
($f = 0.3$ and vaccination rate = 0.8): Same explanation for (A-E) is applied as in **Figure S6-1**.

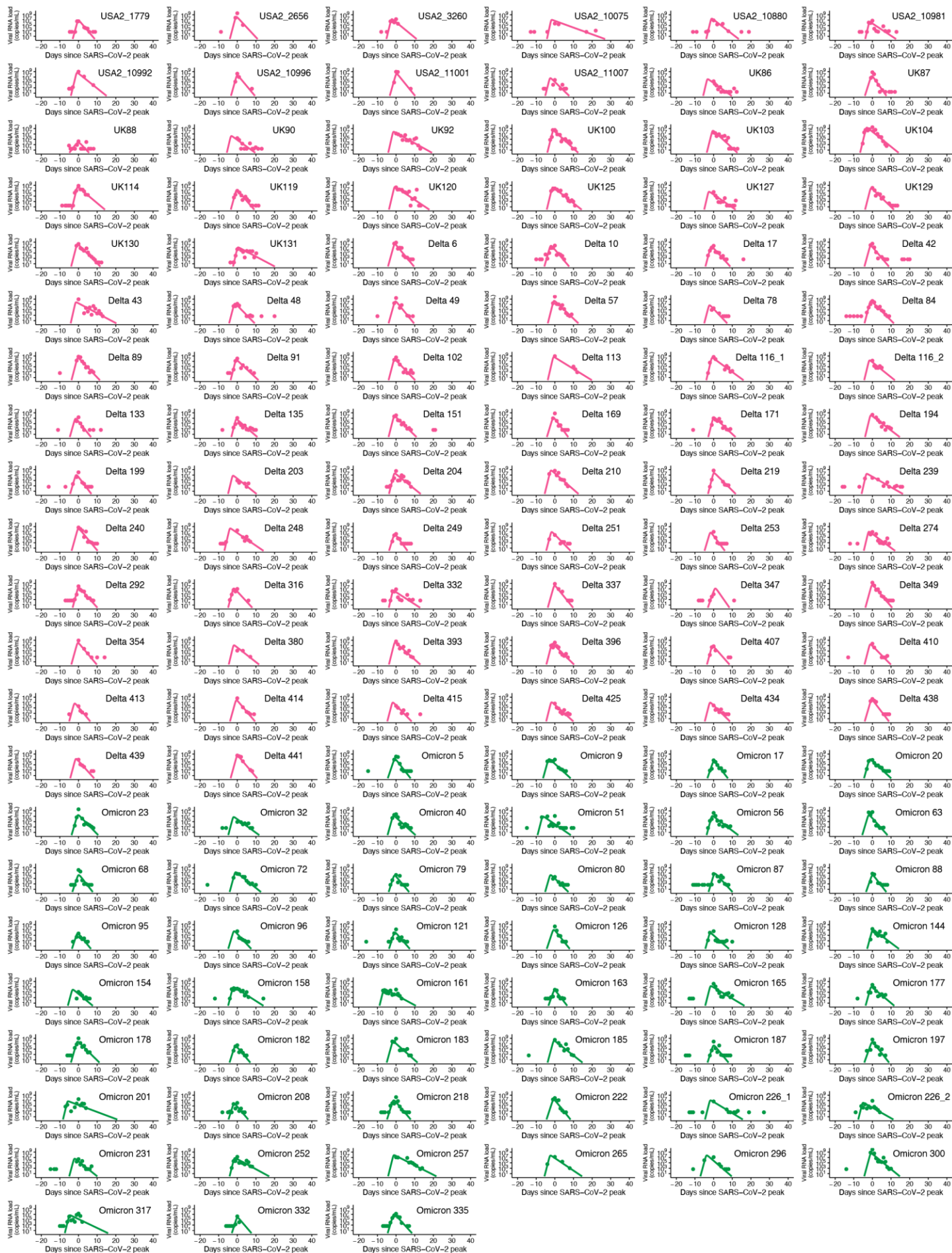


Figure S8. Viral load trajectory for individual patients infected with Delta and Omicron

variants: The estimated viral load for each individual patient (solid lines) along with the observed data (closed dots) are depicted using the best-fit parameter estimates. Delta and Omicron variants are shown in red and green, respectively. The data for the delta variant are same as in **Figure S1**. Source data are provided as a Source Data file.

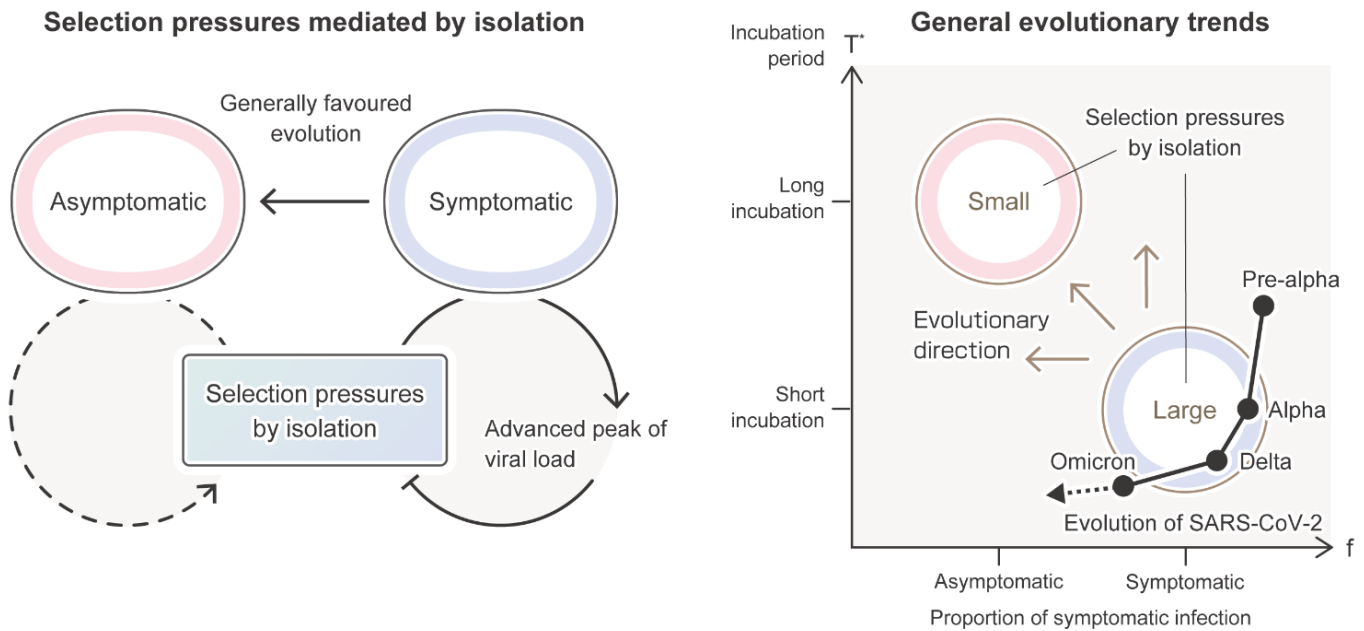


Figure S9. Possible mechanisms of adaptive virus response under isolation: Selection pressures mediated by isolation (left panel) and general evolutionary trends (right panel) are described. The solid circular arrow in the left panel represents that isolation can be a substantial selective force only when a focal patient is symptomatic. In this case, the advanced viral peak evolves to mitigate the selection pressure. However, asymptomatic infection is always favored from a perspective of virus evolution that maximizes the number of secondary infectious individuals because isolation does not limit transmissions. Thus, the dashed circular arrow in the left panel shows that no selective force is generated by isolation when the focal patient is asymptomatic. In the right panel, the possible general evolutionary trends show that a more extended incubation period (i.e., larger T^*) and/or a higher proportion of asymptomatic infection (i.e., smaller f) may generally evolve to mitigate the selection pressure of isolation. The black trajectory represents evolutionary transitions among the pre-Alpha, Alpha, Delta, and Omicron variants of SARS-CoV-2 in our analysis. The incubation period decreases as SARS-CoV-2 mutates, implying the selection pressure by isolation, and therefore the peak viral load is advanced as observed in the Delta variant. In addition, a high proportion of asymptomatic infections has recently evolved. It is also noteworthy that once the higher proportion of asymptomatic infection evolves, other viral phenotypic evolution, such as slower and/or lower peak viral load, may be allowed to evolve as observed in the Omicron variant. These multiple evolutionary outcomes may be counterbalanced during viral evolution under human behavior change (see the main text for further details).

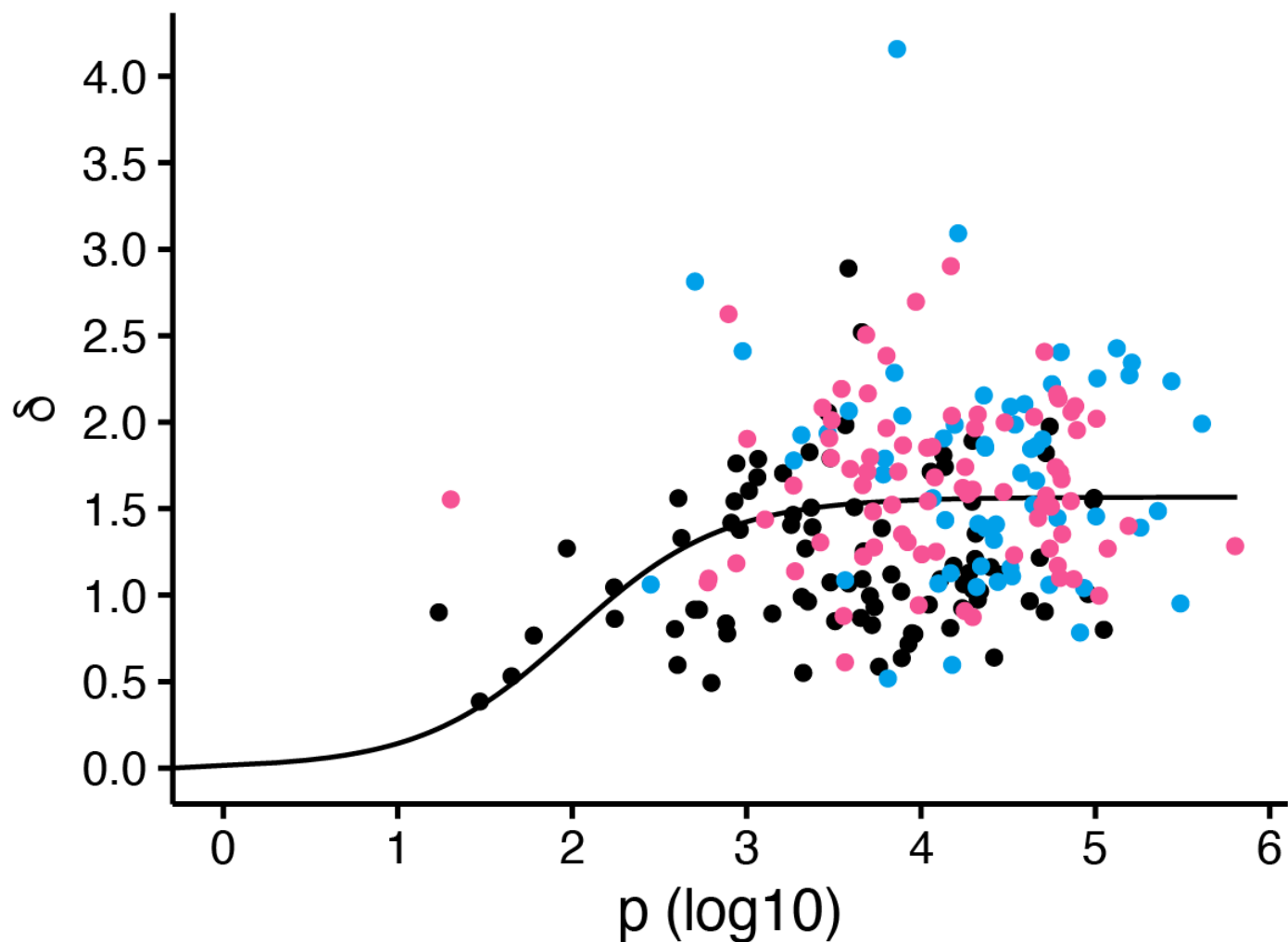


Figure S10. Relation between viral production and death rate of infected cells. Each dot shows the estimated values of p and δ for each individual for infection with the pre-Alpha, Alpha, and Delta strains. The solid line is the best-fitting curve for $\delta = \delta_{\max} p / (p + p_{50})$, whose root mean square error (RMSE) is 0.4. Pre-Alpha, Alpha, and Delta variants are colored in black, blue, and red, respectively. Source data are provided as a Source Data file.

Table S1. Summary of the study data

Country	Number of cases	Specimens	Detection limit	Reference
Pre-Alpha				
USA-1	39	Upper respiratory tract	2.66 log ₁₀ (copies/ml)	(1)
UK	47	Upper respiratory tract	1.49 log ₁₀ (copies/ml)	(2)
Alpha				
USA-2	22	Upper respiratory tract	2.66 log ₁₀ (copies/ml)	(3)
UK	37	Upper respiratory tract	1.49 log ₁₀ (copies/ml)	(2)
Delta				
USA-2	10	Upper respiratory tract	2.66 log ₁₀ (copies/ml)	(3)
USA-3	54	Upper respiratory tract	2.66 log ₁₀ (copies/ml)	(4)
UK	16	Upper respiratory tract	1.49 log ₁₀ (copies/ml)	(2)
Omicron				
USA-3	49	Upper respiratory tract	2.66 log ₁₀ (copies/ml)	(4)

Table S2. Estimated fixed parameters for SARS-CoV-2 pre-Alpha, Alpha, and Delta variants

Parameters	Symbol	Unit	Pre-Alpha	Alpha	Delta
Maximum rate constant for viral replication	γ	day ⁻¹	5.43	6.31 [#]	8.51 [#]
Rate constant for virus infection	β	(copies/mL) ⁻¹ day ⁻¹	2.33×10^{-7}	$4.74 \times 10^{-8\#}$	1.03×10^{-7}
Death rate of infected cells	δ	day ⁻¹	1.11	1.57 [#]	1.53 [#]
Time from infection to peak viral load	T_p	days	7.49	6.49 [#]	4.81 [#]

[#] Statistically different from pre-Alpha variant (the Wald test).

Table S3. Fixed parameters for multi-level population dynamics model

Parameters	Symbol	Value	Reference
The number of uninfected target cells at initial time	$T(0)$	133000	(5)
The clearance rate of the virus	c	20	(6)
The fraction of uninfected target cells compared with that at initial time	$f(0)$	1	(6)
The amount of the virus at initial time	$V(0)$	0.01	(5)
The maximum value of δ	δ_{max}	1.57	Estimated from data
The viral production rate satisfying $\delta = \delta_{max}/2$	p_{50}	100	Estimated from data
The maximum duration of viral shedding	D_{max}	80	Estimated from data
The total viral load at which the duration is half of its maximum	V_{50}	198.58	Estimated from data
The steepness at which duration increases with increasing viral load	D_k	1.17	Estimated from data
The shape parameter of gamma distribution	k	1.5	Fixed as an example
The scale parameter of gamma distribution	θ	1.5	Fixed as an example
The maximum value of β	β_{max}	5.0×10^{-7}	Fixed as an example
The maximum value of p	p_{max}	1.0×10^5	Fixed as an example

1 **Table S4.** Fixed parameters for genetic algorithm (GA)

Parameters	Value
The population size	100
The number of iterations	300
The number of elitism	2
The probability of selection	1.0
The probability of crossover	0.2
The probability of mutation	0.7
The predefined range of β in mutation	0.5×10^{-7}
The predefined range of p in mutation	0.1×10^5

2
3

4 **Table S5.** Estimated fixed parameters for SARS-CoV-2 Delta and Omicron variants

Parameters	Symbol	Unit	Delta	Omicron
Maximum rate constant for viral replication	γ	day ⁻¹	7.83	7.21 [#]
Rate constant for virus infection	β	(copies/mL) ⁻¹ day ⁻¹	1.23×10^{-7}	5.38×10^{-7} [#]
Death rate of infected cells	δ	day ⁻¹	1.60	1.49
Time from infection to peak viral load	T_p	days	4.96	5.46

5 [#] Statistically different from delta variant (the Wald test).

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8 **Algorithm S1.** Procedure of genetic algorithm (GA)

Genetic algorithm

Input: s_i , solution i of combinations of β and p

Input: $P(t = i) = \{s_1, s_2, \dots, s_j\}$, population of solutions in iteration i

$t \leftarrow 0$;

Initialize ($P(t = 0)$) with random β and p ;

Evaluate ($P(t = 0)$);

while not termination do

The scale parameter of gamma distribution

$P(t)_e \leftarrow \text{Elitism } (P(t))$;

$P(t)_p \leftarrow \text{selectSolutions } (P(t))$;

$P(t)_c \leftarrow \text{crossover } (P(t)_e + P(t)_p)$;

Mutate ($P(t)_c$);

Evaluate ($P(t)_c$);

$P(t+1) \leftarrow P(t)_c$;

$t \leftarrow t + 1$;

end while

9

10

11

12 **References**

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