Mechanistic Modelling of Multiple Waves in an Influenza Epidemic or Pandemic (Appendix): Supplementary Tables and Figures

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Table A.1. The parameters and corresponding values used in each model.

Parameter	**AoN**	**PPI**	**2Vi**	**Mut**	**2Reg**	**IoS**	**RRV**	**PTR**	**ATR**	**2Age**	**RN**	**1918-Flu**
$1/\nu$ (mean infective period, day)	2.4	1.0	2.0	1.0	3.6	3.3	9.0	3.0	3.0	36.5	4.0	2.9, 0.9, 2.2, 1.7[a]
$1/\epsilon$ (mean latent period, day)	2.1	1.8	1.5	2.4	/	/	1.65	1.0	1.0	2.4	/	1.9, 0.53[b]
$1/\gamma$ (mean temporary removed period, day)	11.6	5.7	0.3	1.0	/	/	/	/	/	/	/	/
R_0 (basic reproduction number)	11.2	6.9	4.2, 4[c]	9.2	/	/	/	/	/	/	/	/
ρ (reporting rate)	0.71	0.68	0.65	0.69	0.75	0.75	0.90[d]	0.75	0.75	0.75	0.75	0.597, 0.83[e]
S (initial number of susceptible people)	27700	27700	27700	27700, 0[f]	27700, 13850[g]	27700	27700	21994	22160	8310, 6094[h]	*	174334
E (initial number of exposed people)	0	0	0, 0[i]	0, 0, 0, $E^1_{(t=T_m)}$[j]	/	/	0	0	55	0, 0[k]	/	157
I (initial number of infected people)	1	1	20, 10[l]	1, 0, 1, $I^1_{(t=T_m)}$[m]	2, 5[n]	1	1	166	277	33, 28[o]	**	80
R (initial number of removed/recovered people)	0	0	0, 0[p]	0, 0, 0, 0[q]	3, 1[r]	5	5	5540	5208	0, 554[s]	0	0
L (initial number of people who are protected in the long-term against reinfection)	6	6	4, 0[t]	5, 0, $L_{1(t=T_m)} + S_{(t=T_m)} + R^1_{(t=T_m)}$, 0[u]	/	/	/	/	/	/	/	/

$1-\sigma$ (partial protection induced by immunity)	/	0.71	/	0.82	/	/	/	/	/	/	/	/
β (transmission rate, contacts per day)	/	/	/	/	0.89	0.67	0.40	0.8, 0.3[v]	***	0.47, 0.03, 0.15[w]	0.3	1.49, 5.75[x]
T_i (time lag/interval, day)	/	/	/	/	15[y]	5[z]	7[A]	/	/	18[B]	/	/
T (time point, day)	/	/	/	20th[C]	/	35th[D]	45th[E]	/	/	27th[F]	/	/
Inc (initial number of incidence)	/	/	/	/	0, 0[G]	/	0	/	****	/	/	/
other parameters	0.42[H]	/	/	/	/	0.2, 2.5[I]	0.1[J]	/	/	-0.0023, -0.0144, 0.3023, 0.665[K]	0.001, 0.975[L]	174571, 1/(60*365), 0.003, 0.1, 0.51, 0.014, 0.36, 2.14[M]

[a] For wave 1, the mean infective period for people without treatment ($1/\gamma_{1_1}$) is 2.9 days, that for hospitalized people ($1/\gamma_{2_1}$) is 1.9 days; for wave 2, that for people without treatment ($1/\gamma_{1_2}$) is 2.2 days, that for hospitalized people ($1/\gamma_{2_2}$) is 1.7 days.

[b] The mean latent period for wave 1 ($1/\epsilon_1$) is 1.9 days, that for wave 2 ($1/\epsilon_2$) is 0.53 days.

[c] The basic reproduction number of virus 1 (R_0^1) is 4.2, that of virus 2 (R_0^2) is 4.

[d] The ordinary reporting rate (ρ_m).

[e] The reporting rate for wave 1 (ρ_1) is 0.597, that for wave 2 (ρ_2) is 0.83.

[f] When $1 \leq t \leq T_m$, $S = 27700$; when $t > T_m$, $S = 0$. T_m is the time when mutation occurs.

[g] The initial number of susceptible people in subpopulation 1 (S_1) is 27700, that in subpopulation 2 (S_2) is 13850.

[h] The initial number of susceptible children (S_C) is 8310, that of susceptible adults (S_A) is 6094.

[i] The initial number of people exposed to virus 1 (E^1) is 0, and the number of people who are immune to virus 1 but exposed to virus 2 (E_1^2) is also 0.

[j] When $1 \leq t \leq T_m$, the initial number of people exposed to the original virus (E^1) is 0, the number of people who are immune to the original virus but exposed to the mutated virus (E_1^2) is 0; when $t > T_m$, $E^1 = 0$, and $E_1^2 = E_{(t=T_m)}^1$, where $E_{(t=T_m)}^1$

represents the number of people exposed to the original virus at time of T_m, and T_m is the same as that in [f].

[k] The initial number of exposed children (E_C) is 0, that of exposed adults (E_A) is 0.

[l] The initial number of people infected by virus 1 (I^1) is 20, the number of people who are immune to virus 1 but infected by virus 2 (I_1^2) is 10.

[m] When $1 \leq t \leq T_m$, the initial number of people infected by the original virus (I^1) is 1, the number of people who are immune to the original virus but infected by the mutated virus (I_1^2) is 0; when $t > T_m$, $I^1 = 1$, and $I_1^2 = I_{(t=T_m)}^1$, where $I_{(t=T_m)}^1$ represents the number of people infected by the original virus at time of T_m, and T_m is the same as that in [f].

[n] The initial number of infected people in subpopulation 1 (I_1) is 2, that in subpopulation 2 (I_2) is 5.

[o] The initial number of infected children (I_C) is 33, that of infected adults (I_A) is 28.

[p] The initial number of people removed/recovered from virus 1 (R^1) is 0, the number of people who are immune to virus 1 and removed/recovered from virus 2 (R_1^2) is 0.

[q] When $1 \leq t \leq T_m$, the initial number of people removed/recovered from the original virus (R^1) is 0, the number of people who are immune to the original virus and removed/recovered from the mutated virus (R_1^2) is 0; when $t > T_m$, $R^1 = 0$, and $R_1^2 = 0$.

[r] The initial number of removed/recovered people in subpopulation 1 (R_1) is 3, that in subpopulation 2 (R_2) is 1.

[s] The initial number of removed/recovered children (R_C) is 0, that of removed/recovered adults (R_A) is 554.

[t] The number of people who are protected in the long-term against reinfection by virus 1 (L_1) is 4, that against reinfection by both virus strains 1 and 2 (L_{12}) is 0.

[u] When $1 \leq t \leq T_m$, the number of people who are protected in the long-term against reinfection by the original virus (L_1) is 5, that against reinfection by both virus strains (L_{12}) is 0; when $t > T_m$, $L_1 = L_{1(t=T_m)} + S_{(t=T_m)} + R_{(t=T_m)}^1$, $L_{12} = 0$, where T_m is the same as that in [f].

[v] The mean transmission rate (β_0) is 0.8 per day, the cyclic transmission rate (β_1) is 0.3 per day.

[w] The transmission rate between children (β_{CC}) is 0.47 per day, that between children and adults (β_{CA}, β_{AC}) is 0.03 per day, and that between adults (β_{AA}) is 0.15 per day.

[x] The transmission rate of wave 1 (β_1) is 1.49 per day, that of wave 2 (β_2) is 5.75 per day.

[y] The time lag between the epidemic onset dates in two subpopulations is 15 days.

[z] The time interval between the second and first addition is 5 days.

[A] The time that the reporting rate requires to decrease from ordinary value to minimum is 7 days.

[B] The length of the second period of children's susceptibility is 18 days.

[C] The time when mutation occurs is the 20th day.

[D] The time (T_S) when first addition of susceptible people from other regions occurs is

the 35th day.

[E] The time (T_ρ) when the reporting rate begins to decline is the 45th day.

[F] The time (T_C) when the first period of children's susceptibility ends is the 27th day.
[G] The initial number of incidence in subpopulation 1 (Inc_1) is 0, that in subpopulation 2 (Inc_2) is 0.
[H] The probability to develop long-term immunity (α) is 0.42.
[I] The addition proportion of susceptible people at the first time (s_{a1}) is 0.2, that at the second time (s_{a2}) is 2.5.
[J] The changing rate (a) of reporting rate is 0.1.
[K] The changing rate of children's susceptibility during the first period (a_1) is -0.0023, that during the second period (a_2) is -0.01439. The intercept of children's susceptibility during the first period (b_1) is 0.3023m that during the second period (b_2) is 0.665.
[L] The coefficient (θ) multiplied by the total population of each subpopulation to calculate initial number of susceptible people is 0.001. The coefficient (δ) multiplied by m_{ij} to simulate the implementation of traffic control during epidemic is 0.975, where m_{ij} is the average number of individuals moving from subpopulation i to subpopulation j per day.
[M] The total number of all people (N) is 174571. The natural birth (or death) rate (μ) is 1/(60*365) day^{-1}. In wave 1, the relative infectiousness of asymptomatic people (q_1) is 0.003; the proportion of clinically infections (k_1) is 0.1; the diagnostic rate (α_1) is 0.51 per day. In wave 2, the relative infectiousness of asymptomatic people (q_2) is 0.014; the proportion of clinically infections (k_2) is 0.36; the diagnostic rate (α_2) is 2.14 per day.
* The initial number of susceptible people in each of all 333 subpopulations in the RN model can be provided by authors upon request of readers.
** The initial number of infected people in each of all 333 subpopulations in the RN model can be provided by authors upon request of readers.
*** The transmission rate (β_t) in the ATR model is estimated over time and time-varying.
**** The input incidence time series in the ATR model is the weekly reported H1N1 cases in USA during 2009 pandemic, from week 17 to 52, provided by [1].

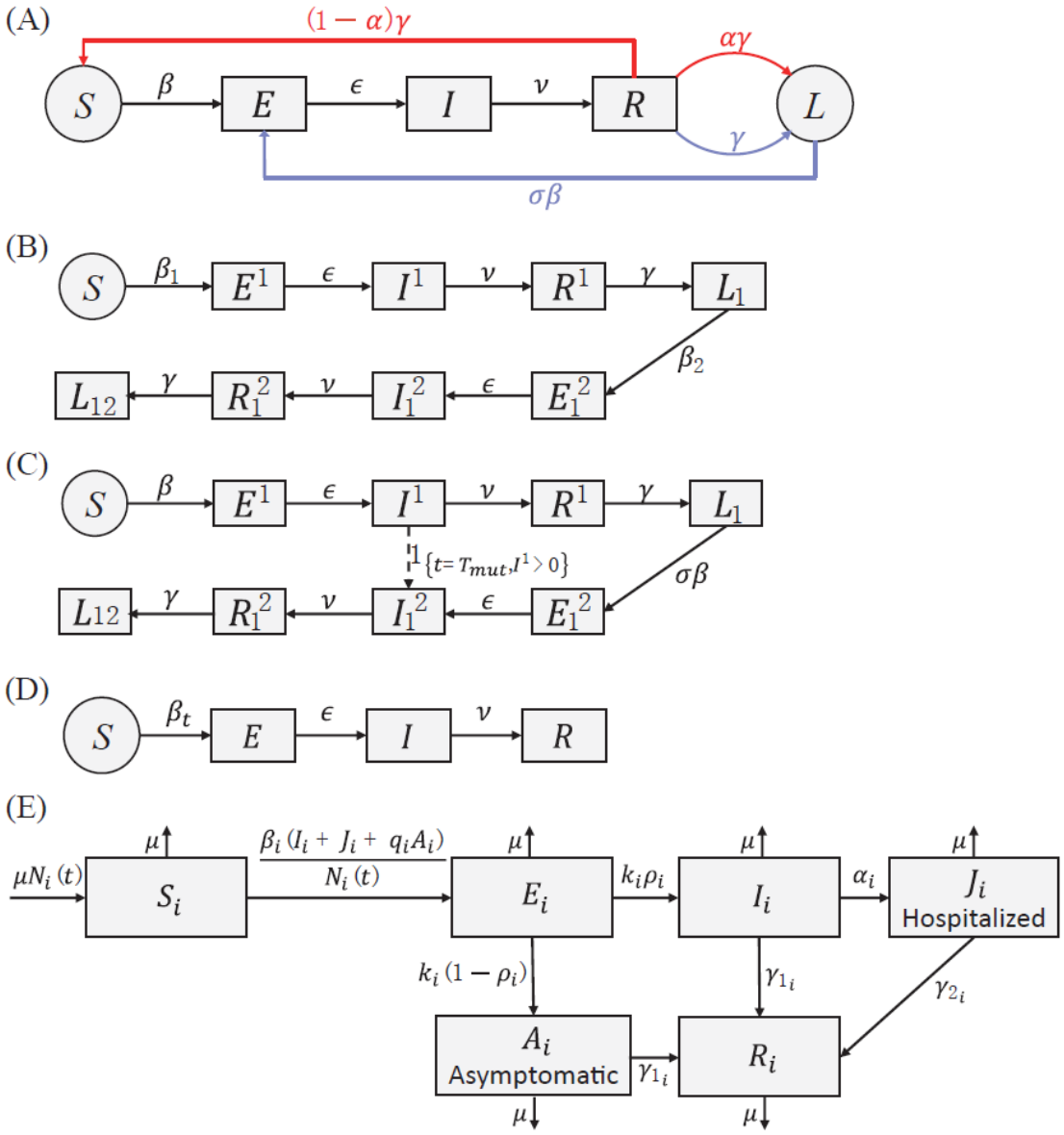


Fig. A.1. The structure diagrams of models adopted from previous research. S, E, I, R, and L represent the number of people who are in five epidemiological states respectively: susceptible, exposed, infectious, recovered/removed, and long-term protected. β, ϵ, ν, and γ are the transmission rate, the reciprocal of latent period, the reciprocal of the infectious period, and the reciprocal of temporary removed period, respectively. (A) All-or-Nothing (red) and Partially-Protective-Immunity (purple) [2]. (B, C) 2 Virus and Mutation [2]. Superscript stands for the infective strain, subscript

for the already-immunized strain. Hosts recovered from strain i enter the L_i class and become completely protected against reinfection by strain i while remaining susceptible to the other circulating strain j. For the Mutation model, the two strains interact through a cross-immunity parameter $\sigma \in [0, 1]$ that acts by reducing the susceptibility to the other strain. The dashed arrow indicates that at time T_{mut} if $I^1 > 0$, one infectious host with the initial strain becomes infectious with the mutated strain. (D) Transmission-Rate-Variation (Periodic-Transmission-Rate and Aperiodic-Transmission-Rate) [1]. β_t is the transmission rate at time t. (E) 1918-Flu [3]. The subscript 'i' takes two values 1 and 2, referring to the first and second infection wave, respectively. N, J, and A represent the number of all people, hospitalized people, and asymptomatic people, respectively. μ, q, k, ρ, α, and γ are the natural birth (or death) rate, the relative infectiousness of asymptomatic people, the proportion of clinically infections, the reporting rate, the diagnostic rate, and the reciprocal of the infectious period, respectively.

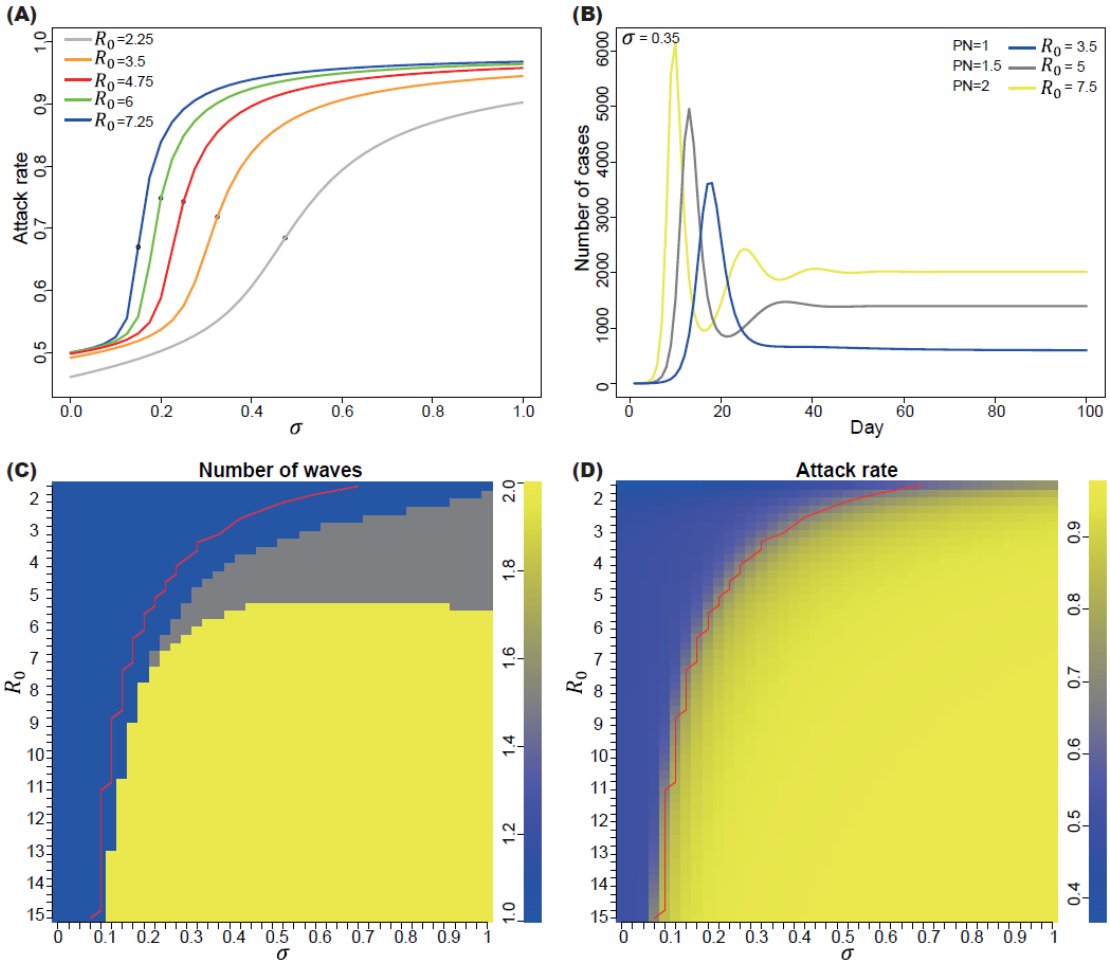


Fig. A.2. Sensitivity analysis of the Partially-Protective-Immunity model. R_0 is the basic reproduction number. 1-σ represents the degree of partial immune protection acquired after former recovery. PN represents the number epidemic waves. (A) Attack rate as a function of σ. Each black dot in the curve indicates the point of the highest slope. (B) Epidemic curves corresponding to different R_0, given σ=0.35. Numbers of epidemic waves (C) and attack rates (D) corresponding to different tuples of (σ,R_0). Red line consists of points of which each corresponds to the locally highest slope along a certain sigmoid curve of attack rate changing with σ when R_0 is fixed.

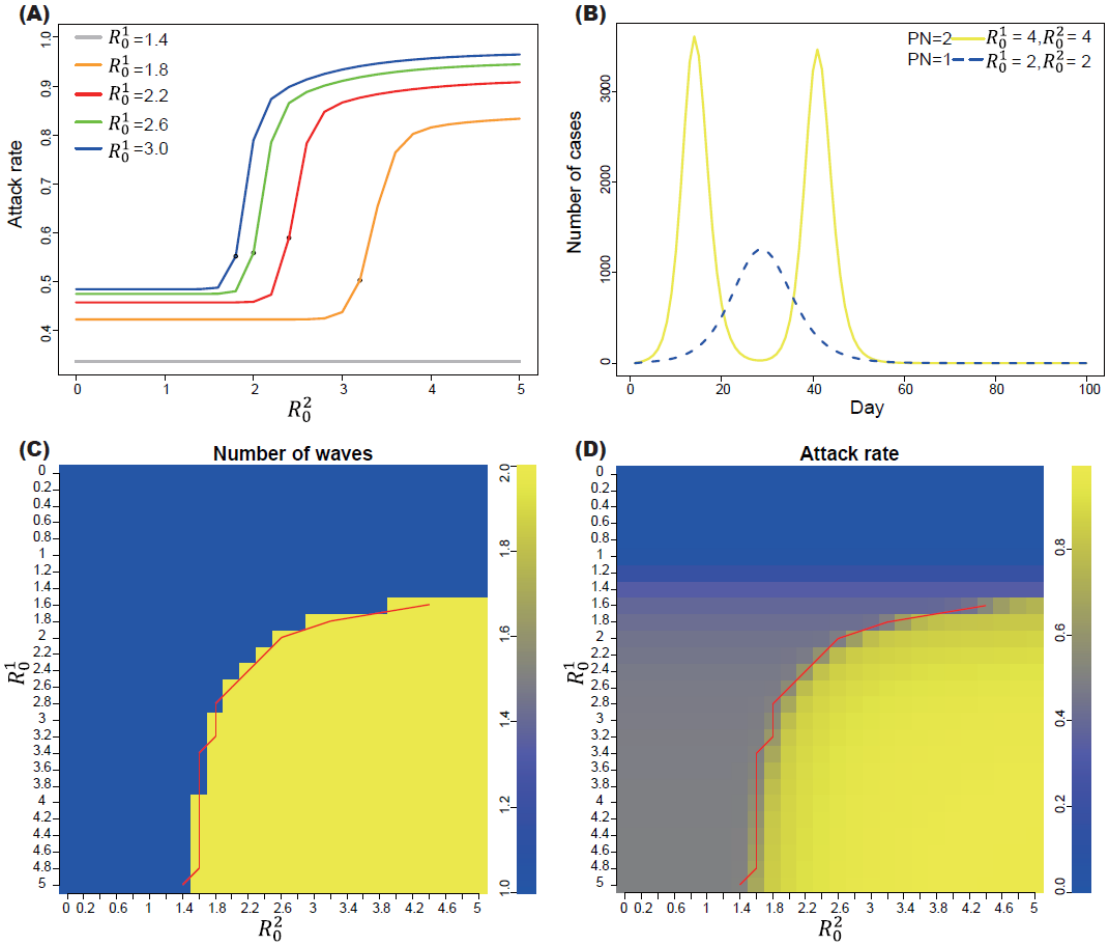


Fig. A.3. Sensitivity analysis of the 2 Virus model. R_0^1 and R_0^2 represent the basic reproduction number of virus 1 and virus 2, respectively. PN represents the number epidemic waves. (A) Attack rate as a function of R_0^2. Each black dot in the curve indicates the point of the highest slope. (B) Epidemic curves of two waves and one wave. Numbers of epidemic waves (C) and attack rates (D) corresponding to different tuples of (R_0^2,R_0^1). Red line consists of points of which each corresponds to a locally highest slope along a certain sigmoid curve of attack rate changing with R_0^2 when R_0^1 is fixed.

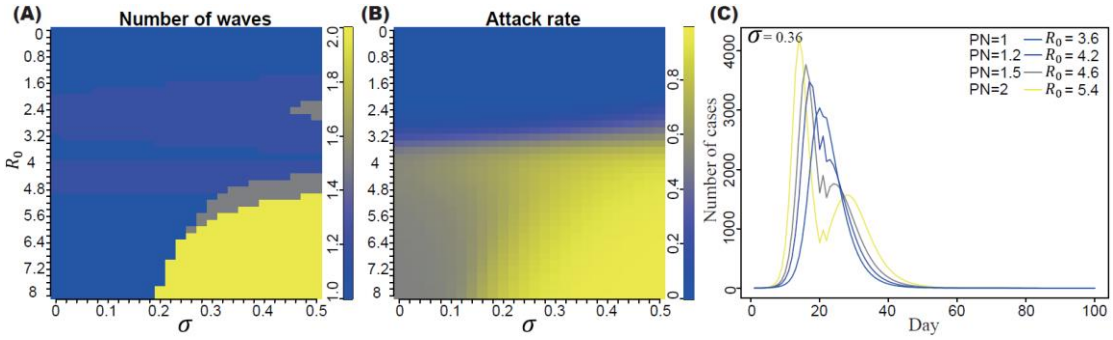


Fig. A.4. Sensitivity analysis of the Mutation model. R_0 is the basic reproduction number of both virus strains. 1-σ represents the degree of cross-immunity acquired after recovering from the former virus strain. PN represents the number epidemic waves. Numbers of epidemic waves (a) and attack rates (b) corresponding to different tuples of (σ,R_0). (c) Epidemic curves corresponding to different R_0, given σ=0.36.

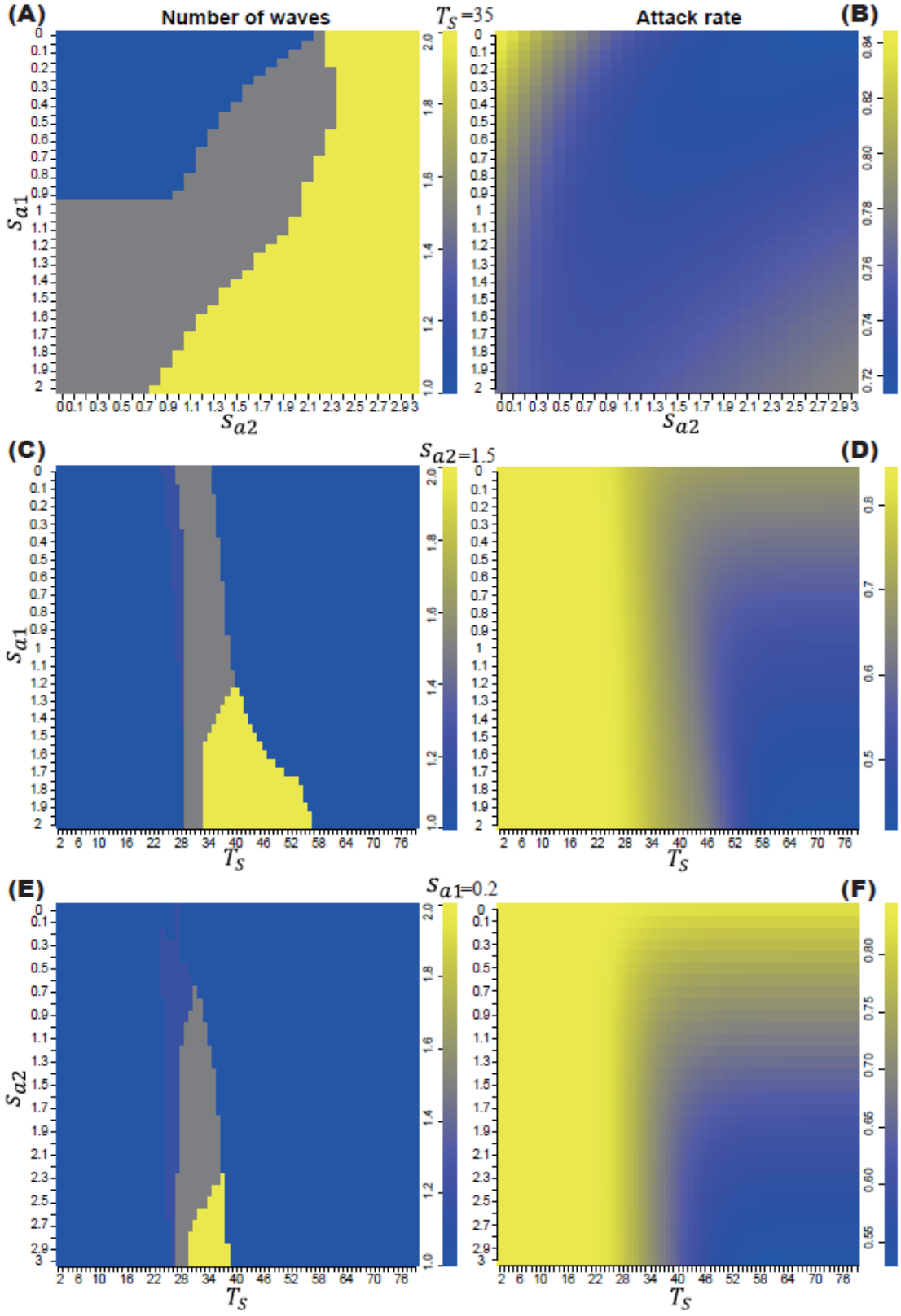


Fig. A.5. Sensitivity analysis of the Importation-of-Susceptible model. s_{a1} is the proportion of added susceptible individuals at the first time (T_S), while s_{a2} is that at the second time. Numbers of epidemic waves (A) and attack rates (B) corresponding

to different tuples of (s_{a2},s_{a1}), given T_S=35. Numbers of epidemic waves (C) and attack rates (D) corresponding to different tuples of (T_S,s_{a1}), given s_{a2}=1.5. Numbers of epidemic waves (E) and attack rates (F) corresponding to different tuples of (T_S,s_{a2}), given s_{a1}=0.2.

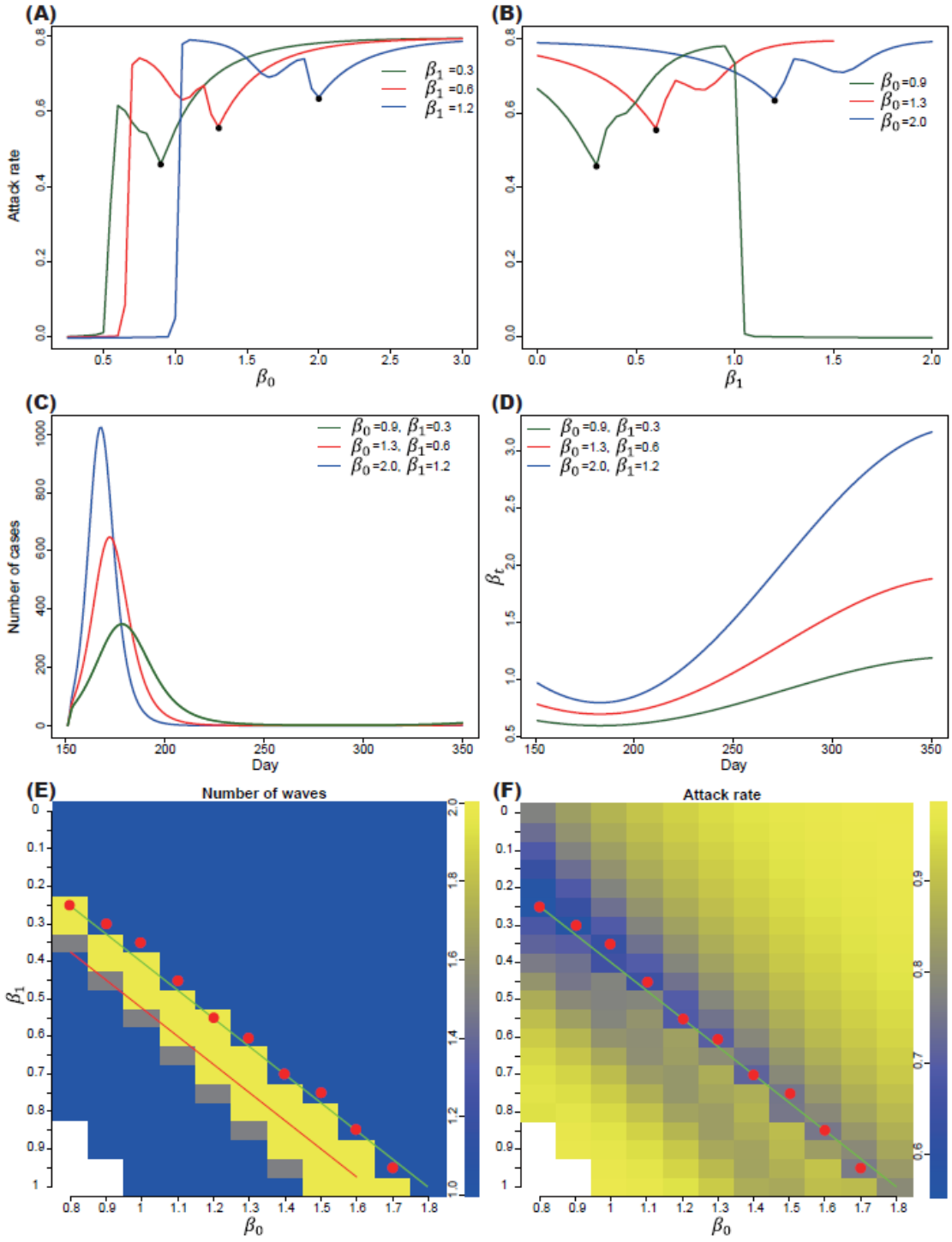


Fig. A.6. Sensitivity analysis of the Periodic-Transmission-Rate model. β_0 is the average value of transmission rate (β) and β_1 is the amplitude of the fluctuating part of β. (A-B) Attack rate as a function of β_0 (A) and β_1 (B). Black dots are the troughs of V-shaped curves. The epidemic curves (C) and periodic transmission rates (D) both correspond to the black dots in (A, B). Numbers of epidemic waves (E) and

attack rates (F) corresponding to different tuples of (β_0,β_1). Red points are determined by (β_0,β_1) corresponding to the locally lowest attack rates, and they could be approximated by a green line (*L1*). (β_0,β_1) corresponding to two infection waves would be approximated by a red line (*L2*). The white grids represent the meaningless situation where $\beta_0 < \beta_1$.

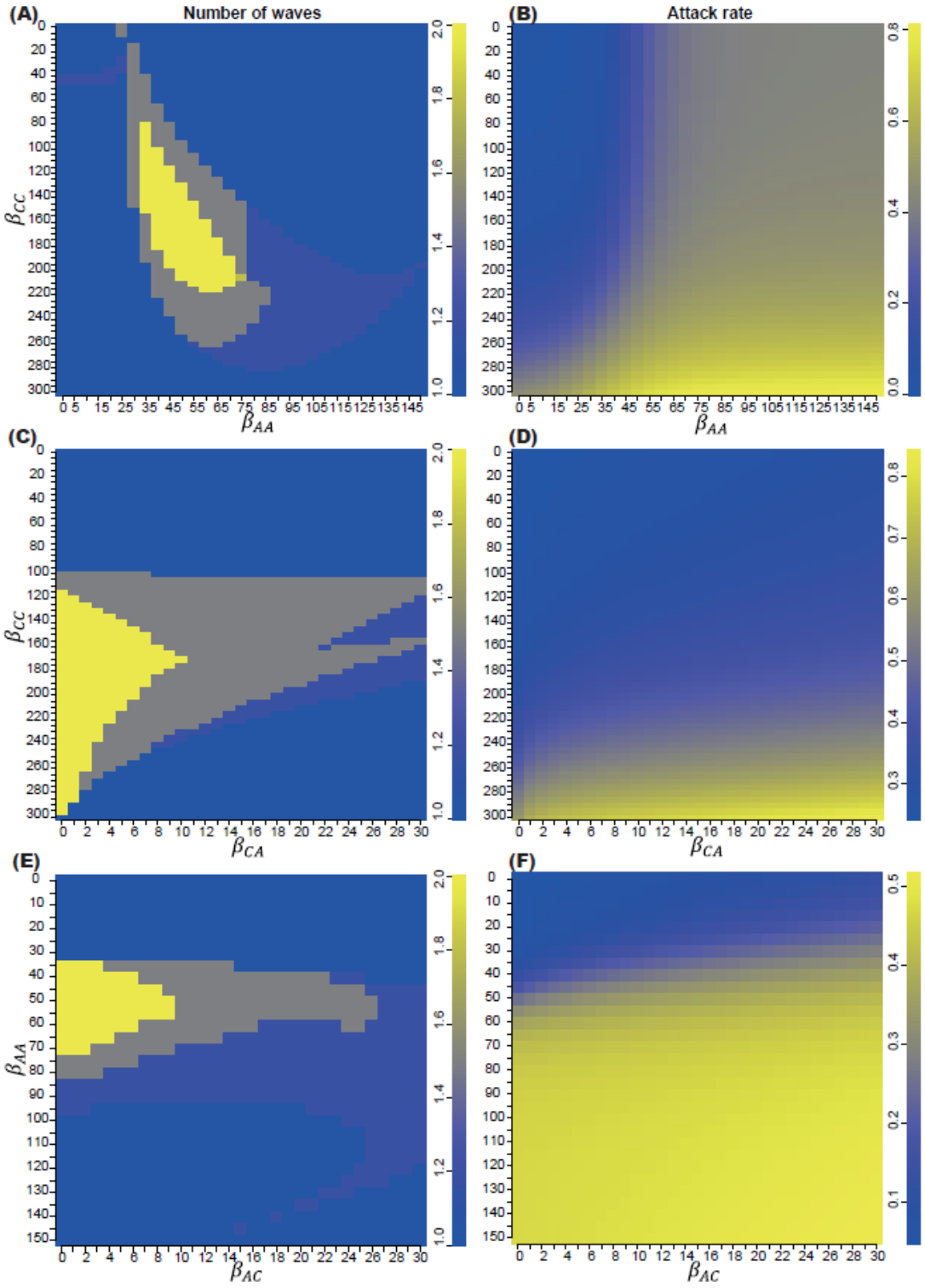
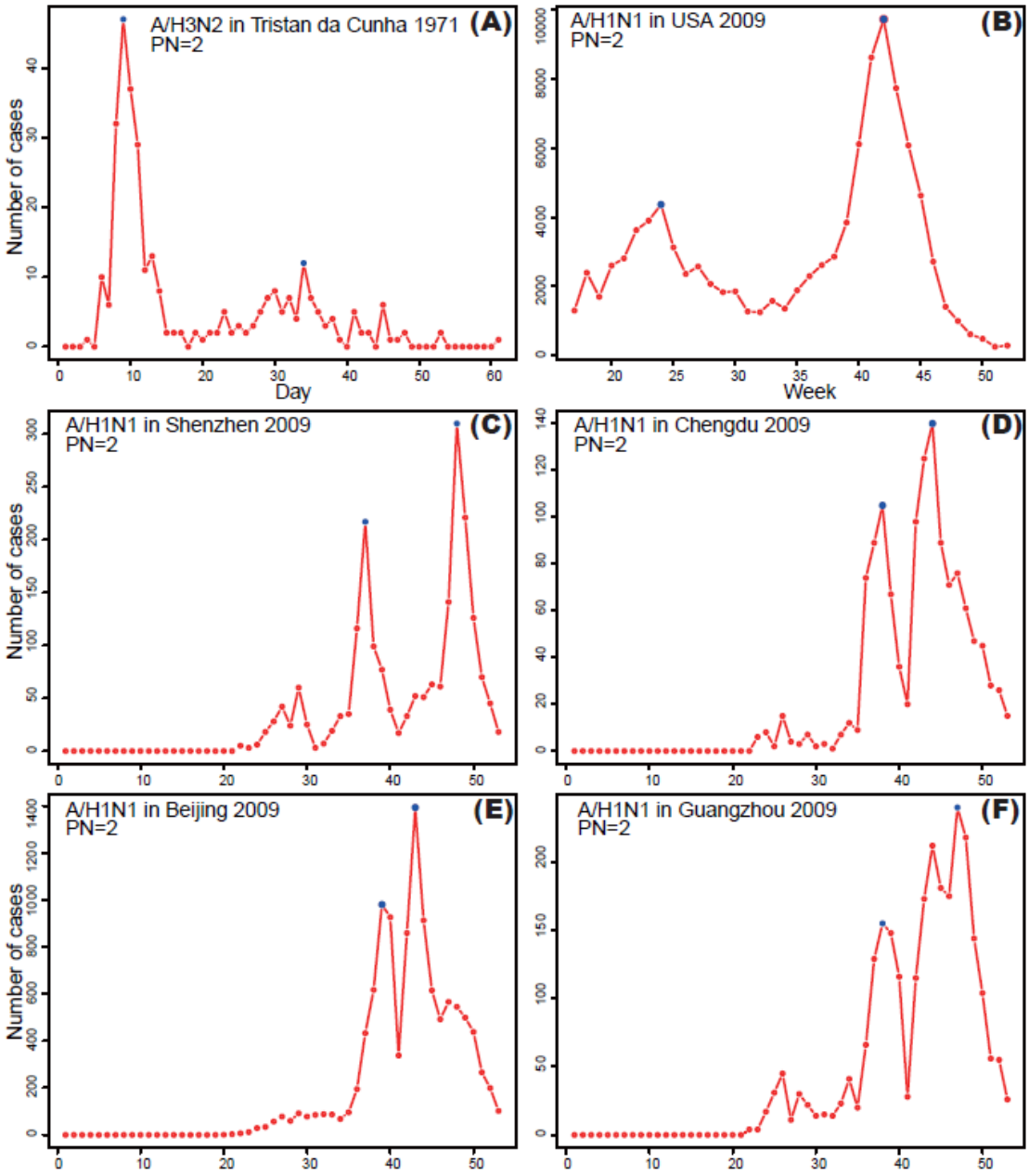


Fig. A.7. Sensitivity analysis of the 2 Age-group model. β_{CC},β_{AA} and β_{CA} (or β_{AC}) represents the number of effective contacts per day among children, among adults, and between children and adults, respectively. Numbers of epidemic waves (A) and attack rates (B) corresponding to different tuples of (β_{AA},β_{CC}) , given $\beta_{CA} = 5/365$.

Numbers of epidemic waves (C) and attack rates (D) corresponding to different tuples of (β_{CA},β_{CC}), given $\beta_{AA} = 53/365$. Numbers of epidemic waves (E) and attack rates (F) corresponding to different tuples of (β_{AC},β_{AA}), given $\beta_{CC} = 170/365$.



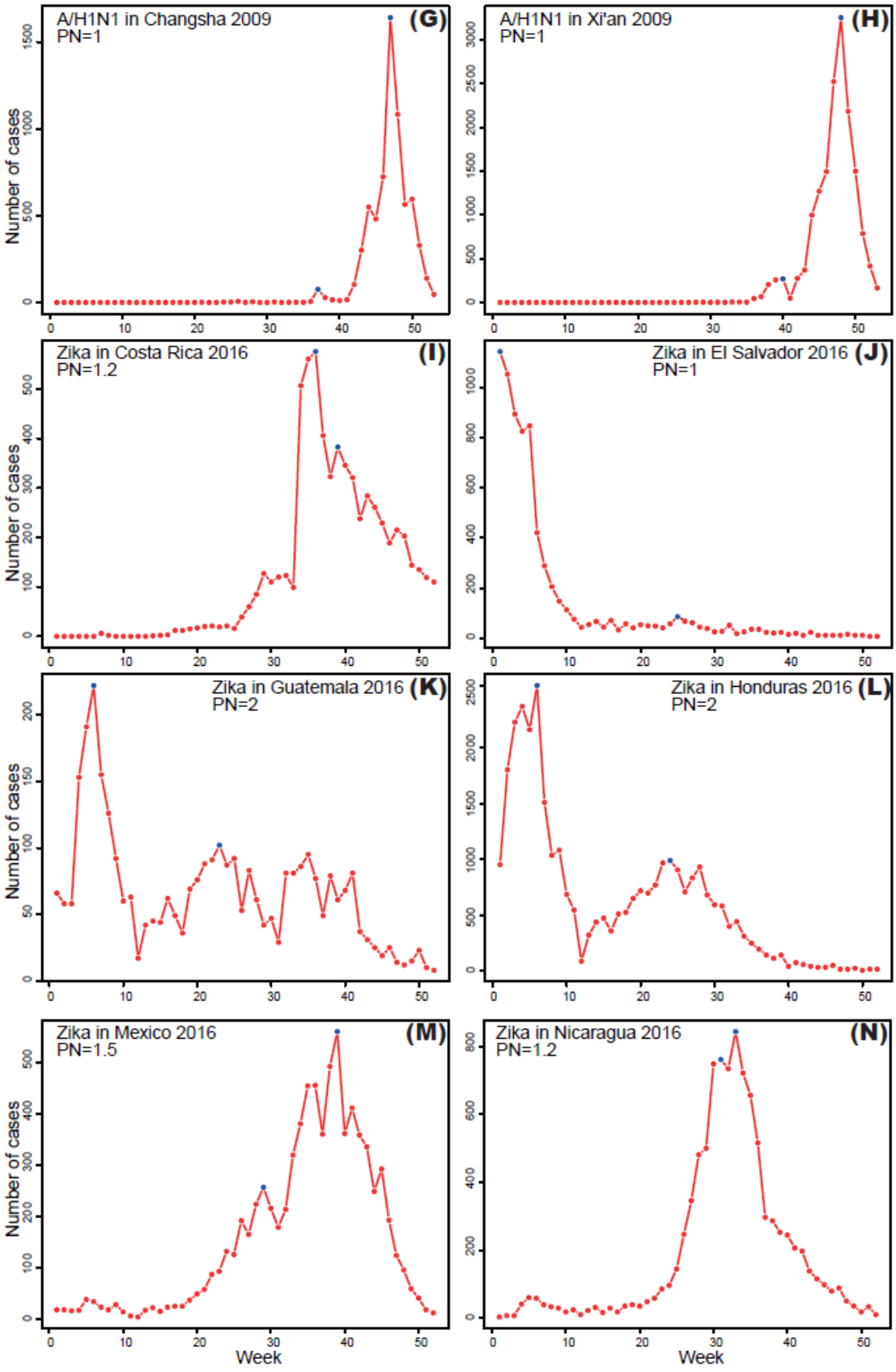


Fig. A.8. The fuzzy numbers of waves (PN) detected by the metrics and criteria proposed in our research when applying them on real datasets. These datasets are time

series of reported cases of A (H3N2) in Tristan da Cunha in 1971 (A), of the 2009 pandemic in America (B) and several cities in mainland China (C-H), and of the Zika virus epidemic in a few Central and South American countries in 2016 (I-N). The two blue dots in each epidemic curve are key points to determine PN of the specific curve using our method.

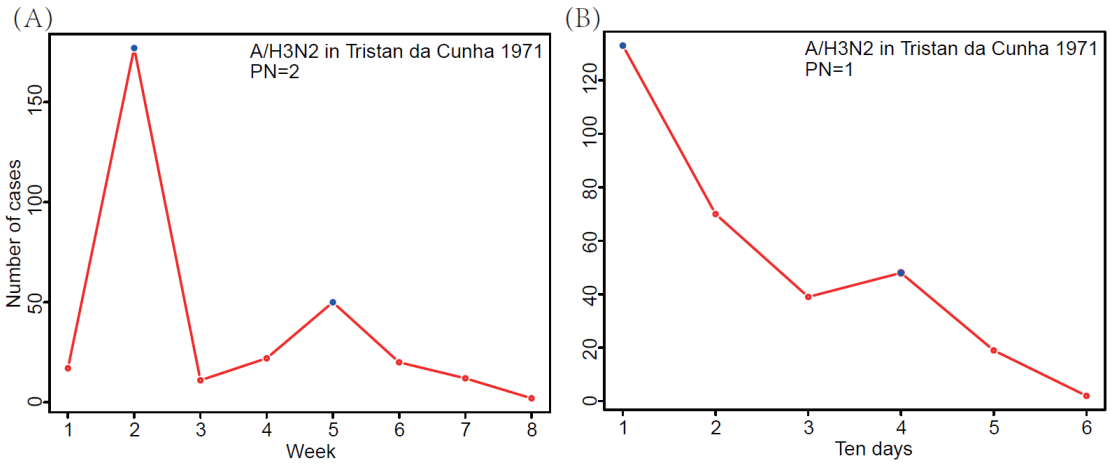


Fig. A.9. The numbers of peaks/waves (PN) of the epidemic curve of A (H3N2) in Tristan da Cunha in 1971, corresponding to a higher (one value per week, (A)) and a lower (one value per ten days, (B)) frequency of data aggregation.

References

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