THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix

Contents

The model

We use the superscripts "S" and "R" to denote the AVS and AVR strains, respectively. For strain $u \in \{S, R\}$, let $R_{jk}^{u}(t)$ be the expected number of secondary cases in age group *j* caused by one infected case in age group *k* at time *t*. The next generation matrix $\left\{R_{jk}^{u}(t)\right\}$ encapsulates all factors that affect transmissibility, including depletion of susceptible population, interventions such as vaccination and school closure, seasonal forcing, etc. Let $f_j^{u}(t)$ be the proportion of strain *u* infections at time *t* that are in age group *j*. Under the base case assumptions (see Methods), AVR fitness does not depend on age groups, i.e. $R_{jk}^{R}(t) = \sigma R_{jk}^{S}(t)$ for all *j*, *k* and *t*. As such, for all time *t*, the age distribution of AVR and AVS infections are the same, i.e. $f_j^{R}(t) = f_j^{S}(t) = f_j(t)$ for all *j*. Let $i_j^{u}(t)$ be the incidence rate of strain $u \in \{S, R\}$ in age group *j* at time *t*. The epidemic dynamics is described by $i_j^{u}(t) = \sum_k R_{jk}^{u}(t) \int_0^t g^{u}(t-a) i_k^{u}(a) da$, where g^{u} is the generation time distribution for strain $u \in \{S, R\}$ which we assume to be independent of age.

Let $\rho_j(t)$ be the proportion of incidence in age group *j* at time *t* that are AVR. Under the base case assumptions, AVS and AVR infections have the same probability of being selected for AVR testing. In this case, $\rho_j(t)$ is also the probability that a subject selected for AVR testing at time *t* is infected by the AVR strain. Thus, we have

$$\begin{aligned}
\rho_j(t) &= \frac{i_j^{R}(t)}{i_j^{S}(t) + i_j^{R}(t)} \\
&= \frac{\sum_k R_{jk}^{R}(t) \int_0^t g^{R}(t-a) i_k^{R}(a) da}{\sum_k \left(R_{jk}^{R}(t) \int_0^t g^{R}(t-a) i_k^{R}(a) da + R_{jk}^{S}(t) \int_0^t g^{S}(t-a) i_k^{S}(a) da \right)} \\
&= \frac{\int_0^t \sigma g^{R}(t-a) \sum_k R_{jk}^{S}(t) i_k^{R}(a) da}{\int_0^t \sigma g^{R}(t-a) \sum_k R_{jk}^{S}(t) i_k^{R}(a) da + \int_0^t g^{S}(t-a) \sum_k R_{jk}^{S}(t) i_k^{S}(a) da} \\
&= \frac{\int_0^t \sigma g^{R}(t-a) i^{R}(a) \sum_k R_{jk}^{S}(t) f_k(a) da}{\int_0^t \sigma g^{R}(t-a) i^{R}(a) \sum_k R_{jk}^{S}(t) f_k(a) da + \int_0^t g^{S}(t-a) i^{S}(a) \sum_k R_{jk}^{S}(t) f_k(a) da}
\end{aligned}$$

We conjecture that the age distribution $f_k(t)$ does not change drastically over the timescale of one generation interval, in which case

$$\rho_j(t) \approx \frac{\int_0^t \sigma g^R(t-a) i^R(a) da}{\int_0^t \sigma g^R(t-a) i^R(a) da + \int_0^t g^S(t-a) i^S(a) da}.$$

and hence $\rho_j(t)$ is independent of age such that

$$\rho_j(t) \approx \rho(t) \approx \frac{\int_0^t \sigma g^R(t-a) \rho(a) i(a) da}{\int_0^t \sigma g^R(t-a) \rho(a) i(a) da + \int_0^t g^S(t-a)(1-\rho(a)) i(a) da}$$

for all time *t*. **Figure A1** shows that this approximation is very accurate for a wide range of plausible epidemic scenarios. Given the data stream for a time series of influenza incidence or its proxy $\tilde{i}(t)$, let $q(t) = \tilde{i}(t)/i(t)$ be the scaling factor at time *t* which encapsulates temporal variation in reporting proportion (for ILI-based proxies), laboratory testing capacity (for daily number of laboratory confirmed cases), internet search behavior (for Google Flu Trends), etc. In reality, it is unlikely that $q(t)$ would drastically fluctuate within one generation interval, in which case

$$\tilde{\rho}(t) \approx \frac{\int_0^t \sigma g^R(t-a) \tilde{\rho}(a) \tilde{i}(a) da}{\int_0^t \sigma g^R(t-a) \tilde{\rho}(a) \tilde{i}(a) da + \int_0^t g^S(t-a)(1-\tilde{\rho}(a)) \tilde{i}(a) da}.$$

This forms the basis for the approximation in equation (1).

Likelihood function

Let Z_d^S and Z_d^R be the number of AVR tests on day *d* that are negative and positive for AVR, respectively. Let *D* be the set of dates for which AVR surveillance data are available, and p_{sens} and p_{spec} be the sensitivity and specificity of AVR testing. The likelihood function is

$$L(\sigma, \rho_0) = \prod_{d \in D} \binom{Z_d^S + Z_d^R}{Z_d^R} p_d{}^{Z_d^R} (1-p_d)^{Z_d^S}$$

where $p_d = p_{sens} \int_d^{d+1} \tilde{\rho}(t) dt + (1-p_{spec}) \left(1 - \int_d^{d+1} \tilde{\rho}(t) dt\right)$ and ρ_0 is the value of $\tilde{\rho}(t)$ at the beginning of AVR surveillance. The AVR fitness σ and ρ_0 are jointly estimated using Markov Chain Monte Carlo methods with flat priors.

Incorporating the inference of generation time distribution into the model

In our case studies, we use the best-fit generation time distribution from the literature for both seasonal influenza A(H1N1) and A(H1N1)pdm09. The estimation of generation time distribution can be easily incorporated into the model. Let θ^u be the parameters of the generation time distribution for strain $u \in \{S, R\}$. Suppose we have data on the generation time (or serial interval which is often regarded as an accurate proxy for generation time) of M_u infector-infectee pairs for strain *u* during the very early stage of the epidemic, denoted by $x_1^u, \ldots, x_{M_u}^u$. The augmented likelihood function is

$$L(\sigma, \rho_0, \theta^R, \theta^S) = \prod_{u \in \{R,S\}} \prod_{j=1}^{M_u} g^u(x_j^u \mid \theta^u) \times \prod_{d \in D} \binom{Z_d^S + Z_d^R}{Z_d^R} {p_d}^{Z_d^R} (1-p_d)^{Z_d^S} \quad .$$

If the data on generation time are not collected during the very early stages of the epidemic (i.e. not reflecting the intrinsic distribution), then adjustments would need to be made (1-3).

Case study 1: Estimating intrinsic AVR fitness and drug pressure on the AVS virus jointly from multiple populations when antiviral intervention is absent in at least one population

Let *N* be the number of populations. We assume that (i) intrinsic AVR fitness is the same in all populations and (ii) antiviral interventions in population *j* reduce the reproductive number of the AVS virus by a proportion μ_j. Without loss of generality, let $\mu_1 = 0$ to reflect the assumption that drug pressure is absent in at least one population. The AVR fitness in population *j* is related to the intrinsic AVR fitness and drug pressure μ_j by $\sigma_j = \sigma_0 / (1-\mu_j)$. The likelihood is simply

$$L(\sigma_0, \mu_2, \ldots \mu_N, \rho_{0,1}, \ldots, \rho_{0,N}) = \prod_{j=1}^{N} \prod_{d \in D} \binom{Z_{d,j}^S + Z_{d,j}^R}{Z_{d,j}^R} {p_{d,j}}^{Z_{d,j}^R} (1-p_{d,j})^{Z_{d,j}^S}$$

where the second subscript *j* in $\rho_{0,j}$, $p_{d,j}$, $Z_{d,j}^S$ and $Z_{d,j}^R$ refer to the index of the population.

Given that oseltamivir was routinely used for treating influenza in Japan only (4), we conduct a sensitivity analysis to estimate the intrinsic AVR fitness by (i) assuming the same intrinsic fitness in all populations and no drug pressure except in Japan; and (ii) simultaneously inferring intrinsic fitness and drug pressure on the AVS strain in Japan. When explicitly modeling the effect of drug pressure in Japan, we estimate that the pooled intrinsic AVR fitness was still 1.04 (1.03-1.05) and

the use of oseltamivir reduced the transmissibility of the AVS strain by -1.7% (-5.7%-2.7%) in Japan.

Case study 3: Estimating intrinsic AVR fitness and drug pressure on AVS virus jointly when antiviral intervention is implemented during an influenza pandemic

In our third case study, we consider a hypothetical scenario in which large-scale antiviral intervention, comprising prophylaxis and treatment, is implemented to reduce disease transmission during an influenza pandemic that comprises both AVS and AVR infections. Let c_p and c_t be the antiviral prophylaxis and treatment coverage, respectively, at the start of antiviral intervention. Suppose antiviral prophylaxis reduces susceptibility to AVS infection by w_p, and treatment reduces the infectiousness of AVS infections by w_t. The AVR fitness is therefore

$$\sigma = \frac{\sigma_0}{1-\mu} = \frac{\sigma_0}{(1-c_t w_t)(1-c_p w_p)}$$

in which σ_0 is the intrinsic AVR fitness when there is no drug pressure on AVS. Suppose the antiviral coverage is reduced to hc_p and hc_t when AVR fitness is estimated to be greater than 1 with high probability where h is known. Let σ_{pre} and σ_{post} be the AVR fitness before and after the coverage adjustment. Then

$$\frac{\sigma_{pre}}{\sigma_{post}} = \frac{1-hc_t w_t - hc_p w_p + h^2 c_t w_t c_p w_p}{1-c_t w_t - c_p w_p + c_t w_t c_p w_p}$$

The terms $h^2 c_t w_t c_p w_p$ and $c_t w_t c_p w_p$ can be ignored because they are relatively small compared to the other terms. To a good approximation, the drug pressure on the AVS virus before coverage reduction is therefore related to h as well as the pre- and post-reduction AVR fitness as follows:

$$\mu \approx \frac{\sigma_{pre} - \sigma_{post}}{\sigma_{pre} - h\sigma_{post}}$$

Estimating nonstationary AVR fitness

Suppose base case assumptions 5 and 6 are relaxed as follows:

1. Drug pressure on the AVS virus can be age-dependent because antiviral intervention coverage differs across age groups. Let μ_j be the reduction in susceptibility to the AVS virus in age group *j* due to drug pressure.
2. The initial proportion of each age group that are susceptible to the AVR virus can be different from that to the AVS virus. Let $S_j^R(0)$ and $S_j^S(0)$ be the initial proportions of age group *j* that are susceptible to the AVR and AVS virus, respectively.

In such scenarios, AVR fitness can vary over time, i.e. nonstationary. We conjecture that such temporal changes in AVR fitness can be well approximated by the piecewise linear model

$$\sigma_{PL}(t) = \begin{cases} \sigma_1 & \text{if } t < t_1; \\ \sigma_1 + \dfrac{\sigma_2 - \sigma_1}{t_2 - t_1}(t - t_1) & \text{if } t_1 \le t \le t_2; \\ \sigma_2 & \text{if } t > t_2. \end{cases}$$

if the values of σ_1, σ_2, t_1 and t_2 are optimally selected. That is, temporal changes in AVR fitness are either insignificant or monotonic. To substantiate this conjecture, we use Latin-hypercube sampling to randomly generate 1,000 epidemic scenarios in the following parameter space:

- Drug pressure for each age group *j* (μ_j) between 0.5 to 1;
- The initial proportion of each age group *j* susceptible to the AVS virus and the AVR virus ($S_j^S(0)$ and $S_j^R(0)$) between 0.3 to 1;
- Mean generation time (T_g) between 2 and 4 days;
- AVR intrinsic fitness (σ_0) between 0.8 and 1.2;
- The proportion of seeding infections that were AVR between 0.1 and 0.9;

We then identify the best-fit piecewise linear model for the true AVR fitness $\sigma(t)$ in each of these 1,000 scenarios using least-squares, i.e.

$$\min_{\sigma_1, \sigma_2, t_1, t_2} \int_0^\infty \left(\sigma(t) - \sigma_{PL}(t)\right)^2 dt$$

Figure A4 shows that this approximation is very accurate, hence verifying our claim that temporal changes in AVR fitness due to relaxation of base case assumptions 5 and 6 can be well approximated by the piecewise linear model when AVR fitness is nonstationary.

To account for the possibility of nonstationary AVR fitness, we extend our method by inferring AVR fitness using this piecewise linear model. When using the piecewise-linear model to estimate AVR fitness at an arbitrary time *T*, the data available up to time *T* may not be sufficient to infer all the parameter values in the best-fit piecewise linear model. As such, at any given time *t*, we infer AVR fitness using all truncated versions of the piecewise-linear model:

1. $\sigma(t) = \sigma_1$ for all $t < T$

   where σ_1 is inferred.

2. $$\sigma(t) = \begin{cases} \sigma_1 & \text{if } t < t_1; \\ \sigma_1 + \dfrac{\sigma_T - \sigma_1}{T - t_1}(t - t_1) & \text{if } t_1 \le t \le T; \end{cases}$$

   where $\sigma_1, t_1,$ and σ_T are inferred.

3. $$\sigma(t) = \begin{cases} \sigma_1 & \text{if } t < t_1; \\ \sigma_1 + \dfrac{\sigma_2 - \sigma_1}{t_2 - t_1}(t - t_1) & \text{if } t_1 \le t \le t_2; \\ \sigma_2 & \text{if } t_2 < t \le T. \end{cases}$$

   where $\sigma_1, \sigma_2, t_1,$ and t_2 are inferred.

The final estimate of AVR fitness at time *T* is then obtained by choosing the best model using Bayesian Information Criterion.

We perform a preliminary analysis on the performance of this extended method. Figure A5 shows an exemplary scenario in which AVR fitness changes over time when base case assumptions 5 and 6 are relaxed. Extended with the piecewise-linear model, our method can accurately track temporal changes in AVR fitness when perfect information on AVS and AVR incidence are (hypothetically) available. In the presence of stochasticity in the data streams, however, the extended method cannot detect temporal changes in AVR fitness unless such changes are sufficiently large. In the exemplar presented in Figure A5, an AVR testing capacity of 25 samples per day or above yields reliable AVR fitness except when the fitness is changing. These preliminary results suggest that compared to the base case of constant AVR fitness, real-time surveillance of nonstationary AVR fitness requires substantially higher AVR testing capacity which is unsurprising because more parameters are needed to describe temporal changes in AVR fitness.

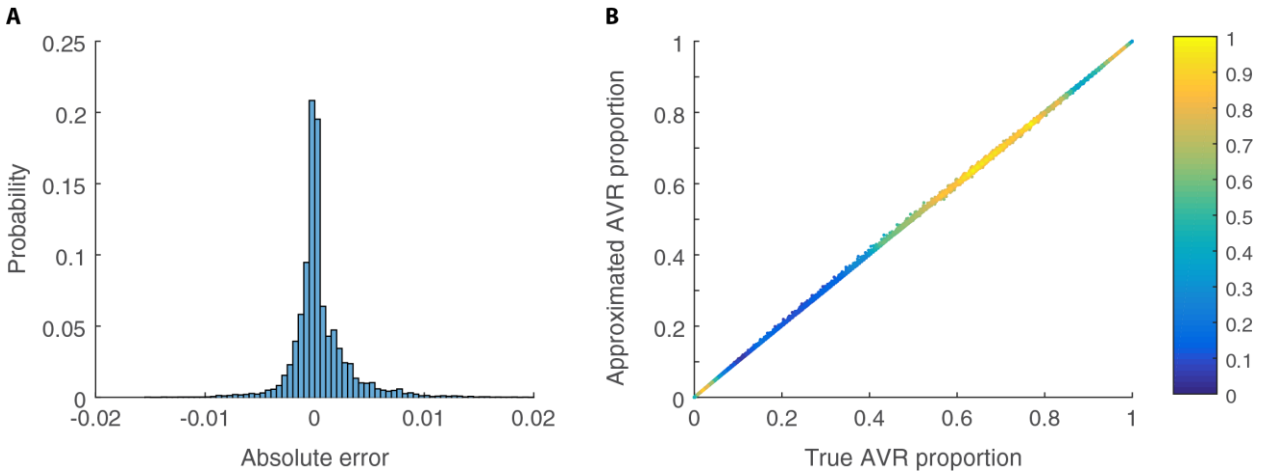

Figure A1. Verifying the accuracy of equation (1). We compare the proportion of incidence that are AVR infections in each age group *j* (denoted by $\rho_j(t)$) with its approximation in equation (1) (denoted by $\hat{\rho}(t)$) on each day *t* of the 100 randomly generated epidemic scenarios described in Methods. **A.** Histogram of the absolute error $\hat{\rho}(t) - \rho_j(t)$ for all *j* and *t*. **B.** The 2-D histogram of $\hat{\rho}(t)$ and $\rho_j(t)$ in which the colors indicate the frequency of $\left(\hat{\rho}(t), \rho_j(t)\right)$ pairs for all *j* and *t* across all scenarios.

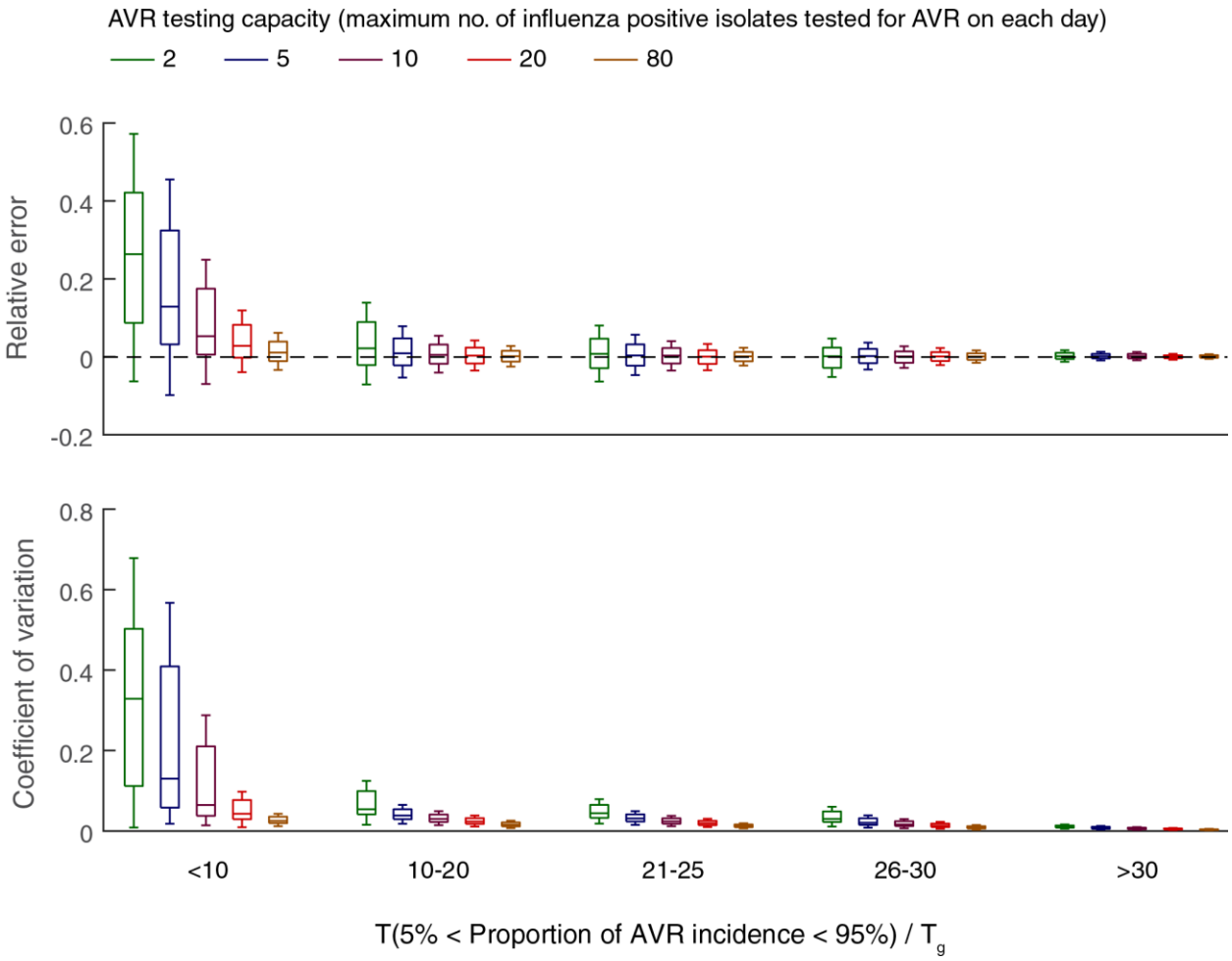

Figure A2. Validating the accuracy and precision of AVR fitness estimates when the sensitivity and specificity of AVR testing are both 90%. The simulated data used here are the same as that in Figure 1 except for the sensitivity and specificity of AVR testing.

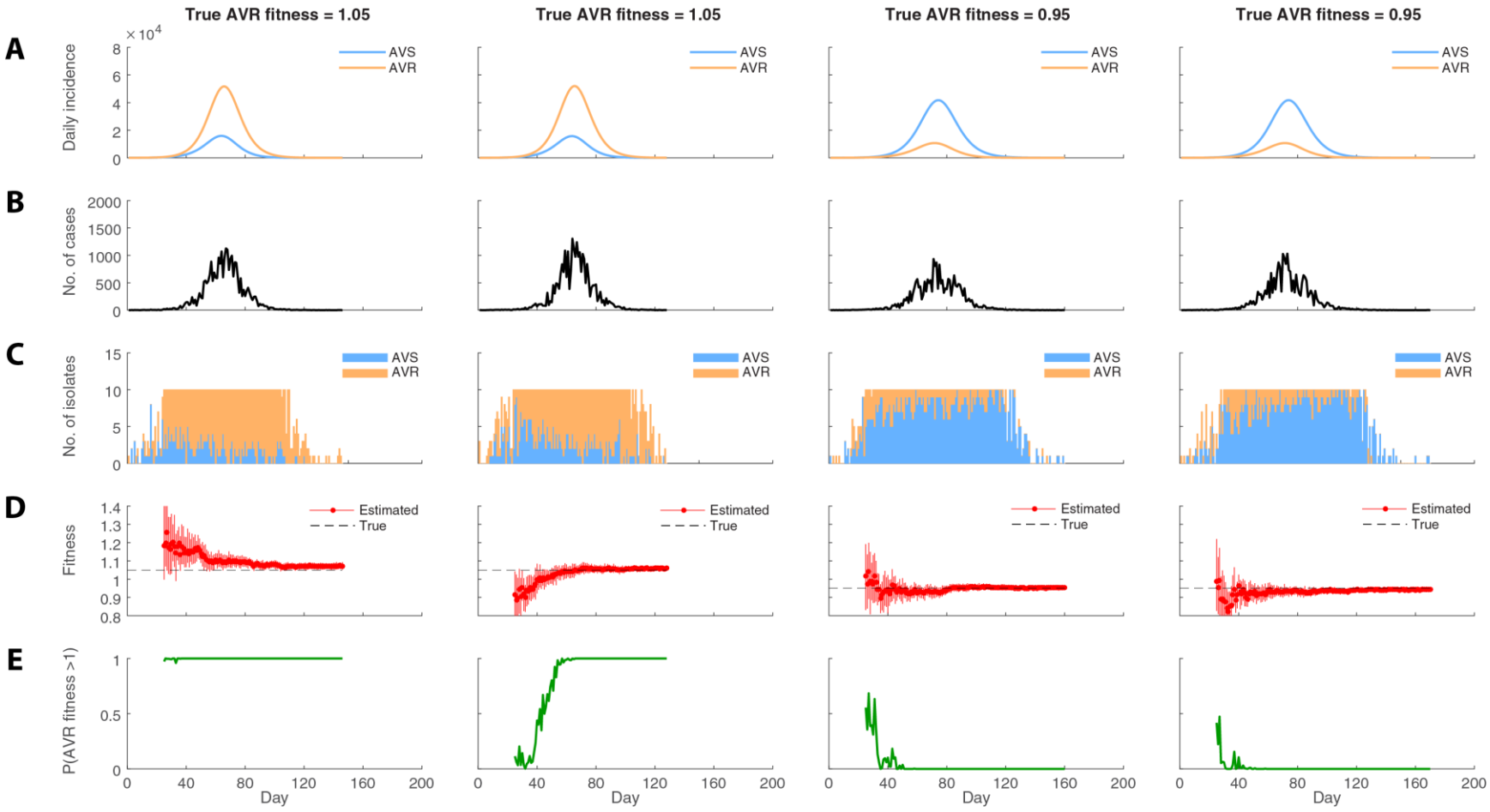

Figure A3. Alternative stochastic realizations of the epidemic scenarios in Figure 2.

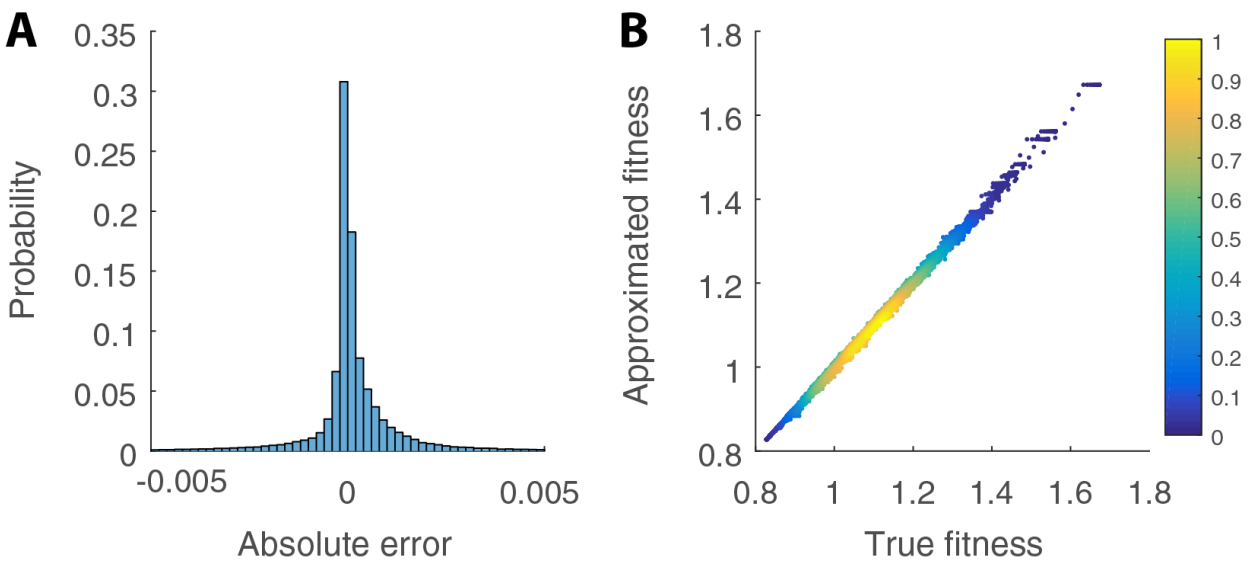

Figure A4. Verifying the accuracy of the piecewise linear model to approximate nonstationary AVR fitness. This figure is analogous to Figure A1. We compare the true AVR fitness with the corresponding best-fit piecewise linear model on each day *t* of the 1,000 randomly generated epidemic scenarios described in the section "Estimating nonstationary AVR fitness" of the appendix. **A.** Histogram of the absolute error for all times *t*. **B.** The 2-D histogram of true and approximate AVR fitness in which the colors indicate the frequency of these pairs for all *t* across all scenarios.

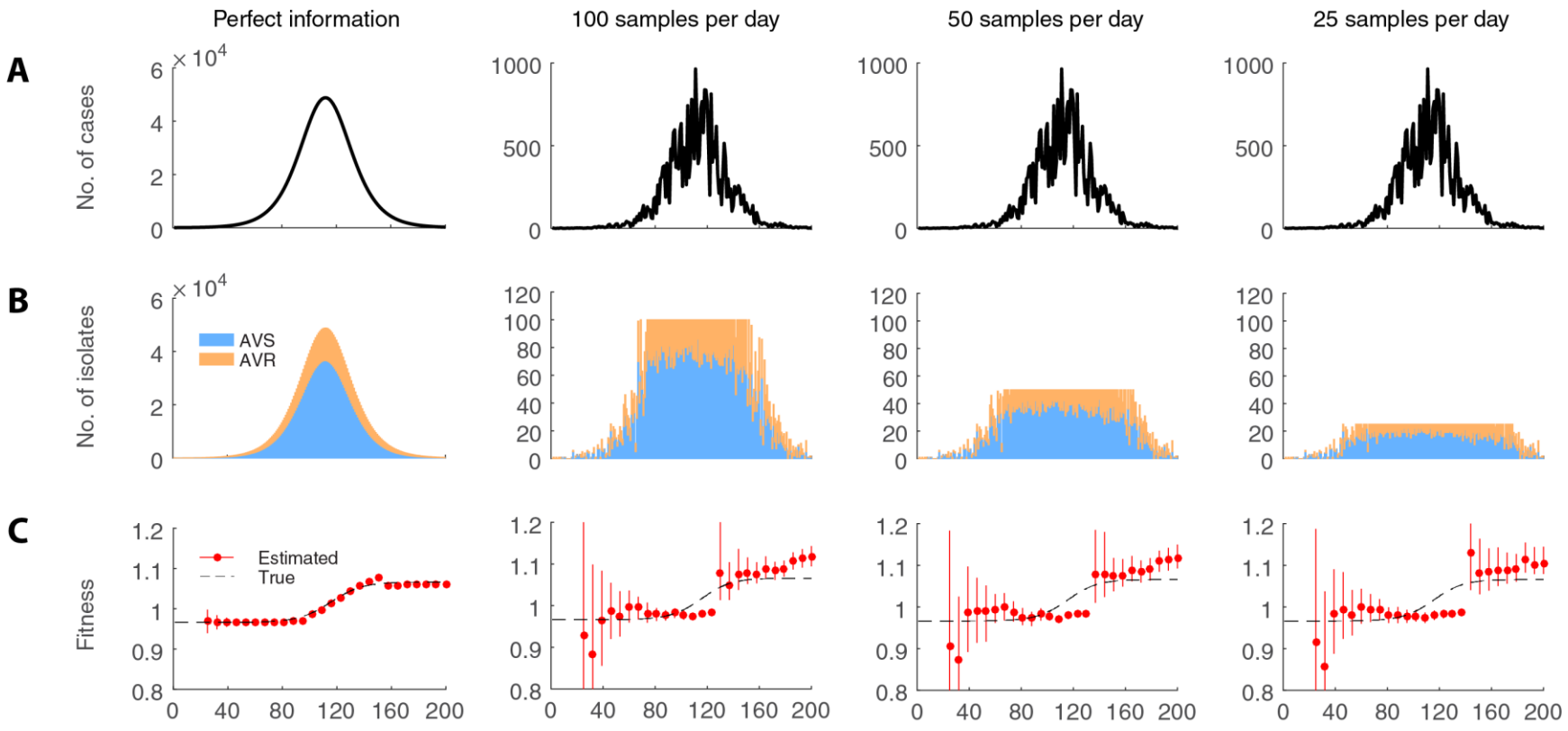

Figure A5. Estimating nonstationary AVR fitness. An exemplary epidemic in which AVR fitness changes over time when base case assumptions 5 and 6 are relaxed. Four scenarios are considered (from left to right): perfect information on AVS and AVR incidence, and daily AVR testing capacity of 100, 50 and 25 samples with daily reporting proportion between 0.5% and 2%. **A** The daily number of reported cases. **B** The daily number of influenza-positive isolates that are AVS and AVR. **C** Posterior distribution of the AVR fitness estimate on each day. Circles and error bars indicate the posterior medians and the 95% credible intervals, respectively.

Year/ Week	Canada[1]	France[2]	Germany[3]	Hong Kong[4]	Japan[5]	Luxembourg[6]	Netherlands[7]	Norway[8]	UK[9]	US[10]
2007/40	0	0	0	4	11	0	0	0	2	17
2007/41	0	0	0	1	10	0	0	0	0	19
2007/42	0	0	0	0	22	0	0	0	0	16
2007/43	0	0	0	0	30	0	0	0	0	16
2007/44	0	0	0	1	23	0	0	0	5	10
2007/45	0	0	0	1	52	0	0	0	1	17
2007/46	0	0	1	0	85	0	0	0	1	24
2007/47	0	0	0	0	68	0	0	2	5	35
2007/48	0	0	0	1	158	0	0	3	10	49
2007/49	4	2	0	0	204	0	0	4	24	35
2007/50	3	1	1	0	322	0	0	8	21	53
2007/51	6	7	12	2	278	0	0	5	54	70
2007/52	8	5	6	4	140	2	0	3	41	80
2008/01	11	11	10	6	46	6	2	7	59	96
2008/02	6	13	22	11	269	9	5	11	95	179
2008/03	18	7	71	14	310	28	5	17	61	220
2008/04	16	22	91	25	430	46	7	30	34	223
2008/05	21	20	120	25	362	33	4	30	35	262
2008/06	17	22	94	36	271	18	6	32	30	268
2008/07	17	10	86	51	159	20	9	30	11	211
2008/08	21	5	88	50	216	18	10	32	22	190
2008/09	11	3	63	85	130	8	3	23	3	132
2008/10	6	2	16	124	76	2	2	14	18	74
2008/11	5	2	16	131	54	0	0	13	3	79
2008/12	6	0	14	58	47	0	2	17	6	49
2008/13	5	1	0	30	21	0	1	2	3	14
2008/14	2	0	3	5	5	0	0	6	0	12
2008/15	1	0	1	16	6	0	0	1	6	6
2008/16	0	0	2	7	2	0	0	2	1	0
2008/17	0	0	1	10	0	0	0	0	1	5
2008/18	0	0	0	8	0	0	0	2	0	1
2008/19	0	0	0	3	0	0	0	0	0	0
2008/20	0	0	0	7	0	0	0	0	1	0

Table A1. Weekly data on seasonal influenza A(H1N1) activity during 2007-2008 from the 10 populations considered in case study 1.

1. Janjua NZ, Skowronski DM, De Serres G, et al. Estimates of influenza vaccine effectiveness for 2007–2008 from Canada's sentinel surveillance system: cross-protection against major and minor variants. Journal of Infectious Diseases 2012: jiA283.
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3. Buchholz U, Buda S, Gruber A, Schweiger B. Abschlussbericht der Influenzasaison 2007/08. 2008. https://influenza.rki.de/Saisonberichte/2007.pdf.
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http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2010/januari/Jaarrapportage_surveillance_respiratoire_infectieziekten_2008.
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http://www.fhi.no/eway/default.aspx?pid=240&trg=Content_6765&Main_6664=6894:0:25,7555:1:0:0:::0:0&MainContent_6894=6765:0:25,7571:1:0:0:::0:0&Content_6765=6729:66508:25,7571:1:6770:18:::0:0.
9. Health Protection Agency UK. Health Protection Report: weekly report. 2008.
10. Centers for Disease Control and Prevention US. U.S. WHO/NREVSS Collaborating Laboratories National Summary, 2004-05 through 2007-08. 2008. http://www.cdc.gov/flu/weekly/weeklyarchiveA2007-2008/data/04-08national.htm.

Year/ Week	Germany[1]		Luxembourg[2]		Norway[3]		United States[4]	
	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive
2007/40	0	0	0	0	0	0	0	0
2007/41	0	0	0	0	0	0	0	0
2007/42	0	0	0	0	0	0	0	0
2007/43	0	0	0	0	0	0	0	0
2007/44	0	0	0	0	0	0	0	0
2007/45	0	0	0	0	0	0	0	0
2007/46	1	0	0	0	3	1	0	0
2007/47	0	0	0	0	3	3	0	0
2007/48	0	0	0	0	4	4	0	0
2007/49	1	0	0	0	8	6	0	0
2007/50	1	1	0	0	5	5	0	0
2007/51	5	0	2	0	2	1	0	0
2007/52	1	0	4	0	7	5	0	0
2008/01	10	0	14	0	15	6	0	0
2008/02	17	2	30	3	17	8	0	0
2008/03	35	2	43	7	22	16	0	0
2008/04	36	3	47	14	31	20	0	0
2008/05	24	0	36	8	29	20	0	0
2008/06	86	12	33	10	25	18	12	1
2008/07	59	10	23	7	32	22	113	11
2008/08	38	7	10	4	22	16	86	11
2008/09	24	6	9	5	11	6	123	7
2008/10	8	1	3	1	17	12	42	6
2008/11	16	7	0	0	5	4	85	8
2008/12	4	1	0	0	5	3	100	12
2008/13	0	0	0	0	4	4	51	2
2008/14	0	0	0	0	1	1	27	11
2008/15	0	0	0	0	1	0	14	3
2008/16	0	0	0	0	2	2	0	0
2008/17	0	0	0	0	0	0	42	8
2008/18	0	0	0	0	0	0	33	6
2008/19	0	0	0	0	0	0	56	5
2008/20	0	0	0	0	0	0	0	0

Table A2. Weekly data on antiviral resistance among seasonal influenza A(H1N1) from Germany, Luxembourg, Norway and the United States during 2007-2008.

1. Buchholz U, Brockmann S, Duwe S, et al. Household transmissibility and other characteristics of seasonal oseltamivir-resistant influenza A (H1N1) viruses, Germany, 2007-8. Eurosurveillance 2010; 15(6): 5888-95.
2. Mossong J, Opp M, Gerloff N, et al. Emergence of oseltamivir-resistant influenza A H1N1 virus during the 2007–2008 winter season in Luxembourg: clinical characteristics and epidemiology. Antiviral research 2009; 84(1): 91-4.
3. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007–08. Emerging infectious diseases 2009; 15(2): 155.

4. Centers for Disease Control and Prevention US. 2007-08 U.S. influenza season summary. 2008. http://www.cdc.gov/flu/weekly/weeklyarchiveA2007-2008/07-08summary.htm.

Year/ Month	Canada[1]		France[2]		Hong Kong[3]		Japan[4]		Netherland[5]		United Kingdom[6]	
	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive	No. tested	No. AVR positive
2007/10	1	0	4	0	0	0	39	0	1	0	0	0
2007/11	18	0	7	1	0	0	100	1	2	0	0	0
2007/12	114	16	91	38	5	0	136	0	7	1	0	0
2008/01	153	26	297	118	80	11	625	11	50	12	162	8
2008/02	126	37	294	153	236	19	413	7	71	27	154	21
2008/03	56	38	34	25	260	38	45	3	9	2	29	9
2008/04	7	6	6	4	0	0	0	0	0	0	0	0

Table A3. Monthly data on antiviral resistance among seasonal influenza A(H1N1) from Canada, France, Hong Kong, Japan, Netherlands and the United Kingdom during 2007-2008.

1. World Health Organization. Preliminary summary on oseltamivir-resistant H1N1 virus: Canada. 2008.
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